UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES

HUMAN RESEARCH ETHICS COMMITTEE

STANDARD OPERATING PROCEDURES

Version 7.2

February 2026

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https://health.uct.ac.za/home/human-research-ethics

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All standard operating procedures (SOPs) and associated documents must only be accessed through the dedicated SOP area of the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee (HREC) webpage (www.health.uct.ac.za/fhs/research/humanethics/sop) to ensure the correct version is being used. The user must ensure that they are always working to the current version of the SOPs and associated document.

Version History Log

Version	Date	Reason for Change	Implementation Plan*
1.0	October 2008	Updated in accordance with the DoH Ethics in Health Research Guidelines (2004); and with requirements for registration with the National Health Research Ethics Council (NHREC)	n/a
2.0	October 2009	Updated in accordance with the DoH Ethics in Health Research Guidelines (2004)	n/a
3.0	January 2013	Updated to comply with latest version of Declaration of Helsinki	n/a
4.0 4.1	March 2015 August 2015	Updated to incorporate SOP for Children in Research; and SOP for Insurance against Research-related Bodily Injury SOP for Informed Consent updated in accordance with the DoH Ethics in Health Research Guidelines (2015)	n/a
5.0 5.1	January 2016 October 2016	Updated in accordance with the DoH Ethics in Health Research Guidelines (2015)	n/a
6.0	July 2018	Updated in accordance with the DoH Ethics in Health Research Guidelines (2015)	n/a
7.0	April 2019	Updated following National Health Research Ethics Council (NHREC) Quality Assurance Audit Report (August 2018)	Ethics Office administrative staff will receive training regarding the new SOPs. All Faculty staff will be notified of the revised SOPs. Updated procedures will be implemented from the SOP effective date.

7.1	October 2019	Minor typographical changes	Updated SOPs will be posted on the HREC website, with a notice on the HREC homepage. A notification will be sent to all Faculty of Health Sciences staff and students.
7.2	February 2026	Minor updates such as aligning with the latest version of the SA Good Clinical Practice Guidelines (2020), National Department of Health's Ethics in Research Guidelines (2024), as well as the updated Declaration of Helsinki (2024).	Updated SOPs will be posted on the HREC website, with a notice on the HREC homepage. A notification will be sent to all Faculty of Health Sciences staff and students.

** Please note that the implementation plan for SOPs version 1.0-6.0 are listed as "n/a", as the SOP for Writing, Revising and Managing Standard Operating Procedures (SOPs) was only developed in April 2019.*

Writing, Revising and Managing Standard Operating Procedures (SOPs)

Policy

The University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee (HREC) Standard Operating Procedures are documents that relate to important tasks and practices associated with HREC functioning; the review and approval of health-related research protocols; requirements for conducting and managing health-related research and continuing review.

Purpose

The purpose of this policy is to describe the preferred method for writing, revising and managing all SOPs of the HREC.

Summary of Responsibilities

All staff and affiliates to whom the HREC SOPs apply are responsible for identifying new SOPs that need to be written; or gaps and deficiencies in current SOPs that need to be revised. The HREC Office must be informed by email (hrec-enquiries@uct.ac.za) of any requests to write or update SOPs.

The Faculty of Health Sciences Ethics Office Manager will be responsible for oversight of the HREC SOPs; plans for writing and revising SOPs; and implementation plans to ensure that all Faculty of Health Sciences staff are informed of SOP revisions and effective dates.

The HREC SOPs may be written or revised by the HREC Chairperson and Deputy Chairpersons or a person delegated to write or revise SOPs by the HREC Chairperson. The HREC Chairperson and Deputy Chairpersons, in collaboration with the Office of Research Integrity, are responsible for ensuring that the SOPs remain accurate, current and compliant with any changes to national and international research ethics guidelines and regulatory environments. The HREC senior administrators may contribute to regulatory or administrative revisions to the SOPs, in consultation with the HREC Chairperson and Deputy Chairpersons. An expert in an area of research ethics may be requested to contribute to the writing, composition and review of SOPs. The HREC SOPs may be circulated to Full Committee members for expert advice and feedback.

Principal investigators and study staff are required to adhere to the processes outlined in SOPs; to assess the impact of new or updated SOPs on studies; to report deviations from described procedures; and to provide feedback to allow for continued development and improvement of SOPs.

Identification of Need for New SOP or Revision

All SOPs must be current and fit for purpose; and as such, must undergo regular review. A review of each SOP must be carried out at least once every two years. Earlier review may be necessary due to introduction of new regulations or procedures; to input or feedback from the National Health Research Ethics Council (NHREC); or where clarifications or additions are required to accommodate situations not well defined by the SOPs.

Existing SOPs may need to be updated where changes are made to national or international research ethics guidelines, regulations governing research or University processes; where gaps in procedures become apparent; or where the need for clarifications, additions or improvements may be identified.

SOP Approval

Minor new SOPs or revised SOPs will be reviewed by the HREC Chairperson, Deputy Chairpersons and senior administrators. Minor new or revised SOPs are defined as having no potential impact on participant safety, rights or welfare, integrity of data or regulatory compliance. The HREC Chairperson will be responsible for final approval of minor new and revised SOPs.

Significant new SOPs or revised SOPs will be reviewed by the Full Committee. Significant changes to SOPs are defined as having a potential impact on participant safety, rights or welfare, integrity of data or regulatory compliance. Feedback from the Full Committee will be incorporated into the writing or revision of SOPs by the HREC Chairperson, Deputy Chairpersons and senior administrators. The Full Committee will be responsible for final approval of significant new and revised SOPs.

Significant new and revised HREC SOPs will be submitted to the Senate Ethics in Research Committee (EiRC) for noting.

Version Control

Version numbers in the format *x.x* must be assigned to every new issue of a SOP. Minor changes (such as annual review that does not change the content of the SOPs or typographical changes) should result in an increment after the decimal point (e.g. 2.0 to 2.1). Major changes should result in a change before the decimal point (e.g. 2.2 to 3.0).

Access and Record Keeping

The Faculty of Health Sciences Ethics Office Manager uploads finalised versions of all SOPs to the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee (HREC) webpage (https://health.uct.ac.za/home/human-research-ethics).

Paper copies of all original (wet signature) SOPs are retained securely by the Faculty of Health Sciences Ethics Office Manager in the HREC SOPs Master File. For each superseded SOP, a note is written on the front page stating, "*This SOP has been superseded by version x on date y*". All pages of the SOP must be clearly marked (right-hand top corner cut-off) to indicate that they must not be used.

Electronic copies of all previous original electronic pdf or Word versions of SOPs are stored by the Faculty of Health Sciences Ethics Office Manager on the HREC Vula site.

Feedback, Change Requests and Deviations

Feedback regarding SOPs should be sent to hrec-enquiries@uct.ac.za.

Requests to change a currently active version of a SOP should be made to hrec-enquiries@uct.ac.za. Unauthorised changes to live SOPs must not be made.

Deviations from processes described within SOPs, whether identified retrospectively or prospectively, must be managed in accordance with the HREC SOPs for Protocol Deviations and Non-compliance respectively. The HREC may revise SOPs based on protocol deviations and non-compliance findings.

Withdrawing SOPs

A SOP may be permanently withdrawn when the procedure described within it is no longer required, or the procedure is described elsewhere. This is not applicable where a document is being superseded by a new version.

References

1. Writing, Revising and Managing SOPs and Associated Documents. Keele University (2018) www.keele.ac.uk. Accessed on 28 April 2019.
2. Template for Generating SOPs. GlobalHealthTrials.org: https://globalhealthlaboratories,tghn.org. Accessed on 28 April 2019.

Ethical and Regulatory Requirements for Human Research

Policy

Human research undertaken in the Faculty of Health Sciences must comply with national and international ethical and regulatory practices.

Purpose

The purpose of this policy is to describe basic ethical requirements and to identify primary sources of regulation governing human research in the Faculty of Health Sciences.

Ethical Requirements for Human Research

In the UCT Research Ethics Code for Research Involving Human Participants[1], the University of Cape Town aims to promote high quality research in the interests of South African society and the human condition as a whole. It aims to do research with:

- Scholarly integrity and excellence.
- Social sensitivity and responsibility.
- Respect for the dignity and self-esteem of the individual and for basic human rights.
- Reference to clearly specified standards of conduct and procedures ensuring proper accountability.

The Human Research Ethics Committee in the Faculty of Health Sciences is committed to the ethical principles laid down in the:

- Belmont Report 1979
- CIOMS International Ethical Guidelines for Health-related Research Involving Humans, 2016
- Declaration of Helsinki 2024
- Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, Republic of South Africa, 2024
- Medical Research Council: Guidelines on Ethics for Medical Research: HIV Preventive Vaccine Research Book 5

More specifically, the Human Research Ethics Committee is committed to the following ethical requirements [2,3]:

Social Value

The research must be worth doing. It must be relevant to broad health and development needs of South Africa and to the individual needs of those who suffer from the conditions under study. Ideally, the findings should translate into mechanisms for improving the health status of South Africans; in reality, the process of translating research results into health improvements is incremental, messy and slow.

Scientific Merit

The design and methods must be scientifically sound. Unless research generates reliable and valid data which address the study's objectives, it will have no social or scientific value and participants may be exposed to risk with no compensating benefit. International multi-centre research undertaken in South Africa should be designed so that the findings will be useful and appropriate to individuals and communities in this country.

Respect for Persons

Respect for persons implies concern for the safety, well-being, beliefs and customs of individuals and communities taking part in research. As a rule, respect for person's manifests through informed consent which allows individuals and communities to choose if they want to participate in research. Valid consent presumes individuals are given information in a form and manner which they understand, and that they are able to choose in circumstances free from undue pressure. Valid informed consent is more than obtaining a signature on a consent form. It is a continuous process of disclosure that involves ongoing communication and trust between researchers and participants. Informed consent must be sensitive to language and the range of contexts in which human research is conducted in South Africa.

Respect for Vulnerable Persons

Researchers must be especially sensitive towards persons whose autonomy is in some way compromised due, for example, to cognitive or other deficits or who are relatively disempowered due to situational factors such as poverty and limited access to health services. Often it is difficult to decide if vulnerable persons should be excluded from research. Yet, preventing persons from making decisions to take part in research conflicts with the principle of respect for persons and may be viewed as paternalistic. In such situations, a balance must be sought between respect for persons and potential harms and benefits for specific participants.

Privacy and Confidentiality

In its positive sense, privacy in the research context, refers to an individual's right to control access to and the distribution of personal information; as a negative right, privacy ensures the absence of interference or the right to be left alone. Researchers must put measures in place which protect individuals and communities from harm which might result from access to personal and sensitive information. The harm which results from invasion of privacy or breach of confidentiality is often termed a 'social harm' as it may lead to stigmatisation, or loss of insurance or employability.

Fair Participant and Community Selection

The benefits and burdens of research must be shared fairly among individuals and communities. To achieve a fair balance between access to the benefits of research and protection from its harms, research must be responsive to the needs of vulnerable populations. Inclusion of vulnerable groups such as children requires a compelling scientific justification as to why the research cannot be conducted among less vulnerable populations, a reasonable chance of direct benefit to individual participants and the absence of significant risk or discomfort. Convenience is not an acceptable reason for including vulnerable groups in research. Historically, justice or fairness in research has focussed on which participants are included in research when they should not be. Yet it is also unethical to exclude classes of people who are likely to benefit from taking part in research or in whom the results of a specific kind of research are likely to be applied. Accordingly, research must not systematically exclude a class or type of person who is likely to benefit from research participation or in whom the results of a specific kind of research are likely to be applied.

Favourable Balance of Benefits and Harms

Because the purpose of research is to advance the frontiers of knowledge, it unavoidably carries some uncertainty. However, to avoid harm, researchers must first learn what is harmful and in the process of obtaining this information persons may be exposed to harm. Harms may be physical, psychological, legal, social and economic. Researchers must aim to maximise benefits and minimise harms to individuals and communities. Where a study offers no direct benefit to individual participants, the social value of the research must be sufficient to justify potential harm or inconvenience.

Collaborative Partnerships

To ensure that research is relevant and acceptable, researchers should engage key stakeholders such as community representatives and policy makers in designing the protocol, conducting the research and distributing the findings.

Moreover, community participation could include input into a suitable informed consent process, appropriate risk reduction interventions, and decisions regarding treatment and care linked to the research. Collaborative partnerships should allow community members to become genuine, active partners in the research process. This requires sustainable forums for regular communication and problem solving. Likewise, in international multi-centre research, collaborative partnerships between researchers and sponsors from developed countries and researchers and communities in the host country are likely to reduce exploitation, facilitate the negotiation of fair benefits and show awareness of and respect for cultural differences.

Ethical Review

A South African-based research ethics committee must review the ethical and scientific rigour of all research conducted in South Africa. No research involving humans can begin until a registered research ethics committee has granted approval. Researchers must obtain ongoing approval, at least annually, throughout the research activity.[4]

Professional Competence

Researchers must be technically competent in their specific fields to conduct a study. The principal investigator carries the primary responsibility for securing participants' safety and well-being during a study. Researchers who perform human research must be suitably qualified by experience and/or training to safeguard participants' rights in their research, and all others involved in a study share this responsibility in varying degrees. In international, multi-centre research, the local principal investigator must be based in South Africa.

Regulatory Requirements for Human Research

The Human Research Ethics Committee in the Faculty of Health Sciences complies with the following regulatory guidance:

International Regulatory Requirements

ICH Harmonised Tripartite Guideline: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) 2018

ICH Harmonised Tripartite Guideline: Clinical Investigation of Medicinal Products in the Paediatric Population E11 2000

United States (US) Department of Health and Human Services (DHHS)

The University of Cape Town holds a federal-wide assurance (FWA) with the Office of Human for Human Research Protections (OHRP) in the Department of Health and Human Services (FWA00001637). Under this assurance, all federally-funded or supported research reviewed by the Human Research Ethics Committee in the Faculty of Health Sciences (IRB00001938) must comply with the code of federal regulations in Title 45 CFR 46, Sub-parts A-D.

US Food and Drug Administration (FDA)

The Human Research Ethics Committee in the Faculty of Health Sciences must ensure that researchers who undertake research under the jurisdiction of the FDA comply with regulations found under Title 21 CFR 50 (informed consent), 21 CFR 50 Sub-part D (additional safeguards for children in clinical investigations), 21 CFR 56 (IRB regulations), 21 CFR 312 (investigational new drug applications), 21 CFR 612 (biological products), and 21 CFR 812 (investigational device exemptions). Whilst the FDA does not require a research ethics committee to be registered, form FDA-1572 'Statement of Investigator' for a study under an IND requires the name and address of the human research ethics committee that will be responsible for the review of the study. When research involving products regulated by the FDA is funded or supported by the Department of Health and Human Services (DHHS), the research institution must comply with both the DHHS and FDA regulations.

The Association of the British Pharmaceutical Industry (ABPI): Clinical Trial Compensation Guidelines

Researchers must ensure that all clinical trials sponsored by the pharmaceutical industry include insurance cover for research-related injuries which complies with ABPI guidelines.

Sponsors

In addition, for all externally-funded research, researchers must comply with procedures for protecting participants specifically stipulated by funding agencies.

National Regulatory Requirements

The South African Health Products Regulatory Authority (SAHPRA)

Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa. Third Edition, 2020. Department of Health, Pretoria, South Africa.

Registration of Clinical Trials Undertaken in South Africa:

https://sanctr.samrc.ac.za/ or https://pactr.samrc.ac.za/

Statutory Requirements for Human Research

The Human Research Ethics Committee in the Faculty of Health Sciences must comply with statutory obligations relating to human research and research ethics committees set out in the National Health Act No. 61 of 2003 and by the National Health Research Ethics Council.

The National Health Act No. 61 of 2003 prescribes diseases in South Africa that need to be notified to the Department of Health. This imposes statutory reporting obligations on researchers.

A Directory of the Legal Rights of Minor Research Participants Including Children and Adolescents compiled by the HIV AIDS Vaccine Ethics Group in collaboration with the Desmond Tutu HIV Centre and the Perinatal HIV Research Unit provides a detailed account of specific legal requirements relating to children and adolescents in research. This includes researchers' statutory obligations such as reporting suspected physical or sexual abuse: http://www.saavi.org.childresearch.pdf http://www.saavi.org.adolescent.pdf

Participants' Rights in Human Research

The Department of Health has produced a booklet for researchers to give to potential participants in clinical trials: 'What you should know when deciding to take part in a clinical trial as a research participant': http://www.doh.gov.za/aids/index.html

The South African AIDS Initiative (SAAVI) has produced a Participant's Bill of Rights for preventive HIV Vaccine Trials: http://www.saavi.org.za/billofrights.htm

No Fault Insurance for Research-related Bodily Injury

The University of Cape Town carries a No-Fault Insurance policy for participants who suffer a research-related bodily injury in researcher-initiated health research (See SOP for Insurance against Research-related Bodily Injury).

References

1. Office of Research Integrity. UCT Research Ethics Code for Research Involving Human Participants, March 2012.
2. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. Journal of Infectious Diseases 2004;189:930-7.
3. Lavery JV, Grady C, Wahl ER, Emanuel EJ. Editors. Ethical Issues in International Biomedical Research. A Casebook. Oxford University Press, New York. 2007.
4. Ethics in Health Research: Principles, Processes and Structures 2nd Edition, Department of Health, Republic of South Africa, 2015.

Definition of Health Research and Human Participants

Policy

All activities, meeting the definition of research and involving human participants, planned by staff or students under the auspices of the Faculty of Health Sciences and affiliated institutions or on its premises, are subject to prior approval by the Human Research Ethics Committee. [1,2]

Purpose

The purpose of this policy is to define those activities that constitute human research and fall under the jurisdiction of the Human Research Ethics Committee. This includes activities not requiring Human Research Ethics Committee approval. The policy also outlines requirements for research conducted off campus or involving other sectors such as education.

Definitions

The Human Research Ethics Committee uses the following definitions to determine what constitutes research and research participant:

Health Research

The National Health Act 61 of 2003 (NHA) provides statutory authority for governance of 'health research' and the necessary research ethics regulatory infrastructure.

'Health research' per the NHA may be understood to include but is not limited to research that contributes to knowledge of

- Biological, clinical, psychological, or social welfare matters including processes as regards humans
- The causes and effects of and responses to disease
- Effects of the environment on humans
- Methods to improve health care service delivery
- New pharmaceuticals, medicines, interventions and devices
- New technologies to improve health and health care

'Health technology' means machinery or equipment that is used in the provision of health services, but does not include medicine as defined in Section 1 of the Medicines and Related Substances Control Act 101 of 1965.

Research Participant

A living individual (or group of living individuals) about whom a researcher conducting research obtains data through intervention or interaction with the person or identifiable private information.[4]

US Department of Health and Human Services (HHS)

For purposes of US federally-funded or supported research, the Human Research Ethics Committee recognises the following definitions:

Research

45 CFR 46.102(d) defines 'research' as a systematic investigation, including research development, and testing and evaluation, designed to develop or contribute to generalizable knowledge.

Human Participant

45 CFR 102(f) defines a human participant as an individual about whom an investigator conducting research obtains data through intervention or interaction with individual or identifiable private information.

Intervention or Interaction includes physical procedures performed on an individual, manipulation, communication or interpersonal contact with an individual or manipulation of an individual's environment.

Private Information includes information that an individual can reasonably expect will not be made public, and information about behaviour that an individual can reasonably expect will not be observed or recorded.

Identifiable means that the identity is or may be readily ascertained by the investigator or associated with information.

Food and Drug Administration (FDA)

Research

Under 21 CFR 56.102, the term 'clinical investigation' is synonymous with 'research' and means any experiment that involves a test article and one or more human participants.

Test Article: 21 CFR 50.3 (j) defines test article as any drug (including a biological product for human use, medical device for human use, human food additive, colour, adaptive, electronic product, or any other article subject to regulation under the jurisdiction of the FDA.

Human Participant

21 CFR 50.3(e) defines human participant as an individual who is or becomes a participant in research, either as a recipient of a test article or as a control.

Research among UCT Staff or Students

UCT STAFF: Researchers must obtain permission from the Executive Director of Human Resources to access UCT staff for research purposes. All requests must have prior research ethics approval for the planned study from the Faculty of Health Sciences Human Research Ethics Committee.

UCT STUDENTS: Researchers must obtain permission from the Executive Director of Student Affairs to access UCT students for research purposes. All requests must have prior research ethics approval for the planned study from the Faculty of Health Sciences Human Research Ethics Committee.

Research Conducted Off-UCT Campus or Involving Other Sites and Sectors

Western Cape Public Sector Health Facilities

To coordinate health research, facilitate efficient use of limited health research resources, and minimise the impact of research on staff and patients in the public health sector, the Western Cape Health Research Committee will perform its own administrative review research[5]:

https://www.westerncape.gov.za/service/research-ethics-committee

In addition, researchers must obtain administrative permission from medical superintendents or health facility managers to undertake research in their facilities. Failure to obtain permission may result in the institutional suspension of the study. Copies of approval letters must be forwarded to the Human Research Ethics Committee for filing with researchers' protocols.

Research in Educational Facilities

In addition to approval and oversight from the Human Research Ethics Committee, health-related research in schools requires approval of the Western Cape Education Department, school principals and written parent/legal guardian consent.

Research in Other Facilities

In addition to approval and oversight from the Human Research Ethics Committee, researchers must obtain permission from relevant authorities to undertake health-related research in institutions such as homes for the aged, homes for children in need of care or for the disabled.

Note: Even though the FHS Human Research Ethics Committee may approve a study, it may not necessarily receive approval from the Western Cape Health Research Committee or other institutional authorities described above. When planning their studies, researchers must allow for the extra time incurred in obtaining these permissions.

Activities that may not need Human Research Ethics Committee approval

- Research using existing publicly available documents or data.
- Quality assurance and programme evaluation activities and performance reviews usually do not constitute research. However, if there is any potential for these activities to be published, it is prudent to obtain ethics approval before the study begins. The HREC may not grant retrospective ethics approval.

The implications of engaging in activities which qualify as research that requires prior HREC review without obtaining such review are serious. Results from such activities may not be used or published unless HREC approval had been obtained prior to collecting the data. To do so violates University of Cape Town policy and the DoH Ethics in Research Guidelines (2024).

Furthermore, such data cannot be used for thesis or dissertation purposes. Since many journal editors require research ethics committee approval as a condition of publication of human research, including activities such as audits, record reviews and quality improvement projects, researchers are encouraged to consult journals' publishing policies before initiating these projects without prior ethical approval. The Human Research Ethics Committee does NOT give retrospective approval for completed medical audits or medical record reviews. Additionally, since UCT requires research ethics approval for all human research (however defined), researchers are advised to obtain prior research ethics approval for all research-like interventions.

Clinicians and other researchers who routinely collect patient-related data and biological samples for non-research purposes are encouraged to register patient databases and/ or repositories with the Human Research Ethics Committee which will facilitate use of these data for research purposes at a later date (See the related standard operating procedure: Databases, Registries and Repositories).

Researchers should seek the opinion of the Human Research Ethics Committee if they have any doubts about the applicability of this guidance to a particular study prior to commencing any research-related activities.

References

1. Office of Research Integrity. UCT Research Ethics Code for Research Involving Human Participants, March 2012.
2. Barnes K. Important notice regarding research ethics approval. Deputy Dean of Research, Faculty of Health Sciences, 27 July 2012.
3. National Health Act 61 of 2003.
4. Ethics in Health Research: Principles, Processes and Structures 2nd Edition, Department of Health, Republic of South Africa, 2015.
5. Western Cape Research Committee. https://www.westerncape.gov.za/service/research-ethics-committee. Accessed on 28 April 2019.

Institutional Lines of Authority and Responsibilities

Policy

All parties involved in human research in the Faculty of Health Sciences must understand their responsibilities.

Purpose

The purpose of this policy is to outline the responsibilities of parties involved in human research: the University, the Research Directorate, the Human Research Ethics Committee, Principal Investigators, Heads of Department and Departmental Research Committees, Faculty Supervisors, Students and the Administration.

Procedures

University of Cape Town

The University, in line with its FWA contractual obligations, must provide the Human Research Ethics Committee with sufficient human, physical and administrative resources to ensure researchers comply with relevant university, national and international ethical and regulatory guidance.

Research Directorate in the Faculty of Health Sciences

Deputy-Dean of Research

As Head of the Research Directorate in the Faculty of Health Sciences, the Deputy-Dean is responsible for putting in place mechanisms to ensure that research involving human participants meets the highest ethical standards.

Human Research Ethics Committee

The Human Research Ethics Committee which reports to the Dean of Health Sciences is responsible for developing and implementing policies and procedures to protect the rights and welfare of human participants in research. All research involving human participants conducted on the premises or under the auspices of the Faculty of Health Sciences, including affiliated institutes and health facilities, must be reviewed and approved by the Human Research Ethics Committee prior to commencement of a study. Faculty of Health Sciences' researchers may include academic staff, non-academic staff, post-doctoral fellows, graduate and undergraduate students and visiting scholars. Multicentre or collaborative research must have a principal co-investigator associated with the Faculty of Health Sciences.

The primary function of the Human Research Ethics Committee is to protect the safety, rights and welfare of human participants in research. The Human Research Ethics Committee has the authority to:

- Approve, require revisions or disapprove all research submitted for review: the Committee determines whether proposed research is acceptable based on ethical principles, regulatory guidance, applicable law, scientific merit of the study design, sensitivity to community standards and attitudes, and professional standards of practice and conduct. To approve human research, the Committee must review the full research proposal, the consent forms, and all supplementary information such as recruiting materials and, if applicable, the investigator's brochure. (See SOP for The Protocol Review Process).
- Conduct ongoing review of approved research, at a minimum annually.
- Suspend or terminate approval of research not conducted according to sound ethical and scientific principles or regulatory requirements, or that is associated with unexpected harm to participants.
- Audit, or have a third-party audit, the conduct of the research to verify compliance with the Human Research Ethics Committee requirements.
- Similarly, observe, or have a third party observe, the consent process.
- Respond to complaints from investigators and participants about the unethical conduct of a study. The Human Research Ethics Committee must protect whistle-blowers who, in good faith, disclose unethical conduct from retaliatory action. Additionally, any persons can forward a complaint to the National Health Research Ethics Council if the response of the Committee to complaints is inadequate.

Principal Investigator Responsibilities

The principal investigator has the ultimate responsibility for the ethical, scientific, financial and administrative conduct of the study. All official Human Research Ethics Committee correspondence is addressed to the principal investigator. All official correspondence from the sponsor must be directed to the Human Research Ethics Committee via the principal investigator. This is to ensure that the principal investigator is fully aware of what is happening in his or her study. Only in exceptional circumstances will the Human Research Ethics Committee accept direct correspondence from the sponsor.

The principal investigator must:

- Observe the ethical and regulatory principles detailed in the Human Research Ethics Committee's Standard Operating Procedures.
- Have thoroughly read, understood and critically analysed, considering the broader South African and more local site-specific context, the protocol and all accompanying documentation including the patient information and consent forms and, where applicable, the investigator's brochure.
- Submit prospective research for departmental peer review to determine its scientific merit prior to submission for ethics review.
- Notify the departmental research committee if and when the protocol receives Human Research Ethics Committee approval.
- Obtain approval from the Human Research Ethics Committee before beginning any research involving human participants.
- Provide the Human Research Ethics Committee with enough information and related materials about the research (for example, study protocol with synopsis or executive summary, sample consent forms, questionnaires, budget) so that the Committee can fulfil its responsibilities to protect participants' safety and wellbeing in accordance with national and international ethical and regulatory guidance.
- Declare any conflicting interests. A conflict of interest is defined as a set of conditions in which a researcher's judgement concerning a primary interest (e.g. participants' welfare, integrity of a study) could be biased by a secondary interest (e.g. personal or financial gain). An investigator's financial interests also include the financial interests of his or her spouse and dependent children.

  Examples of financial conflicts of interest include:
  - Serving as a director, officer or other decision-maker for a commercial sponsor of a study.
  - Holding any stock or stock options in a commercial sponsor of a study, unless held in a diversified, independently-managed mutual fund.
  - Receiving consulting fees or honoraria from a commercial sponsor of a study.
  - Personally accepting payment from a study sponsor for non-research travel or gifts.
  - Receiving payment based on the research outcomes.
  - Obtaining royalties or being personally named as an inventor on patents or invention reports for the product(s) being evaluated in the study.
  - Having a financial interest in companies with similar products known to the investigator to be competing with the product under study.
- Ensure that adequate resources and facilities are available to carry out and complete the study.

- Ensure that all listed investigators and personnel assisting with the research are qualified and competent to conduct the segment of the study in which they are involved.
- Ensure that all co-investigators and other personnel assisting in the research are fully informed of current and amended study procedures and requirements for obtaining consent.
- Address concerns and questions raised by any member of the research team. **This includes:**
    - Meeting regularly with team members to review the progress of the research and to encourage discussion of any concerns about the research in general or about a particular research participant.
    - Informing team members that they are free to raise concerns without fear of repercussions.
    - Fully investigating concerns and reporting back to the individual who raised them.
    - Reporting to the Human Research Ethics Committee any articulated issues that raise concerns about participants' safety, compliance with the research protocol, informed consent violations or the integrity of the research data.
- Protect participants' privacy and the confidentiality of their data. In general, this will involve removal of personal identifying information from data collection forms and computer files, storing codes linking individuals to data in a locked cabinet, and allowing access to identifying data only via authorised persons and/or password-protected control.
- Use data and biological samples only for purposes approved by the Human Research Ethics Committee.
- Ensure the ongoing ethical conduct of research approved by the Human Research Ethics Committee:
    - Obtain written informed consent from participants or their legally authorised representatives prior to participants taking part in the research.
    - Investigators must offer a copy of the informed consent document to each participant (or the participant's legally authorised representative) and keep the signed original or a copy for their records. Investigators may delegate to suitably qualified and trained individuals the authority to obtain consent; however, they are ultimately responsible.
    - Keep participants fully informed of any new information that may affect their willingness to continue taking part in the study.
    - Obtain Human Research Ethics Committee approval for any modifications of previously approved research, including changes to the informed consent process and document, except those necessary to prevent immediate hazards to participants.

If the investigators change the research to eliminate apparent immediate hazards to the participants without Committee approval, they should report those changes promptly to the Committee.

  - Promptly report to the Human Research Ethics Committee acts of serious or continuing non-compliance with the currently approved research protocol.

- Submit progress reports in time for the Human Research Ethics Committee to carry out continuing review before the expiry date of the current approval.
- Promptly report to the Human Research Ethics Committee and, if applicable, sponsor and regulatory authorities any unanticipated problems or serious adverse events involving risks to participants. The principal investigator must submit all external monitoring reports and reports issued by Data Safety Monitoring Boards to the Human Research Ethics Committee.
- Ensure that, in the event of an adverse event, every reasonable effort is made to provide the participant with adequate care to correct or alleviate the consequences of the adverse event.
- Maintain up-to-date and accurate records of research data, consent forms, correspondence with the Human Research Ethics Committee and sponsors, amendments and progress reports and adverse events.
- Inform the Human Research Ethics Committee, giving reasons, if a research study is discontinued before the expected finishing date.
- Submit to the Human Research Ethics Committee a closure or completion report at the end of a research study. **In addition**:
  - Honour any other commitments agreed to as part of the approved research, for example, providing information about the study results to participants.
  - In collaborative research with pharmaceutical or other companies, make sure there is no interference with the right to publish.
  - Where applicable, submit a summary of trial results to the South African Clinical Trial Register within a year of trial completion.
- Address concerns raised by participants before, during or after the conduct of a study.
- Maintain research records for fixed periods on completion of the research (15 years in the case of clinical trials).

A comprehensive account of the responsibilities of the principal and other investigators in clinical trials is provided in Section 3 of Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa. Third Edition, 2020 (SAGCP, 2020).

Principal Investigator's Declaration

In line with the above responsibilities, a signed Principal Investigator Declaration must be included in the initial protocol submission to the Human Research Ethics Committee in which the investigator agrees, among others, to:

- Undertake only scientifically sound research designed to produce valid results.
- Conduct the study according to the protocol approved by the Human Research Ethics Committee.
- Be appropriately qualified to conduct the research and have a working knowledge of ethical and regulatory requirements applicable to the study.
- Ensure all research personnel are adequately trained and supervised.
- Protect the rights and welfare of participants, including their privacy and confidentiality.
- Disclose any potential conflict of interest.
- Follow relevant professional standards.
- Report promptly any new information, changes or unanticipated problems.
- Implement changes to a study only after approval by the Human Research Ethics Committee.
- Obtain annual re-approval as required.

Principal Investigator's Signature

A principal investigator's signature on a protocol application will testify that all the actions, procedures and interventions performed in the study will be conducted according to applicable University, national and international ethical and regulatory policies governing research with human participants, and any modifications to the protocol as originally approved will be submitted to the Human Research Ethics Committee for approval prior to implementation.

Principal Investigators and Non-compliance

Every researcher must be familiar with the policies and regulations governing research in the Faculty of Health Sciences.

Non-compliance with these policies and regulations includes, but is not limited to, the following:

- Failure to disclose a conflict of interest.
- Conducting research with human participants without a protocol and/or without Human Research Ethics Committee approval.
- Allowing Human Research Ethics Committee approval to expire without renewal.
- Not complying with the requirements of continuing review, including annual progress reports, amendments, serious adverse events and unanticipated problems.

- Conducting research not covered by the approved protocol or contradictory to the protocol (also defined as a protocol violation).

The Human Research Ethics Committee takes non-compliance seriously and, depending on the degree of non-compliance, may open an investigation of research misconduct. See related policies: Protocol Deviations, Non-compliance, Suspension and Termination and Compliance Audits.

Responsibilities of Heads of Departments or Divisions and Chairs of Departmental Research Committees

Departmental or Divisional Heads and Chairpersons of Departmental (or equivalent) Research Committees must ensure that:

- Only well-designed and scientifically-sound research is submitted for ethics review.
- Scientific reviewers are:
  - Independent of the study and research team under review.
  - Experienced researchers in the field of study under review.
- Researchers are sufficiently competent to undertake the research.
- In light of other departmental duties, such as teaching and clinical care, researchers have sufficient time to carry out the research.
- Postgraduate-level research meets the stringent university-wide scientific requirements for postgraduate degrees. The Human Research Ethics Committee cannot make this assessment although it will indicate when a protocol so lacks scientific merit that it is unethical.
- The department or division has suitable facilities and resources for the conduct of the study.
- The department or division will administer research funds according to University-policy.

Signature of Head of Department

The signature of the head of the department assures that the principal investigator has appropriate qualifications/training/resources to conduct the research and sufficient time to oversee the conduct of the research. If the principal investigator is also the head of department, the protocol application must be signed by an authorised impartial replacement.

Signature of Chair of the Departmental Research Committee

The signature of the Chair of the Departmental Research Committee testifies that the protocol is of sound scientific design which is adequate and appropriate to answer the research question(s) posed and minimises risks to human participants. If the principal investigator is also the Chair, the protocol application must be signed by the deputy-chair or an authorised impartial replacement.

Responsibilities of Faculty Supervisors

Faculty supervisor refers to any academic staff member who supervises undergraduate and post-graduate human research, including course coordinators who assign research projects as part of course requirements.

Responsibilities of faculty supervisors include:

- Assisting the student to develop a research proposal which is well-designed, has scholarly merit and is ethically sound.
- Ensuring the research proposal receives scientific and ethics approval by the relevant committees before any research activity begins.
- Confirming the student has adequate training, experience and resources to complete the research in the allocated time frame.
- Ensuring ongoing compliance with the Faculty's research ethics policies.
- Ensuring the level of risk inherent in a study is compatible with a student's level of research experience and the extent of oversight the faculty supervisor will provide.
- Meeting the student on a regular basis to monitor research progress and addressing problems that arise during the study.
- Ensuring the study undergoes continuing review, if applicable.
- Ensuring the student reports unanticipated problems or serious adverse events, if applicable.
- Arranging for an alternative faculty supervisor to assume direct responsibility for the study during periods of absence such as sabbatical or annual leave.

The faculty supervisor and student are jointly responsible for the ethical conduct of a study, from inception to dissemination of findings. Both must sign the Human Research Ethics Committee application form to conduct a new study.

Signature of the Supervisor

The signature of the supervisor confirms that the protocol is scientifically and ethically sound, a willingness to provide the necessary oversight through-out the research, and that the amount of risk in the study is proportionate with the student's level of research experience.

Responsibilities of Student Researchers

With assistance from their supervisors, student researchers' responsibilities include:

- Complying with the Faculty's policies for conducting ethical human research.
- Developing a protocol which has scientific merit and written quality.
- Submitting the protocol for Human Research Ethics Committee review prior to starting the research.
- Submitting the study for ongoing Human Research Ethics Committee review, if applicable.
- If part of collaboration, ensuring the larger study has received research ethics approval.
- Where applicable, obtaining additional permission to conduct research in designated facilities such as public hospitals, community-based health services, schools or non-governmental organisations.
- If required, reporting findings to appropriate stakeholders.
- Submitting a closing report to the Human Research Ethics Committee.

Responsibilities of the Ethics Administration Office

The Research Directorate provides administrative support to the Human Research Ethics Committee via the Faculty Research Office, Research Diligence Unit. This Office manages the day-to-day activities of the Human Research Ethics Committee. The HREC Administrative team is solely dedicated to the administration of the Human Research Ethics Committee.

Specific responsibilities of this office include:

- Keeping copies of the Human Research Ethics Committee's written policies and procedures. These policies and procedures are also available electronically on the UCT/ Faculty of Health Sciences website.
- Preparing and posting on the website an annual schedule of dates and deadlines for Human Research Ethics Committee meetings and protocol submissions. The Committee meets on the last Friday of every month, except December.
- Providing logistical support for monthly Human Research Ethics Committee meetings: a meeting place, parking, food and drinks; and, if needed, assisting lay members with travel arrangements.

- Screening protocol applications or resubmissions for completeness and number of copies prior to review. The list of materials will depend on the nature of the study and whether it requires initial or continuing review:
    - Proof of scientific review by a departmental research committee or equivalent body
    - Human Research Ethics Committee application form
    - Full protocol and, where applicable, the investigator brochure
    - Principal investigator-prepared lay summary or synopsis of the study
    - Informed consent forms and information sheets
    - Recruitment materials, including advertisements, posters, videos, radio scripts, website materials and brochures
    - Interview and survey questionnaires, patient diaries
    - Summary of budget and entity into which research funds will be deposited.
- Serving as a resource for researchers on general administrative information and assisting with forms and applications for Human Research Ethics Committee review.
- Preparing, with assistance from the Chair, and circulating the agenda prior to full committee meetings. Examples of agenda items include:
    - Review and approval of minutes from previous meeting
    - Urgent matters
    - Matters arising
    - New matters
    - Reports of unanticipated problems and adverse events
    - Reports of expedited reviews
    - New studies submitted for review
    - Studies previously voted as requiring 'full committee review'
    - On-going studies submitted for continuing review
- Timely distribution of meeting materials to committee members: main reviewers receive a full package of materials and all members receive synopses, consent documents, questionnaires and surveys, and recruitment aids. In addition, members can, on request, review the complete documentation of specific studies prior to a meeting.
- Assigning studies to reviewers with assistance from the Chair and Deputy-chair.
- Following-up with reviewers to ensure feedback in time for monthly meetings.
- Determining attendance for upcoming full committee meetings.

- Taking minutes during meetings in sufficient detail to show attendance, actions taken by the Committee and the basis for requiring changes in or disapproving research, and a summary of controversial issues and their resolution.
- Distributing minutes to members prior to next committee meeting; and filing minutes once approved.
- In the week following the meeting, sending letters to investigators detailing the committee's decision relating to their submissions.
- Processing and responding to all correspondence between researchers, sponsors and the Human Research Ethics Committee.
- Maintaining a database and tracking system of all protocols submitted to the Human Research Ethics Committee. The database includes, among others, the following information:
    - Reference Number
    - Date received
    - Date of meeting
    - Protocol title
    - Principal Investigator
    - Co-investigators
    - Title of principal investigator
    - Initials
    - Department (for example, surgery, medicine, public health and family medicine)
    - Address
    - Reviewer 1 (name, department, date sent)
    - Reviewer 2 (name, department, date sent)
    - Status: approved, not approved
    - Levy (yes/no)
    - Levy notes (invoice information, address)
- Ensuring that each protocol file contains the following information, preferably in chronological order:
    - Original protocol application and informed consent forms
    - Sponsor materials: for drug studies, the Investigator's Brochure, including current amended versions and all previous versions
    - Copy of the South African Health Products Regulatory Authority (SAHPRA) approval, if appropriate
    - Recruitment materials, posters, flyers, letters

- Questionnaires, interview schedules, surveys, diaries or any other documents or aides used in the study
- Reviewers' comments
- Human Research Ethics Committee actions regarding approval and subsequent actions and responses from investigators
- Human Research Ethics Committee letter of approval
- Continuing re-approval forms, correspondence, and subsequent approvals, including updated approved consents and approvals
- Reports of adverse events and unanticipated problems, and subsequent correspondence
- Data and Safety Monitoring Board reports
- Results of any external monitoring activities
- Amendments and/or revisions, subsequent correspondence, and notification of approval
- Reports of any injuries and subsequent correspondence
- Reports of any deviations and violations and subsequent correspondence
- Statements of significant new findings provided to participants
- Any communications or emails that offer additional information relevant to a protocol
- Documentation of study closure
- [In summary, each protocol file should be organised to allow a reconstruction of a complete history of all Human Research Ethics Committee actions related to review, approval and oversight of the protocol.]

- Storing files in a secure, locked room. All files are considered confidential documents. Only authorised representatives of regulatory agencies, accrediting bodies and other any persons at the Chair's discretion shall be granted access for copying or inspection.
- Performing periodic random audits of protocol files to verify completeness and chronological ordering of contents.
- Arranging for the out-sourced electronic storage of all protocols.
- Maintaining a current Human Research Ethics Committee membership roster, including names, qualifications, occupation, and representative capacity: scientific or non-scientific, core or alternate. The Manager: Research Grants shall promptly notify the US Office for Human Research Protections of any changes in Committee membership.
- Referring investigators' requests for amendments and continuing reviews, adverse events information and data safety and monitoring board reports to the Chair or Deputy for further action.

- Keeping accurate records of all correspondence to and from the Human Research Ethics Committee that is not related to a research protocol. This information is filed in the Manager's office.
- Maintaining intra-institutional relationships with, for example, the Department of Research and Innovation and Departmental Research Committees.
- Generating information for invoicing Committee reviews of sponsored research.

NOTE: Because of the volume of active studies at any one time, the administrative office cannot guarantee timely notification of protocols requiring annual renewal. Therefore, principal investigators carry ultimate responsibility for submitting applications needing continuing approval either by expedited or full committee review.

Human Research Ethics Committee: Composition and Documentation of Activities

Policy

The Faculty of Health Sciences has appointed a Human Research Ethics Committee to oversee the safety, rights and welfare of human participants in research. The composition and functions of the Committee must meet standards laid down in the Department of Health's Ethics in Health Research: Principles, Processes and Structures 3rd Edition, 2024, and requirements specified in the US Federal Wide Assurance. The Committee aims to meet these requirements as far as reasonably possible.

Purpose

The purpose of this policy is to outline measures for appointing the Chairperson and committee members, to describe their responsibilities and to define the Committee's operational procedures.

Chairperson: Selection and Responsibilities

The Chair is appointed by the Dean of the Faculty of Health Sciences on the recommendation of the Deputy Dean of Research for a three-year renewable term of office.

Qualities and Responsibilities

The Chair should:

- Play a leadership role in developing and implementing sound Human Research Ethics Committee policies and procedures.
- Possess a comprehensive knowledge of national and international research ethics and regulation, institutional policies and relevant legislation.
- Have leadership and management skills to facilitate and direct discussion at convened meetings. This includes the ability to foster open and collegial discussion among all Human Research Ethics Committee members whilst maintaining focus on the issues at hand (i.e. enabling the systematic review of protocols).
- Have respect for committee members from diverse backgrounds, perspectives and sources of expertise, in particular the contributions of non-scientists.
- Be able to function in a team, often under stressful circumstances.
- Be able to promote a culture of respect within the research community for the Human Research Ethics Committee process and for research ethics in general.

- Have the courage and confidence to uphold Human Research Ethics Committee judgements that may not be popular with investigators, the research community or University officials.
- Pursue continuing education in research ethics.

The Chair's responsibilities are to:

- Conduct monthly Human Research Ethics Committee meetings.
- Conduct expedited reviews or delegate this task to suitably qualified individuals who may or may not be Committee members.
- With the assistance of the Deputy, select reviewers with necessary expertise to perform initial and ongoing protocol reviews.
- Advise and consult with researchers on research ethics-related issues.
- Prepare an annual report for the Dean summarising the nature and volume of the Human Research Ethics Committee's activities.
- Participate in non-compliance investigations.
- Contribute to the development of Human Research Ethics Committee policies and procedures.
- Serve as a liaison between the Human Research Ethics Committee, investigators, the Research Directorate and Dean and other relevant stakeholders.
- Ensure that the committee receives appropriate and sufficient administrative support, meeting space and resources to function efficiently, and report deficiencies to the Deputy-dean of Research in the Faculty of Health Sciences.
- Assist the Human Research Ethics Committee administration to prepare the agenda before meetings, and to review the minutes after meetings.
- Review and sign letters to researchers conveying the Committee's decisions relating to their protocols.
- Consult with Chairs from human research ethics committees across the campuses of the University of Cape Town to encourage and facilitate cross-disciplinary research.
- Consult with Chairs from other human research ethics committees through-out the country in order to:
    - Improve participants' welfare and safety, particularly in multicentre trials.
    - Develop and promote best practices in research ethics oversight.

Deputy-chairpersons: Selection and Responsibilities

Two Deputy-chairpersons are nominated and selected by members of the Human Research Ethics Committee for a three-year renewable term of office.

The deputy chair's responsibilities include:

- Performing functions delegated by the Chair, including expedited review.
- Conduct expedited reviews or delegate this task to suitably qualified individuals who may or may not be Committee members.
- With the assistance of the Deputy, select reviewers with necessary expertise to perform initial and ongoing protocol reviews.
- Advise and consult with researchers on research ethics-related issues.
- Prepare an annual report for the Dean summarising the nature and volume of the Human Research Ethics Committee's activities.
- Participate in non-compliance investigations.
- Contribute to the development of Human Research Ethics Committee policies and procedures.
- Serve as a liaison between the Human Research Ethics Committee, investigators, the Research Directorate and Dean and other relevant stakeholders.
- Assist the Human Research Ethics Committee administration to prepare the agenda before meetings, and to review the minutes after meetings.
- Review and sign letters to researchers conveying the Committee's decisions relating to their protocols.
- General responsibilities which accompany committee membership.

Human Research Ethics Committee Composition

The primary mandate of the Human Research Ethics Committee is to protect the rights and welfare of human participants in research. In fulfilling this brief, the Committee requires diverse membership to provide expertise in and sensitivity to a broad range of scientific and ethical considerations.

Human Research Ethics Committee members are appointed by the Dean on the recommendation of the Chair for three-year renewable terms. New appointments are staggered to ensure appropriate balance and maintain continuity. Members will receive a formal letter of appointment.

Human Research Ethics Committee membership is continuously monitored to ensure appropriate representation. The Chair and Deputy Chairs perform an annual review of the composition, expertise and contribution of members. When a member resigns from the committee, the choice of a replacement takes into account the overall balance of the committee and specific expertise that is needed.

The University will provide legal protection in respect of liabilities that may arise when members are acting in good faith whilst performing their Human Research Ethics Committee activities.

In keeping with US federal regulations, the Administrative Manager will report any changes in the committee's membership to the Office for Human Research Protections.

In line with Department of Health requirements as laid down in 'Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health 2024', the Human Research Ethics Committee membership must satisfy the following requirements:

- At least nine members with a quorum being a simple majority
- Where the number of members is more than 15, the quorum may be 33%
- At least one layperson
- At least one member with knowledge of, and current experience in, the professional care, counselling or health related treatment of people. Such a member might be e.g. a medical practitioner, psychologist, social worker or nurse
- At least one member with professional training and experience in qualitative research methodologies
- Members with professional training and experience in quantitative research methodologies
- A member with expertise in biostatistics
- A member with expertise in research ethics
- At least one member who is legally qualified
- Ethnically and culturally diverse members and an appropriate mix of males and females
- Include at least one scientific member with expertise in areas of research regularly reviewed by the committee.

Members' responsibilities include:

- All REC members should have documented proof of research ethics training, refreshed at least once within the period of appointment.
- REC members who review clinical trial proposals should have GCP training, evidenced by a certificate issued not more than 2 years previously.
- Attending meetings on a regular basis and not leaving until meetings are adjourned.
- Members are requested to attend a minimum of seven meetings per year (excluding sabbatical or other leave periods).
- Maintaining strict confidentiality regarding protocol information, reviews and decisions and all matters discussed at committee meetings.

- Disclosing conflicting interests and where a conflict does exist with respect to a study, not reviewing the protocol or leaving the room during discussion of and voting on the protocol.
- Members must indicate with a tick on the attendance register that they will maintain confidentiality of all proceedings and declare any conflicts of interest.
- Respecting each other's views and the deliberative process.
- Deciding independently if the design and conduct of proposed studies will protect participants' safety, rights and welfare.
- Remaining impartial and objective when reviewing protocols.
- Serving as main reviewers for research in their areas of expertise.
- Serving as general reviewers of all research discussed at full committee meetings.
- Deciding by vote or consensus, whether to approve, require revisions, not approve or defer studies following deliberation at full committee meetings.
- Performing expedited reviews of minimal risk research.
- Keeping up-to-date with national and international research ethics and regulatory guidance.
- Taking part in research ethics-related continuing education.

Consultants or Ad Hoc Reviewers

The Human Research Ethics Committee may use consultants or ad hoc reviewers where additional or specialised expertise is needed to review specific protocols. Consultants may be asked to review an individual protocol or attend a meeting to provide education on any issue of general interest. Consultants do not count as part of a quorum or vote.

The committee or the Chair/Deputy Chairs may invite consultants from inside or outside the Faculty of Health Sciences who have special expertise to act as consultants or ad hoc reviewers of human research. Reasons for seeking additional or special competence may include but are not limited to the need for:

- Additional scientific, clinical or scholarly expertise.
- Particular knowledge about potentially vulnerable populations.
- Broader understanding of gender or cultural issues.
- Greater sensitivity to community perceptions.
- A statistical opinion.

Potential consultant resources include:

- Various specialty clinical departments in the Faculty of Health Sciences.
- The University of Cape Town's Bioethics Centre.
- Representatives of community advisory boards.
- Representatives of specific participant populations.

Consultants and ad hoc reviewers:

- Must have access to all documents submitted to the Human Research Ethics Committee relevant to the specific study under review.
- May take part in deliberations and may make recommendations concerning a study but they may not vote.
- Must affirm that they have no conflict of interest with respect to the specific studies they are invited to review.
- Must maintain strict confidentiality with respect to the specific protocol and the meeting's proceedings.
- May provide information about a specific study by written report, attending the meeting, or both.

Observers and Guests

Observers and guests may attend a full Human Research Ethics Committee meeting at the Chair's discretion or invitation. Guests and observers are individuals with an interest in research ethics and the review process and may or may not attend regularly. Guests and observers:

- Do not count as part of the quorum.
- Must maintain confidentiality with respect to protocols and proceedings during the meeting.
- May not observe the final discussion and vote for any protocols in which they have a potential or actual interest.

Observers with a special interest or expertise in research ethics and who regularly attend monthly meetings will be invited to join the Committee as alternate members as vacancies arise. Observers can also put themselves forward for nomination. In this way, the Committee will serve a capacity-building and mentorship role in research ethics more generally. In turn, the Committee will be able to appoint new members with experience of the review process and a demonstrated commitment to encouraging ethical research in the Faculty.

Ex-officio Members

Ex-officio member means an individual is an automatic Committee member by virtue of the individual's status. Ex officio members:

- May take part in the Committee's deliberations to provide information and expertise.
- May not vote on any Committee decision.
- Must comply with the Committee's conflict of interest requirements.

Permanent ex-officio representatives on the Human Research Ethics Committee are the:

- Dean of the Faculty of Health Sciences
- Deputy Dean of the Research Directorate in the Faculty of Health Sciences.

Quorum Requirements and Voting at Human Research Ethics Committee Meetings

Except when an expedited procedure is used, the Human Research Ethics Committee must review initial and continuing studies at full committee meetings at which a quorum is present.

Quorum and voting requirements:

- As the full committee membership is greater than 15, in accordance with the Department of Health requirements as laid down in 'Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, 2024', the quorum is 33% .
- The Chair and Deputy count towards the quorum.
- A quorum must be maintained for each vote. If a quorum fails, further studies cannot be approved and must be held over until the next convened meeting.
- Any member with a conflict of interest with respect to a specific study must leave the room during deliberations and decision-making relating to the study. This member may not vote on the study.
- Voting by proxy is not allowed.
- Consultants, ad hoc reviewers and ex officio members may not vote.
- Generally, decision-making at full-committee meetings is by consensus. At the Chair's discretion, voting may be decided by a show of hands.
- All full committee decisions relating to studies regulated by the US Common Rule are decided by a vote and must include at least one member whose primary concerns are non-scientific. A licensed physician must be present for decisions relating to FDA-regulated studies.

- The full committee may:
  - Approve a study as submitted. An investigator need not change any aspect of the protocol or consent forms.
  - Require that conditions are met before a protocol is approved. When conditions are minor, i.e. they require simple agreement from the researcher, the committee may authorise the Chair or a designee to approve the researcher's response to the terms via an expedited procedure. When, based on the magnitude and/or number of concerns, the committee may determine that the study requires substantive revision.

    The committee will decide whether the revisions must be submitted to a convened meeting, the main reviewer(s), the Chair or a designee for a decision to approve or require further changes. All protocols under the scope of the US Common Rule requiring substantive review must be resubmitted to a full-committee meeting for a decision.
  - Offer non-binding recommendations with the above decisions.
  - Not approve a study in its present form.
  - Defer a decision until the following meeting. A protocol may be held over to the next convened meeting for one or more of the following reasons:
    - Lack of appropriate expertise at the meeting.
    - Insufficient information to conduct an adequate review.
    - Loss of a quorum.
    - Lack of time.

Human Research Ethics Committee Sub-Committees

The Chair or full committee may convene sub-committees on an ad hoc basis. The term 'sub-committee' refers to a group of Committee members organised to manage a specific task or make a particular decision or recommendation relating to the functioning or standard operating procedures of the Human Research Ethics Committee. For example, a sub-committee comprising interested and expert members may be assembled to develop a policy concerning the translation of informed consent forms in student research. Sub-committees as described do not need to meet the quorum requirements which apply to full committee meetings. Sub-committees will be dissolved once the ad hoc task is deemed to be satisfactorily completed.

Conflict of Interest: Human Research Ethics Committee Members

Any Human Research Ethics Committee member must disclose a conflicting interest to the Chair and leave the room during discussion of the study and the related decision, except if the member is providing information at the committee's request. The meeting minutes will document the recusal.

The definition of conflicting interest extends to consultants and ad hoc reviewers who are asked to review a study because of their expertise. This policy applies to all research reviewed by the Committee, including initial and continuing reviews.

A conflicting interest of a Human Research Ethics Committee member generally includes the following:

- Participation in a study where the Human Research Ethics Committee member is listed as an investigator or is a member of the research team.
- Supervision of a study where the Committee member is the faculty supervisor.
- Financial interest where the Human Research Ethics Committee member holds significant equity or stock options, receives or expects to receive compensation with a value that may be affected by the outcome of the study, has an ownership interest (including patent, trademark or copyright interest) in the drug, product or technology that is the subject of the research, or receives a significant amount annually as a salary, consulting income or other compensation from the sponsor.
- The Committee member has a 'personal relationship' with the investigator. This means the member has an immediate family relationship or other close relationship with the investigator ('immediate' family' means the Committee member's spouse or domestic partner and dependent children).
- The Committee member has a fiduciary relationship to the sponsor. This means the Committee member serves as an executive to a company sponsoring the research or serves on the company's board of directors.
- Other examples of conflicting interests include but are not limited to the following:
    - Human Research Ethics Committee member has an interest that he or she believes conflicts with the member's ability to review a project objectively.
    - Human Research Ethics Committee member is in direct competition with the investigators for limited resources, funding, sponsorship or research participants, or the Committee member is considered a personal or professional adversary of the investigators. Since such situations may depend on the circumstances, the Committee member should raise such a situation as soon as possible with the Chair. The standard used by the Chair is whether an independent observer could reasonably question whether the individual's actions or decisions would be based on factors other than the rights, welfare and safety of participants.
    - Any other reason for which the Committee member believes he or she has a conflicting interest with the research.

Procedure for handling a Human Research Ethics Committee member's conflicting interest:

- The Human Research Ethics Committee member with a conflict of interest should not accept the protocol for review and should return it for assignment to another reviewer.
- The Chair must ensure that a Committee member who discloses a conflict of interest does not participate in the deliberative discussion or vote on the protocol and leaves the room.
- If committee members need information on the study from the member with a conflicting interest, then the member may remain in the meeting room during presentation of the study. The member must then leave the meeting room during the deliberative discussion and voting on the protocol.
- The Committee member with a conflict of interest will not be counted as part of the quorum for the review of the study. If the quorum fails, the Committee cannot take further action or vote on the study.
- The name of the person leaving the room due to a conflicting interest will be recorded in the Minutes as recused.

Preparation of the Minutes

The two main methods of documenting Human Research Ethics Committee activities are through the minutes of Committee meetings and the maintenance of comprehensive records of protocols reviewed by the Committee. Good minutes should allow readers not present at a meeting to determine exactly how and with what justification the Committee reached its decisions. The minutes should also provide the Committee with enough detail to reconstruct its decisions at a later date, if necessary, to protect itself and the institution. Additionally, comprehensive minutes show concern for participants' rights, safety and well-being.

Draft minutes prepared by the administrative staff are reviewed by the Chair and Deputy. Prior to a convened meeting, a copy of the draft minutes is electronically circulated to Committee members, including the Dean and Deputy-Dean of Research. A call for corrections or comments is made at the convened meeting. If none is made, a motion to approve the minutes is made and voted on. After approval, the administrative manager files a hardcopy of the minutes in the Human Research Ethics Committee office.

Minutes must reflect the agenda of each meeting and must record the discussion and action taken on each agenda item.

The minutes must include the following:

- Meeting logistics: starting time, ending time, date and location.
- Review and approval of minutes from previous meeting.
- The minutes will identify all individuals attending the meeting: administrative staff, Committee members and alternates, consultants, guests and observers, and researchers (if invited to present their protocol).
- The minutes will reflect when an alternate member substitutes for a regular member and for whom the alternate is substituting.
- The minutes will document when a member is recused from discussion and voting due to a conflict of interest. The minutes will also indicate whether prior to recusing him or herself the member remained in the room to provide information at the committee's request.
- For all protocols under review at the meeting, the minutes must reflect:
    - The Human Research Ethics Committee reference number, principal investigator and study title.
    - Deliberations, actions and votes (if applicable) on each study undergoing initial or continuing review, and each amendment or revision requiring full-committee review.
    - Actions taken: voting is recorded as follows:
        - Approved
        - Requires revision
        - Not approved
        - Deferred
    - If a protocol is approved conditionally (i.e. revisions are required before approval), the minutes must state whether the committee determines that the revisions and/or recommendations are to be reviewed by the Chair, a designee or by the full committee.
    - Reasons for specific decisions.
    - Duration of approval.
- The minutes will include a summary of the discussion of controversial issues and resolutions. Minutes shall be written impersonally and opinions expressed by members shall not be attributed to them.
- In order to encourage open and frank discussion at committee meetings, minutes will not normally be made available to others outside the University administration unless otherwise required by law or external regulations.
- The minutes will include a summary of expedited approvals, and any other business relevant to the Human Research Ethics Committee meeting.

Communicating Meeting Results to the Principal Investigator

The letter to the principal investigator must state clearly the Committee's decision, including any conditions that must be met before approval. Letters should be educational and respectful. The administrative staff is responsible for drafting letters, which are reviewed and signed by the Chair or Deputy before they are sent to the researchers. Wherever possible, letters are sent in the week following the committee meeting.

The following information is included in each letter:

- Protocol reference number.
- Title of study.
- If commercially-sponsored, the version date of the protocol and consent forms.
- The Committee's decision: approved, revisions required, not approved, deferred.
- Date of meeting.
- If approved, the duration of approval and date of re-review.
- If revisions are required, a list of conditions with reasons, and a statement that the study may not begin until the researcher receives formal notification of Committee approval after review of the response to the revisions.
- If disapproved, the basis for the decision.
- If deferred, the reasons why the study has to held over until the next meeting.

Final approval letters provide an opportunity to remind investigators of ethical and regulatory requirements governing their research. These may include the following, depending on the nature of the study:

- The study must be conducted in strict accordance with the protocol approved by the Committee.
- Changes to the protocol or its related consent documents must be approved by the Committee before implementation.
- Adverse events or unanticipated problems must be reported promptly to the Committee.
- Participants must receive a copy of the consent document, if appropriate.
- The principal investigator is responsible for the ongoing conduct of the study.
- Any future correspondence must include the protocol reference number, the study title and its most recent version.

To comply with the Federal Wide Assurance, the Human Research Ethics Committee approval letters for US federally-funded research must also include the following:

- A valid Federal Wide Assurance (FWA) number.
- A valid IRB number.
- The actual IRB meeting date and the protocol approval date.
- The complete protocol title, and approved version date.
- List of all reviewed and approved additional materials, e.g. consent forms, brochures, pamphlets. (Version dates must be included.)
- Name of Principal Investigator.
- Cooperative Agreement number or funding tracking number.

Principal investigators are responsible for notifying Departmental Research Committees of the Committee's findings and actions relating to their protocols.

References

1. Amdur RJ. Institutional Review Board Subcommittees. In: Bankert EA and Amdur RJ editors. Institutional Review Board, Second Edition. Jones and Bartlett Publishers, Canada, 2006. Pp.83-86.
2. Department of Health and Human Services. Final Guidance Document. Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection. May 2004.
3. OHRP. Guidance on Written IRB Procedures, July 1, 2011.
4. OHRP Guidance on IRB Approval of Research with Conditions, November 10, 2010.

The Protocol Review Process

Policy

All protocols must undergo scientific review by a departmental research committee or other equivalent body prior to submission to the Human Research Ethics Committee. In turn, protocols must undergo ethical review by the Human Research Ethics Committee prior to commencement of a study.

Purpose

The purpose of this policy is to outline requirements or criteria for scientific and ethical review and describe the process of full-committee and expedited ethical review.

Departmental Scientific Review

Departments, Divisions or Institutes are responsible for establishing an explicit and formal scientific review process that evaluates the scientific merit and potential risks of each protocol before that protocol is submitted to the Human Research Ethics Committee. The Committee retains the authority to examine a study's scientific design to determine its impact on the safety and well-being of potential participants.

Scientific quality is improved when study objectives and methods are clearly thought through and described. A well-written protocol facilitates high quality science and is an invaluable tool as investigators develop and conduct their studies. A protocol is the formal design or detailed action plan of a study. The protocol explains what will be done, when, how, where and why.

The research question and methodology must be presented in enough detail to permit evaluation of the scientific merit of the study. At a minimum any protocol, including retrospective chart or database reviews, requiring departmental scientific review must include the following elements:

- Study purpose and rationale
- Description of study population, inclusion and exclusion criteria
- Statement of recruitment practices
- Sample size and how sample size was determined
- Design and detailed description of methodology
- Definition of end points
- Measurement instruments, data collection forms
- Data analysis plan
- Ethical considerations

- References

The following criteria, where applicable, should be considered during the scientific review of quantitative or clinical research:

- Are the specific aims, research questions and corresponding hypotheses clearly stated?
- Are the primary and secondary outcomes (endpoints) stated and defined?
- Is the literature review adequate, current and relevant (wherever possible, the literature review must include pertinent references to local research in the proposed field of study)?
- In the context of previous studies, what is the contribution of the present research?
- Will the question or hypothesis being tested add important knowledge to the field?
- Are there adequate preliminary data in the literature (or pilot studies) to justify the research?
- Will the study design (e.g. cross-sectional survey, medical record review, clinical trial) address the study's aims and objectives?
- Is it feasible or reasonable to achieve the results in the proposed time frame, including the time to recruit, retain, or follow participants?
- Are the proposed tests or measurements appropriate, valid and reliable to answer the scientific question in the local context?
- Are ALL the proposed tests or measurements needed to answer the scientific question?
- Is the use of socially constructed categories, such as race, ethnicity, gender, adequately justified, for instance is the use of racial classification required by the funding agency? Have these categories been explicitly defined?
- Are the individuals conducting the research properly qualified and trained to perform the study interventions or measurements?
- Does the research present risk to participants and, if so, is it acceptable?
- Does the research design minimise risk to participants?
- How do the risks of the new treatment or therapy compare to standard treatment or therapy?
- Is any standard of care denied as part of this study?
- If the study includes a placebo or a requirement to withhold treatment that might present a risk (no matter how small) to participants, are these interventions essential for the conduct of the study? Have or should other designs be considered?
- Is the location of the study adequate to assure participants' safety and comfort (e.g. appropriate equipment for monitoring and emergencies, a child-friendly setting for paediatric research)?

- Is there an appropriate plan for safety monitoring? Is there a need or plan for performing an interim data analysis? Is there a need for an independent data and safety monitoring board? Are there explicit, operationally defined stopping rules?
- Is the study adequately powered and statistically sound?
- Are potential limitations or criticisms of the study discussed?
- Is there a plan for disseminating the findings?
- Is the bibliography complete? Is the style of referencing consistent?
- Are the ethical issues described and justified? Although assessment of ethical issues is not a requirement of scientific review, it makes sense to highlight ethical omissions or to seek research ethics advice prior to submission for Human Research Ethics Committee review.

The following criteria should be considered during the scientific review of qualitative research:

- Is the phenomenon of the study clearly stated?
- Is the aim of the study clearly stated and related to the strengths of a qualitative design?
- Is the significance of the study adequately explained?
- Are the variables operationally defined?
- Is the literature review clear? Does it identify gaps in the literature, is it appropriately detailed depending on the qualitative method chosen, and does it discuss the major concepts being studied?
- Is the theoretical premise of the method clearly described?
- Is the design clearly described and appropriate?
- Are the population and sample clearly described?
- Is the method of sample selection appropriate and clear as to how the researcher will determine when adequate sampling has occurred?
- If the sample size cannot be delineated before the study begins, are a rationale and plan provided?
- Is the procedure for data collection explicit and appropriate for the specifically chosen qualitative design?
- Are data analysis plans explicit, appropriate to the question and design, and complete with plans to address the rigour of data collection and analysis?
- Are the limitations stated, complete and appropriate to the specifically chosen qualitative design?
- Does the researcher demonstrate an understanding of the qualitative paradigm and method chosen?
- Does the researcher have experience in conducting qualitative research?
- Is the scope of the study feasible within the available time and resources?

Human Research Ethics Committee Review

The primary responsibility of the Human Research Ethics Committee is to safeguard the rights and welfare of human participants. Therefore, a principal investigator must provide enough information for the Committee to determine that human participants will be adequately protected and that the research will comply with ethical and regulatory requirements.

Requirements for Human Research Ethics Committee Review

The following criteria should be considered when an investigator is preparing a protocol for submission for Human Research Ethics Committee review:

Synopsis or Executive Summary

With the exception of the two or three primary reviewers, remaining Committee members rely on the synopsis and supporting materials (informed consent forms, questionnaires, recruitment aids) to evaluate a proposal. As a rule, all-purpose sponsor-produced synopses are too general and lack enough relevant detail, specific to the local site, to allow the committee to undertake a thorough ethical assessment. It is therefore in researchers' interests to include in the synopsis sufficient information for Committee members to evaluate the proposal independently of any other protocol documentation.

The synopsis must:

- Be written in simple, non-technical and jargon-free language which is readily understood by Committee members who include non-scientists, non-experts in the field and who represent the community. Acronyms must be spelt out when used for the first time.
- Specify how the research will be conducted at the local, i.e. the principal investigator's, site; for example, what is the socio-demographic and educational background of participants at the local site, where will participants be recruited for research at this site, how will the study advance health and scientific knowledge in this population.
- Describe the objectives of the study and hypotheses being tested.
- Succinctly identify the study's purpose in the context of currently available and relevant knowledge.
- Explain the design of the study. In the case of clinical research, carefully distinguish experimental interventions from the standard of care.
- Provide a brief overview of inclusion and exclusion criteria.
- Describe how participants will be recruited. Specifically address how, when, where and by whom participants will be identified and approached.

- Describe the frequency, severity, duration and reversibility of foreseeable harms: physical, psychological, social and economic.
- Describe site-specific measures to protect participants' privacy and the confidentiality of the collected data.
- Explain how risks will be minimised and how safety will be protected.
- Describe expected benefits to individual participants and potential societal benefits within the local setting.
- Indicate whether post-trial treatment will be available for local participants and, if not, why not.
- Explain how, when, where and by whom consent and assent will be obtained.
- Clarify special protections for vulnerable participants such as children, cognitively impaired, terminally or critically ill.
- Provide information on availability of compensation for research-related costs (e.g. travel) and inconvenience.
- Provide information on availability of insurance for research-related injuries.
- Briefly describe what measures and protections will be in place for collection and storage of biological specimens.
- Identify and justify any aspects of the study that could reasonably be considered morally controversial such as the use of a placebo, withholding standard of care, deception, commercial drug or device trials where interventions are unlikely to be affordable in the local setting. Describe how ethical issues will be addressed and what extra protections, if any, will be put in place.
- Knowledge of and familiarity with the local setting in which a study will take place make the principal investigator the best person to prepare a contextually-relevant and ethically-sensitive synopsis.

General Requirements for Human Research Ethics Committee Review

Researchers should consider, where appropriate, the following criteria when preparing a research proposal for submission to the Human Research Ethics Committee:

Specific Aims, Background and Significance

- Are the study aims and objectives clearly specified?
- Are there adequate preliminary data to justify the research?
- Are adequate references provided?
- Why is this research important to conduct?
- Why is it worth doing in this particular setting?

Scientific Design

- Is the scientific design adequate to answer the study's questions?
- Is the scientific design adequately described and justified?
- Does the study involve a placebo?
- If so, why is a placebo needed?
- Could the study be done without a placebo?
- Are study aims and objectives achievable in the given time frame?
- Does the protocol have scientific merit?
- Do the principal and co-investigators have adequate experience to conduct the study?

Inclusion and Exclusion Criteria

- Are inclusion and exclusion criteria clearly stated and reasonable?
- Are any individuals inappropriately included as participants?
- Are any individuals inappropriately excluded as participants?
- Does the study include vulnerable groups such as children, prisoners, psychiatric patients, individuals with impaired decision-making capacity? If yes, are adequate safeguards included to protect their rights and welfare?
- Is the inclusion of vulnerable populations justified?
- Can the study be done without involving vulnerable populations?
- Will the study target or exclude a particular ethnic or language group?
- Who, in the research team, will decide if an individual participant is eligible?
- Is the selection of participants appropriate for the question being asked?
- Are laboratory parameters appropriate?

Recruitment and Enrolment

- Are recruitment methods well-defined?
- How and by whom will individuals be identified for recruitment into the study?
- Is the individual responsible for recruitment suitable for the task?
- Is the location, setting, and timing of recruitment acceptable?
- Are all recruitment materials submitted and acceptable, e.g. flyers, posters, advertisements, radio announcements?
- Are procedures for screening participants prior to recruitment acceptable?
- If recruitment will occur during a critical or stressful period, what precautions are in place to assist voluntary decision-making?

Research Procedures

- Are the rationale and details of research procedures adequately described and acceptable?
- Is there a clear differentiation between research procedures and standard of care?
- Are there adequate plans to inform participants about specific research results, e.g. incidental findings, clinically relevant findings?
- Are there adequate plans to inform participants about specific research results that might affect their decision to continue participation?
- Are individuals who are performing procedures adequately trained?
- Is the location for performing procedures acceptable?

Drug, Device and Biologics Considerations

- Is the status of the drug or device adequately described?
- If necessary, is the supporting documentation from the sponsor included with the submission; for example, investigator's brochure, package inserts/ labelling, South African Health Products Regulatory Authority (SAHPRA) approval?
- What has the preclinical or initial clinical research shown?
    - Does any evidence suggest the possibility of clinically significant toxicities, such as carcinogenesis or teratogenesis?
    - Is there any evidence of immunogenicity?
    - Is there any evidence to suggest either that it may be unsafe to undertake the study or to justify special safety monitoring?
- Are the drug dose and route of administration appropriate?
- Are the drug or device safety data sufficient to warrant the proposed phase of testing?
- If the study involves a marketed drug or device for an unapproved or off-label indication is South African Health Products Regulatory Authority (SAHPRA) approval necessary?
- Does the protocol describe acceptable measures for storage, access and control of the drugs, devices or biologics?

Risks and Benefits

- Are risks and benefits adequately identified, evaluated and described, including physical, psychological, social, and economic?
- Are there risks to the community or a particular group of individuals, e.g. stigmatisation?
- Do risks stated in the protocol match the risks described in the informed consent form?
- Are risks reasonable in relation to anticipated benefits?

- Are risks reasonable in relation importance of knowledge to be gained?
- Are risks minimised to extent possible?
    - Study uses procedures which are consistent with sound research design.
    - Study uses procedures which do not unnecessarily expose participants to risk.
    - Where possible, study procedures are already being performed on participants for diagnostic or treatment purposes.

Note: Financial or other forms of compensation are not considered to be a benefit but rather recompense for research-related inconvenience.

Process of Obtaining Informed Consent and Assent

- Is the process well-defined?
- Does the process minimise the possibility of undue influence?
- Does the process provide sufficient time, privacy and an adequate setting for participants to decide?
- Who will obtain consent or assent? Is the individual obtaining consent or assent adequately trained?
- Is the setting where individuals are being recruited or would report for research-related activities the same as where they are seen for clinical care? If so, this may cause confusion about what is research activity and what is standard care.
- Are issues relating to participants' comprehension considered?
- How will a researcher decide if a participant has decision-making capacity to choose to enrol in a study?
- Is the language used in the consent form appropriate for participants' level of understanding?
- Are terms such as 'randomisation' clearly defined and illustrated (e.g. like flipping a coin)?
- Will an interpreter be necessary to obtain consent?
- Will consent forms need translation? Participants are entitled to information in the language of their choice.
- Do consent forms include all the elements needed to comply with regulatory and ethical standards?

Privacy and Confidentiality

Privacy refers to persons and to their interest in controlling access of others to themselves. Confidentiality refers to data. (See related policies: Collection of Data or Biological Specimens for Research and Databases, Registries and Repositories)

- Are provisions to protect participants' privacy adequate? If participants will be contacted in person, it should be by someone who has reason to know confidential information.
- Are provisions to protect confidentiality of data during and after research adequate?
- Are provisions for storage, coding and use of identifiers adequate?
- If the data are not going to be destroyed, who will be responsible for maintaining anonymity, confidentiality and security over time?
- In the case of focus groups, are participants told that confidentiality cannot be guaranteed as group members may disclose what was discussed when they leave the research setting?
- If audio or videotaping is used, how will tapes be stored and for how long?

Note: Legal requirements relating to private health information under the US Health Insurance Portability and Accountability Act (HIPAA) do not apply to research conducted in South Africa.

Storage of Human Biological Specimens

- Will the study generate new samples, use existing samples or both?
- If the study uses existing samples, how were they obtained and were donors informed of their intended use?
- If samples are identifiable, how will donors' privacy and confidentiality be protected?
- Will biological specimens be stored for future use?
- In the case of uniquely identified specimens, especially those containing genetic material, do the participant and his family understand where and how their genetic material will be stored and protected and who will have access to it and why?
- How will this understanding be verified, and what will be done if a participant withholds or withdraws consent for such a donation?
- Does the PI anticipate potential future use of samples, given technological progress? If so, is this addressed in the informed consent form?
- Does the PI anticipate sharing the samples with other investigators? Is this addressed in the informed consent form?

Data Analysis and Monitoring

- Does the protocol include a well-formulated plan for interpretation of data and statistical analysis?
- Is the rationale for the proposed number of participants reasonable?
- Are the plans for data and statistical analysis defined and justified, e.g. stopping rules, end points?
- Are there adequate plans for monitoring data?
- Is a data safety monitoring board part of the study? If so, where is the board located, who are its members, and how will the principal investigator communicate with the board? Is it independent?
- In the case of non-interventional or qualitative research is there a mechanism, such as a reference or event monitoring group, to provide ongoing oversight and impartial analysis of unanticipated incidents?

Resources

- Are the resources to conduct the study appropriate and sufficient (equipment, staff, space, funding)?
- Will counselling or support services be available, if required?

Reimbursement

- Is the compensation to participants reasonable?
- If the participant does not complete the study, will compensation be pro-rated?
- Are there adequate plans to avoid out-of-pocket expenses and costs incurred by participants (e.g. travel expenses, parking costs, and lost wages)?
- If children or adolescents are involved, who receives the compensation?
- Does compensation cover extra costs when parents or caretakers are expected to accompany participants on research visits?

Insurance

- Is there provision for insurance for research-related injuries, if applicable?
    - Does it comply with ABPI Guidelines for commercially sponsored research?
    - In the case of investigator-initiated research, is there cover in terms of UCT's no-fault insurance policy?

What Happens at the End of the Study?

- In the case of Phase III safety and efficacy trials, will the investigational intervention, if proven safe and efficacious, be offered to participants at the end of the study and under what conditions; for example, until the drug is licensed in South Africa or for a specified period? If a sponsor does not intend to provide post-trial access, the informed consent document must spell out in bold lettering:
    - That even if a participant's condition improves on the study drug it will no longer be provided by the sponsor at the end of the study.
    - How participants/patients will be managed at the end of a clinical trial, for example will they resume their previous treatment regimen?
- Will the study offer long-term benefits to the community in the form of capacity building and/or medical or research infrastructure?
- If proven safe and efficacious, is it likely that the investigational drug will be available in an open-label extension study?
- How will participants be informed of important findings?
- How will findings be disseminated to the wider population and research community?

Stakeholder Participation

- Who are the major stakeholders in the research? Describe how those affected by the study can express their views, clarify their needs and contribute to the research.

Conflicts of Interest

- Will any research staff receive incentives for recruiting participants or for any other purpose directly related to the study?
- Do any personnel involved in the design, conduct or analysis of the research have any proprietary interests (e.g. royalties, patents, trademarks, copyrights or licensing agreements) involving any agent, device or software being evaluated in the study?

Authorship

- Is there a plan to determine fair and legitimate authorship?

General

- Does the study comply with the latest version of the Helsinki Declaration?
- Is there a table of contents for long protocols so that submissions are easier to read and review?
- Are pages numbered consecutively?

- Has the principal investigator or a colleague proofread the proposal and performed a spell-check?

Primary Reviewer System

The Human Research Ethics Committee uses a system of primary or main reviewers for initial reviews, continuing reviews, and reviews of amendments and adverse or unanticipated events. The Chair and/or Deputy Chair selects two or three primary reviewers for reviews requiring full committee review based on members' knowledge, experience or expertise. If a Committee member or consultant believes that he or she cannot be a reviewer for any reason, including lack of expertise or a conflict of interest, the Chair or administrative staff should be notified immediately. If no Committee members have the required expertise, a consultant will be invited to perform the review. The Chair, Deputy Chair or designee serves as primary reviewer for research meeting the criteria for expedited review. Each Committee member must receive sufficient information to be able to actively and constructively take part in the discussion of the protocol.

Responsibilities of Primary Reviewers

Primary reviewers must:

- Conduct an in-depth review of the research materials using review criteria outlined under 'General Requirements for Human Research Ethics Committee Review'.
- At reviewers' discretion, contact investigators directly or via the administrative staff to clarify issues identified during the review.
- Lead the discussion on the initial or ongoing reviews at full committee meetings.
- Submit a written report for presentation if unable to be present at the convened meeting.
- At reviewers' discretion, make 'editing' recommendations directly onto consent forms in legible handwriting. Documents with suggested changes can be returned to investigators.
- Make a decision for expedited reviews (approve, require revisions, send for full committee review).

Categories of Review

Expedited Review

The type of review depends on the level and type of risk involved. Expedited review is a valuable mechanism that allows the Human Research Ethics Committee to triage studies to an appropriate level of review. This means that the time and resources of full committee meetings can be concentrated on protecting participants facing the greatest levels of risk or discomfort. Criteria for approval by expedited review are the same as those of the full committee and the expedited review should be as substantive and rigorous as that of a convened meeting.

The Chair or Deputy Chair has the final responsibility for determining which new protocols, continuing reviews and amendments are eligible for expedited review and has the authority to designate one or more experienced Committee members to perform an expedited review. No member with a conflict of interest may serve as a reviewer for any expedited item. A monthly report of all research approved through an expedited procedure is distributed to members before the full committee meeting.

Eligibility for Expedited Review

Types of research that may undergo expedited include:

- Research classified as no greater than minimal risk, depending on the details of the study. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations.
- Annual renewals of studies that initially qualified for expedited review or were determined to be minimal risk at a convened Committee meeting, provided no serious adverse events or ethical problems have occurred.
- Amendments to previously approved research where changes to the study protocol or consent documents do not result in significantly increased risk to participants.
- When, in the Chair's opinion, using an expedited procedure would be in the public interest.
- Additional categories of minimal risk research as defined by a convened Committee meeting.

Expedited Review of US Federally-funded or Supported Research

Protocols that may be reviewed under expedited review are limited to categories listed in 45 CFR 46.110(a) and 21 CFR 56.110(a) if the research involves no more than minimal risk and meets all the stipulated applicability criteria:

Applicability Criteria

- Research activities that:
  - Present no more than minimal risk to human participants, and
  - Involve only procedures listed in one or more of the following categories.
- The categories in the list below apply regardless of participants' age, except as noted.
- The expedited process may not be used where identification of participants and/or their responses would reasonably place them at risk of criminal or civil liability; be damaging to their financial standing, employability, insurability, or reputation; or be stigmatising, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited process may not be used for classified research involving human participants.
- Categories one to seven pertain to both initial and continuing review.

Research Categories

Category 1

Clinical studies of drugs and medical devices only under the following conditions:

a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required, but only if the research does not significantly increase the risks, or decrease the acceptability of the risks, associated with the use of the product.
b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required, or (ii) the medical device is cleared or approved for marketing and the medical device will be used according to its cleared or approved labelling.

Category 2

Collection of blood samples by finger prick, heel stick, ear stick or venipuncture as follows:

a) From healthy, non-pregnant adults who weigh at least 50 kg. Amounts drawn may not exceed 550 ml in an eight-week period and collection may not occur more frequently than two times per week; or

b) From other adults and children, considering age, weight and health, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. The amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an eight-week period and may not occur more than two times per week.

Category 3

Prospective collection of biological specimens for research purposes by non-invasive means. Examples:

- Hair and nail clippings in a non-disfiguring manner.
- Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
- Excreta and external secretions, including sweat.
- Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or applying a dilute citric solution to the tongue.
- Placenta removed at delivery.
- Amniotic fluid obtained at the time of rupture of the membrane prior to or during labour.
- Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished according to accepted prophylactic techniques.
- Mucosal or skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
- Sputum collected after saline mist nebulisation.

Category 4

Collection of data through non-invasive procedures (that do not involve general anaesthesia or sedation) routinely employed in clinical practice, excluding procedures that involve X-rays or microwaves. Where medical devices are employed, they must be cleared or approved for marketing. Examples:

a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the participant or an invasion of the participant's privacy.
b) Weighing or testing sensory acuity.
c) Magnetic resonance imaging.
d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.
e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given age, weight and health of the individual.

Category 5

Research involving materials (data, documents, records or specimens) that have been collected or will be collected solely for non-research purposes such medical treatment or diagnosis.

Category 6

Collection of data from voice, video, digital, or image recordings made for research purposes.

Category 7

Research on individual or group characteristics or behaviour (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behaviour) or research that employs survey, interview, oral history, focus group, programme evaluation, human factors evaluation, or quality assurance methodologies.

Category 8

Continuing review of research previously approved by the convened IRB as follows:

a) The research is (i) permanently closed to the enrolment of new participants, and (ii) all participants have completed all research-related interventions, and (iii) the research remains active only for long-term follow-up of participants; or
b) No participants have been enrolled and no additional risks have been identified; or
c) The remaining research activities are limited to data analysis.

Category 9

Continuing review of research, not conducted under an investigational new drug application or investigational device exemption, where categories two (2) through eight (8) do not apply, but the HREC has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Full Committee Review

All research involving greater than minimal risk is reviewed at a full committee meeting where at least 30% of voting members are present and including at least one member whose primary concerns are non-scientific.

Initial Reviews

For initial reviews requiring full committee approval, the following materials are sent to the primary reviewers about three weeks before a scheduled meeting:

- Human Research Ethics Committee application.
- Full research protocol, including sponsor-generated protocol for commercial trials.
- Investigator's brochure, if applicable.
- Informed consent and assent documents in English (translation is required only once the English version is approved).
- Recruitment materials such as advertisements, flyers, posters.
- Questionnaires, surveys, interview or focus group scripts and assessment tools or scales.
- Genetic addendum, if applicable.
- Letters of support or approval from off-site health or educational facilities.
- South African Health Products Regulatory Authority (SAHPRA) approval or application, if applicable.
- Principal investigator's CV, if applicable.
- Budget summary

Each Committee member receives, at a minimum, a synopsis or executive summary of the protocol, informed consent and assent documentation, copies of questionnaires, surveys, and recruitment materials. A copy of complete documentation for each protocol is available to all Committee members on request prior to or during a meeting. See related policy 'Human Research Ethics Committee: Composition and Documentation of Activities' for more information on the Committee's decision-making process.

Duration of Approval

The Human Research Ethics Committee must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once a year. (See related policy: Continuing Review).

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1. Amdur RJ. Evaluating Study Design and Quality. In: Bankert EA and Amdur RJ editors. Institutional Review Board, Second Edition. Jones and Bartlett Publishers, Canada, 2006. Pp.126-128.
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Appeals and Complaints

Policy

In accordance with the DoH Ethics in Health Research Guidelines (2024), research ethics committees should have a complaints process that is accessible to researchers and other interested persons.

Appeals may arise when the HREC rejects a research proposal; adjudges a protocol deviation, non-compliance finding or protocol violation to be sufficiently serious to merit suspending or terminating the research; or requires additional protections or conditions before approving a protocol; and the Principal Investigator (PI) objects to the decision of the HREC and wishes to appeal.

Complaints arise because of alleged HREC procedural irregularities, breach of researcher confidentiality, unacceptable delays or conflict of interest.

Purpose

The purpose of this policy is to provide guidance on processes for appeals and complaints as required by UCT's Faculty of Health Sciences, the DoH Ethics in Health Research Guidelines (2024) and research governed by the US Federal Wide Assurance.

Appeal Process

The appeal process must initially involve the HREC in the first instance. If the HREC agrees or prefers, the matter may be referred to the Senate Ethics in Research Committee (EiRC) to be finalised. However, to retain the decisional integrity and independence of a HREC within its own institution, PI's may not appeal directly to the EiRC. If the PI is not satisfied with the HREC's decision; he/she/they may then appeal to the EiRC for relief.

The researcher also retains the right to appeal to the National Health Research Ethics Council (NHREC), if the research falls under the jurisdiction of the NHREC (that is, fulfils the definition of 'health research' as defined in the National Health Act 61 of 2003 (NHA). The NHREC has been given the mandate by the NHA to investigate and manage complaints related to the review and approval of 'health research' as defined in the NHA, by research ethics committees.

With respect to US federally-funded or supported research, no-one at the University may approve a study that the Human Research Ethics Committee has disapproved (45 CFR 46.112; 21 CFR 56.112).

Appeal Process (HREC-level)

Where a PI is dissatisfied with an HREC decision, he or she has the right to obtain from the HREC written reasons for its decision. The PI should exercise this right before launching an appeal.

If still not satisfied; a PI may appeal the HREC's decision through submitting an appeal in writing to hrec-enquiries@uct.ac.za. The HREC Chairperson is required to refer the appeal to the Senate Ethics in Research Committee (EiRC) within seven days of receipt.

Researchers conducting 'health research' retain the right to complain or appeal to the National Health Research Ethics Council (NHREC) in the event that they remain dissatisfied with the outcome of the HREC-level appeal process.

Appeal Process (Senate EiRC-level)

In the event of a failure to reach resolution at the HREC-level of appeal, the PI may proceed in terms of the appeal process outlined below, in accordance with the Appeal to Senate Ethics in Research Committee Standard Operating Procedure (last updated July 2012). An external PI (i.e. someone not affiliated to UCT) who has applied for ethics clearance may also use this appeal process.

Procedure

Notice in writing of the intention to appeal the decision must be given by the PI to the HREC Chairperson and the Chair of the (Senate) Ethics in Research Committee (EiRC).

The Chair of the EiRC must notify the Registrar and the DVC responsible for Research of receipt of the notice of intention to appeal.

The basis of the appeal and all the relevant documentation must be submitted in writing to the Chair of the EiRC by the PI within seven (7) days of the notice of intention to appeal above.

The Chair of the EiRC must forthwith make the appeal documents available to the HREC Chairperson, who must submit a written response to the Chair of the EiRC within seven (7) days of receipt by him/her/they.

The Chair of the EiRC must make a copy of the HREC's response available to the PI.

The appeal is usually heard on the basis of written submissions only, that is, no oral evidence is led. It is therefore important that both the PI and the HREC Chairperson ensure that all the information that is relevant from their respective points of view is before the Appeal Panel of the EiRC. The PI, the HREC and other interested parties may make submissions to augment the existing record, in accordance with the timelines set out by the Chair of EiRC (see below under Appointment of Appeal Panel).

Composition of Appeal Panel

The appeal will be heard by an independent panel made up of 3 – 5 members, who will ordinarily be members of the EiRC, but may be other persons if deemed necessary by the Chair of the EiRC.

The members of the panel must include one member from the Faculty concerned. The members of the panel must not be members of the HREC.

In the case where special expertise might be needed to deal with technical aspects of the substance of the appeal, then such expertise should be sought without compromising the independence of the panel.

Appointment of Appeal Panel

The panel must be appointed by the Chair of EiRC who must draw up timelines for the submission of documentation, for the hearing of the appeal and for delivery of the panel's decision.

Powers of Appeal Panel

The appeal panel is empowered:

- To request further information if needed;
- To interview the parties; but if it does so, it must be in the presence of both parties, failing which, it must report to the other party the substance of the submissions or answers given and allow an opportunity to rebut;
- To require the parties to seek to resolve the matter through mediation or seek some other route as to a possible resolution of the dispute; and
- To uphold the appeal; or to dismiss the appeal.

The Appeal Panel must keep careful minutes of the appeal proceedings and must draw up a report to support its finding at the conclusion of proceedings. The decision of the Appeal Panel is final and can only be taken on procedural review to a Deputy Vice Chancellor nominated by the Vice Chancellor in the case of a procedural irregularity.

Complaints process

All complaints against the HREC, for matters as described above, should be submitted directly to the HREC Chairperson; who should make every effort to investigate the complaint thoroughly, resolve the issue and communicate the outcome of the investigation to the complainant.

Only complaints that cannot be resolved effectively by the HREC Chairperson, or that are deemed to be irresolvable by either the researcher or HREC Chairperson; should be submitted to the Senate Ethics in Research Committee (EiRC).

The EiRC Chair shall notify the HREC Chairperson that a complaint has been made against the HREC; inform the HREC Chairperson of the nature and substance of the complaint; and request that the HREC Chairperson responds in writing to the complaint, providing sufficient detail.

The EiRC Chairperson may shall appoint an ad-hoc committee to investigate the complaint and report back to the full EiRC at a forthcoming meeting. Where necessary the subcommittee may need to interview the complainant, the HREC Chairperson and/or other persons.

The EiRC shall compile a report of its findings and recommended action. The report shall be submitted to the Deputy Vice-Chancellor of Research, the HREC Chairperson, the complainant and other parties if deemed necessary by the EiRC.

As previously stated, researchers conducting 'health research' retain the right to complain to the National Health Research Ethics Council (NHREC) in the event that they remain dissatisfied with the outcome of the complaints process.

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Continuing Review

Policy

The mandate of the Human Research Ethics Committee is to protect human research participants. Continuing review of ongoing research is one aspect of this commitment. Continuing review must be substantive and meaningful focussing on whether the balance of risks and benefits for a particular study has changed, whether there are unanticipated findings involving risks to participants and/or others, and whether any new information regarding risks and benefits should be provided to participants. Review must occur within one year of the last approval date, unless the Committee determines that review should occur more frequently. The South African Health Products Regulatory Authority (SAHPRA) requires six monthly progress reports for clinical trials under its jurisdiction. Progress reports using the SAHPRA format are acceptable to the Human Research Ethics Committee. Continuing review is additional to the review required for all amendments, serious adverse events and unanticipated problems.

For protocols initially reviewed by the full committee, the Committee must decide whether ongoing reviews/approvals require full-committee or expedited review. The Chair or a designee will perform expedited continuing reviews. The US Common Rule requirements for continuing review will only apply to federally-funded or supported research. These are detailed in this standard operating procedure and in OHRP Guidance (See Reference #2).

When conducting continuing review, the Human Research Ethics Committee should start with the working presumption that the research, as previously approved, does satisfy the prescribed criteria. The Committee should focus on whether there is any new information provided by the investigator, or otherwise available to the Committee, that would alter the Committee's prior determinations, particularly with respect to its prior evaluation of the potential benefits or risks to participants. The Committee should also assess whether there is any new information that would necessitate revision of the protocol and/ or the informed consent document.

Purpose

The purpose of this policy is to provide guidance on the continuing review process as required by UCT's Faculty of Health Sciences and research governed by the US Federal Wide Assurance. The policy also clarifies the consequences for an investigator failing to submit an annual progress report.

Procedures

Department of Health Guidelines

According to the Department of Health's Research Ethics Guidelines (2024), the Human Research Ethics Committee must monitor the ongoing conduct of approved research. The frequency and type of monitoring should reflect the degree of risk to participants. The Committee must receive, at least annually, reports from principal investigators on the following issues:

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

Further, a research ethics committee may conduct random inspections of research sites, data and signed consent forms and records of interventions (with prior consent and knowledge of participants). As a condition of approval of each protocol, researchers must report:

- Serious or unexpected adverse effects on participants.
- Proposed changes in the protocol.
- Unforeseen events that might affect continued ethical acceptability of the study.
- If a study is stopped before the expected date of completion and provide reasons.

Continuing Review in the Faculty of Health Sciences

Continuing review is a broad term that covers a range of possible procedures depending on the level of risk inherent in a study. For example, depending on the level of risk, the Human Research Ethics Committee may request:

- More frequent, than annual, continuing review.
- Sequential continuing review, for instance after the enrolment of a few participants.
- Independent monitoring of the consent process and rigorous evaluation of participants' understanding of the protocol and of being a research participant.

The Human Research Ethics Committee must determine at the time of the initial and at the time of each continuing review whether it is necessary for future continuing reports to be submitted more frequently.

Criteria which may be used to determine whether continuing review should occur more frequently include:

- Magnitude of risks.
- Participants' vulnerability.
- The experience of investigators in conducting research.
- The Committee's previous experience with the investigators (e.g., compliance history, previous problems with the investigator obtaining informed consent, or prior complaints from participants about the investigator).
- Magnitude of adverse events which may be irreversible, life threatening or disabling (the more so when there are no off-setting direct benefits to participants).
- The type and magnitude of a risk is unknown, for instance in proof of concept research involving initial attempts to find out if a laboratory discovery or hypothesis with potential clinical applicability works as expected when used in humans. The risks cannot be fully described until they are tested in humans and may be irreversible.
- Previous experience indicating that the frequency of adverse events is a potential concern.
- There have been non-compliance concerns which warrant more frequent monitoring.
- A protocol raises ethical concerns about research design or implementation for which there is no consensus or where available ethical or regulatory guidance is ambiguous or contradictory, for example using placebos in studies when there is a known effective treatment for a condition such as hypertension.
- The projected rate of enrolment.
- Whether the research involves novel interventions.

When the Human Research Ethics Committee is concerned about the levels of risk in a study, in addition to specifying a time interval between continuing reviews, it may specify a participant enrolment number as a threshold for determining when continuing review is to occur. For example, at the time of initial review and approval of a high-risk clinical trial, the Committee might require that continuing review occur either in 6 months or after 5 participants has been enrolled, whichever occurs first. The minutes of full committee meetings should clearly document the approval period (continuing review interval).

Documentation for Continuing Review

The principal investigator is responsible for timely submission of a protocol summary and status report on the progress of the research which includes:

- Number of participants enrolled.
- Number of participants who withdrew.
- Number of participants lost to follow-up.
- A summary of any complaints about the research since the last Committee review.
- A summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last Committee review.
- Any relevant multi-centre trial reports.
- Any other relevant information, especially about risks associated with the research. (Have risks and benefits been consistent with those originally anticipated?)
- Information regarding requests for changes.
- Changes in sponsors or funders.
- Changes in research personnel.
- A copy of the current informed consent documents, including Afrikaans and Xhosa translations if applicable.
- Any newly proposed consent documents.
- A summary of any unanticipated problems and available information regarding adverse events. In many cases, such a summary could be a brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document and any investigator's brochure.

If the Chair or designees has determined that a protocol requires continuing review at a full committee meeting then, two weeks before the convened meeting, all members must receive and review an electronic protocol summary and a status report on the progress of the study, and at least one member must receive the complete protocol. The following materials are sent to the main reviewer:

Continuing review application which includes:

- A summary containing the relevant information required to determine whether the protocol continues to fulfil the criteria for approval.
- A status report on the progress of the research, including any changes previously approved by the Committee.

When reviewing the informed consent document(s), the Committee must ensure that:

- The currently approved or proposed consent document is still accurate and complete; and
- Any significant new findings that may relate to the participant's willingness to continue taking part are given to participants.

To efficiently accomplish its continuing review workload, the Chair summarises the progress of a study; a typical summary might include the following information:

- The research is proceeding according to the Human Research Ethics Committee-approved protocol.
- The rate of participant enrolment is as expected.
- There have been no unanticipated problems.
- The rate and pattern of adverse events are as expected.
- No participants have complained about the conduct of the research or withdrawn from the research.
- There is no new published or unpublished information that would alter the Committee's prior determinations, particularly with respect to the Committee's evaluation of the potential benefits and risks to participants and the informed consent process.
- No changes to the protocol or informed consent documents are needed.

In the absence of the Chair raising any concern about the research, the Committee should be able to complete its continuing review deliberations for such a project within a brief period of time.

On the other hand, the following continuing review of a randomised control trial is likely to raise concerns which need more lengthy deliberation:

- The rate of serious adverse events occurring in participants is significantly higher than expected.
- A completed research project recently reported in the literature identified previously unrecognised risks for the same experimental intervention being tested in the clinical study undergoing continuing review.
- The investigator is proposing several substantive revisions to the protocol in response to the new risk information, including the addition of new exclusion and new safety monitoring procedures for participants.
- The investigator is proposing substantive changes to the informed consent document which include a description of the new information regarding reasonably foreseeable risks.

In these circumstances, the Human Research Ethics Committee needs to spend significantly more time carefully reassessing whether the risks to participants are sufficiently minimised and reasonable, given the new information presented and informed consent document proposed by the investigator, or whether additional changes should be required.

The protocol must be approved by a majority of the core (or alternative) members present. After the meeting the investigator is notified in writing of the action taken. Written notification will include the signed annual progress report form (fhs016) The Committee's conditions, if any, must be met before continuing approval may be granted.

When approving research with conditions at the time of continuing review, the Committee must specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions.

Expedited review of annual progress reports by the Chair or designee follows the substantive approach outlined above.

As a rule, initial approval for a research study is for one-year only, with approval expiring on the one-year anniversary date of the original approval date. The continuing review date is set according to the date on which final approval is granted, either by full-committee or expedited review. [Note: this does not apply to US federally-funded or supported research – see below for separate guidance.]

Principal investigators are responsible for ensuring that annual progress reports are submitted with enough time for continuing review to take place before the expiry date of the study. The Human Research Ethics Committee does not have the resources to notify investigators when their studies require annual renewal. If an annual progress report is not submitted prior to the expiry date, a study's approval will lapse, and no data may be collected or used during the period of lapsed approval. Where no applications for renewal are forthcoming, a study may be closed.

If the full committee (or Chair or designee) does not approve the continuation of a study, it must inform the principal investigator in writing, with reasons for its decision. The principal investigator is invited to respond in person or in writing providing justification for revising the decision or a proposal to change the protocol. The fact that an appeal by the principal investigator is on-going does not change the expiry date of prior approval or the consequences of a lapse in such approval. If the principal investigator appeals the decision the Committee must ensure there is a fair hearing of the appeal.

No Human Research Ethics Committee member may undertake or participate in a continuing review of a study in which he/ she has a conflict of interest, except to provide information requested by the Committee.

Continuing Review of Federally-funded or Supported Research

An application to continue an active study shall be reviewed based on approval criteria that are the same as for initial reviews (45 CFR 46.111):

- Minimisation of risk
- A reasonable balance of risks and anticipated benefits
- Equitable selection of participants
- Informed consent is adequate and appropriately documented
- Adequate safety monitoring
- Adequate provisions to protect privacy and confidentiality
- Protection of vulnerable participants

Protocols that require full committee review for their initial reviews generally need it for their continuing reviews. The expedited process may be used when:

- The Human Research Ethics Committee documented in its decision that the study involves 'minimal risk' and is eligible for future expedited review (expedited category 8).
- The protocol is permanently closed to enrolment of new participants, all enrolled participants have completed all study-related procedures and interventions, and the research remains active only for long-term follow-up of participants (category 8a); or
- No participants have been enrolled and no additional risks have been identified (category 8b); or
- The remaining research activities are limited to data analysis (category 8c).
- Studies that were initially approved by expedited review and during the course of the study the risks have not increased (category 9).

Note: The OHRP provides a detailed explanation of continuing review of expedited categories 8 & 9 in its Guidance on IRB Continuing Review of Research, November 10, 2010, pp.24-29.

After the meeting the investigator is notified in writing of the action taken. If approved, the informed consent dates must be modified to reflect the new period of approval and expiry.

Setting the Continuing Review Due Date

Note: The OHRP provides a detailed explanation for determining the effective date of initial IRB approval and the date for continuing review in its Guidance on IRB Continuing Review of Research, November 10, 2010, pp. 30-47:

'*Except when an expedited review procedure is used, the protocol continuing review date is set according to the date of approval by a full committee meeting. Of note, IRB review of an amendment to a research project during the period for which approval is authorised does not constitute continuing review of the project as a whole, and thus does not extend the date by which continuing review must occur (e.g. beyond one year from the effective date of the initial approval or the most recent continuing review approval). In order for the research to be approved by the IRB at a convened meeting, it must receive the approval of a majority of the core (or alternative) members present at the meeting (45 CFR 46.108(b)). (Put simply, review of amendments does not alter the date by which continuing review must occur because continuing review examines the full protocol, not simply a change to it.)*'

Determining the first continuing review date for research reviewed by the Committee at a convened meeting at the time of initial review and approved for one year

When the Committee reviews and approves research without conditions at a full committee meeting

When the Committee conducts the initial review of a research project at a convened meeting and approves the research for one year without requiring either (a) changes to the protocol or informed consent document(s), (b) submission of clarifications or additional documents, the effective date of the initial approval is the date of that Committee meeting. In such circumstances, the expiry date of the initial approval period and the date by which the first continuing review must occur may be as late as one year after the Committee meeting at which the research project was initially approved (See OHRP Guidance for an example, p. 41).

When the Committee reviews and approves research with conditions at a full committee meeting without requiring further review at a subsequent convened meeting

A much more common scenario is when the Committee conducting the initial review of a research project at a convened meeting takes the following set of actions:

- Approves the project for one year
- As a condition of approval, requires (a) changes to the protocol or informed consent document(s), or (b) submission of confirmations of specific assumptions or understandings on the part of the Committee or additional documents, and
- Directs that the Committee Chairperson (or other individual(s) designated by the Committee) to review and determine on behalf of the Committee whether the changes, clarifications, and/ or additional documents to be submitted by the investigator(s) are satisfactory.

Under this scenario, further review by the Committee at a subsequent convened meeting is not necessary for the initial approval to become effective, and the effective date of the initial approval is the date on which the Committee Chairperson (or other individual(s) designated by the Committee) has reviewed and accepted as satisfactory all changes to the protocol or informed consent documents, or any other responsive materials, required by the Committee from the investigator. In such circumstances, the expiry date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after that effective date of initial Committee approval. The OHRP notes that the first continuing review in these circumstances may occur earlier; for example, for logistical reasons the Committee may choose to set the expiry date of the initial approval period at one year from the date of the Committee meeting at which the research project was initially approved with conditions.

The Committee records must include documentation of the date when the Committee Chairperson (or other individual(s) designated by the Committee) determined that all conditions of Committee approval have been satisfied and the approval becomes effective, and the expiry date of the initial Committee approval.

Determining the date for the second and all subsequent continuing reviews for research reviewed by the Committee at convened meetings and approved for one-year intervals, including how to maintain a fixed anniversary date for the expiry of annual Committee approvals

The Committee must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Given this requirement, it is important to recognise that the use of the 'effective date' of Committee approval (i.e. the date on which the Committee Chairperson or other individual(s) designated by the Committee has determined that the conditions of approval have been satisfied) – as opposed to the date of the convened meeting at which the Committee approved a research study with conditions – to determine the latest permissible date for continuing review only applies to the first continuing review. For all subsequent continuing reviews of a research study, since there will be an ongoing approved study, the date of the convened meeting when the Committee conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

Anniversary dates for approvals

Given the logistical advantages of keeping the expiry date of the Committee approval period constant from year to year through-out the life of a project, when (a) the Committee grants approval for one year at the time of each continuing review, and (b) the Committee performs continuing review and re-approves (with or without conditions) the research within 30 days before the Committee approval period expires, the Committee retains the anniversary of the expiry date of the initial approval as the expiry date of each subsequent one-year approval period. For example, if the Committee conducts the initial review of a research study and approves it without conditions on October 1, 2017 for one year, the Committee may conduct its first continuing review anytime between September 1 and October 31 2018, and re-approve the research for another one-year period that expires on October 1, 2019. The same timing can be applied to each subsequent continuing review until the research activities involving human participants are completed. (See OHRP Guidance for examples, p. 42-45).

Ultimate responsibility rests with the principal investigator to monitor and track approval periods and to ensure continuing reports are filed in time for Human Research Ethics Committee review, in particular where review by the full committee is needed.

The US federal regulations make no provision for a grace period extending the conduct of research beyond the expiry date of approval. Therefore, continuing review and re-approval of research must occur on or before the date when approval expires.

If an investigator fails to provide continuing review information to the Human Research Ethics Committee or the committee has not reviewed and approved a study by the specified continuing review date, the research must stop, unless the committee finds that it is in the best interests of individual participants to continue taking part in the research interventions or interactions. Enrolment of new participants, participant follow-up and data collection may not occur after a study has expired. When continuing review of a study does not occur prior to the end of the approval period specified by the Committee, the Committee's approval expires automatically. Depending on its administrative capacity, the Human Research Ethics Committee will send a letter informing the principal investigator of the suspension but the responsibility rests with the researcher to suspend enrolment.

The determination regarding whether it is in the best interests of already enrolled participants to continue to participate in the research after Committee approval has expired may be made initially by the investigator, possibly in consultation with the participants' treating physicians (if the investigator is not the treating participants' physician, but the investigator as soon as possible must submit a request for confirmation that the Committee agrees with the determination. The determination by the Committee may be made by the Committee Chairperson, by another Committee member or group of Committee members designated by the Committee Chairperson, or at a convened meeting of the Committee Furthermore, this determination maybe made for all enrolled participants as a group or for each individual participant. If the investigator or Committee determines that it is not in the best interests of already enrolled participants to continue to participate, investigators must stop all human participants research activities, including intervening or interacting with participants and obtaining or analysing identifiable private information about human participants.

When Committee approval of an ongoing research project lapses and the Committee subsequently re-approves the project, the Committee may approve the project for one year and establish a new anniversary date for the expiry date of subsequent approval periods, or it may re-approve the project for a period of less than one year so as to retain the original anniversary date on which prior approval periods expired.

When continuing review of a research project does not occur prior to the end of the approval period specified by the Committee, Committee approval expires automatically. The OHRP does not consider such an expiry of Committee approval to be a suspension or termination of Committee approval. Therefore, such expiries of Committee approval do not need to be reported to the OHRP as suspensions or terminations of Committee approval under the Common Rule.

However, if the Committee notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the Committee itself is frequently not meeting the review dates), the Committee should determine whether such a pattern represents serious or continuing noncompliance that needs to be reported to appropriate institutional officials, the Health and Human Services Agency that supported the research, and the OHRP (45 CFR 46.46.103(b)(5).

Additionally, researchers who allow a lapse of an annual renewal or who fail to respond to feedback regarding a proposed amendment or adverse or unanticipated event, may be informed that their funding has been frozen, that other proposals will not be reviewed, or that they have triggered a higher level of continuing review, such as an internal audit process.

Communicating the Human Research Ethics Committee's Continuing Review Determination to Investigators and the Institution

The Committee must notify the investigator and the institution in writing of its decision to approve or disapprove proposed research or of modifications required to secure Committee approval of the research. If the Committee decides to disapprove the research, it must include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. The OHRP recommends that the Committee notifies any sponsor or co-ordinating centre of a study (possibly through the investigator) of any decision to disapprove the research and the reasons for its decision.

The HREC's written notification of approval must state:

- The period of time for which the project is approved
- Any conditions of the IRB's approval
- The date by which the next continuing review must occur.

Written notification includes the return of the signed Annual Progress Report Form (FHS016).

Suspension or Termination of HREC Approval of Research or Disapproval of Research at the Time of Continuing Review

The Committee has the authority to suspend or terminate approval of research that is not being conducted in accordance with the Committee's requirements or that is associated with unexpected serious harm to participants (45 CFR 46.113). A suspension or termination of Committee approval of research may occur at any time during the period for which Committee approval has already been given.

For a multicentre research project for which many or all institutions engaged in the research project choose to rely on their local Committees' review of the project, a local Committee's decision at one institution to suspend or terminate its approval of the research only applies to the conduct of the research project at that institution.

The Committee must promptly report any termination or suspension to the investigator, appropriate institutional officials, the Health and Human Services (HHS) agency that supported the research and the OHRP (45 CFR 46.103(b)(5) and 46.113). Such reports must include the reasons for the Committee's action (45 CFR 46.113).

Committees must follow written procedures for ensuring such reporting (45 CFR 46.108(a)). When reporting the suspension or termination of Committee approval of a research project to the OHRP, the OHRP recommends that the report include the following information:

- The name of the institution (e.g. university) conducting the research
- The title of the research project and the title of any related grant, contract or cooperative agreement
- The name of the principal investigator for the research project
- The HREC REF number and the number of HHS award(s) (e.g. grant, contract)
- The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged non-compliance, educate the investigator, educate all research staff, and require monitoring of the investigator or the research project).

When the Committee (a) suspends or terminates its approval during the period for which the Committee approval has already been given or (b) disapproves a research project at the time of continuing review, the Committee should establish procedures to ensure the rights and welfare of currently enrolled participants are protected, participants are not put at risk, and participants receive appropriate care, if indicated, during the period of suspension or following the cessation of the research. This is particularly important in the context of clinical trials. For example, the Committee, in consultation with the principal investigator and the participants' physicians, may need to determine whether it is in the best interests of currently enrolled participants to:

- Continue receiving the interventions that were being administered to participants under the research project
- Be transferred to another institution engaged in the research so that participants' participation in the research can continue
- Be transitioned to medical management outside the research context.

Continuation of participants on interventions that were being administered under the research project may be appropriate at least temporarily, for example, when those interventions hold the prospect of direct benefit to participants or when withholding those interventions poses increased risk to the participants. If the Committee decides that already enrolled participants should continue to receive the interventions administered during the research, data collection (especially safety information) should also continue for such participants.

Identifying the Point when Continuing Review is No Longer Necessary

Continuing review and re-approval of a research project at least annually is required so long as the research involves human participants. The OHRP considers a research project to continue to involve human participants as long as the investigators conducting the research continue to obtain:

- Data about the participants through intervention or interaction with them
- Identifiable private information about the participants in the research.

With respect to obtaining identifiable private information, the OHRP considers this to include obtaining identifiable biological specimens originating from living individuals. This includes:

- Collecting or receiving identifiable private information (including identifiable biological specimens) from any source (i.e., not already in the possession of the investigator)
- Collecting identifiable private information by observing or recording private behaviour without interacting or intervening with human participants
- Using, studying or analysing identifiable private information (including identifiable biological specimens), even if the information was already in the investigator's possession before the research begins. This includes using, studying or analysing any of the following:
    - Identifiable private information obtained by interacting or intervening with human participants
    - Identifiable private information stored in documents, records, photographs, images, video recording or audio recordings provided to the investigators from any source
    - Identifiable private information stored in documents, records, photographs, images, video recording or audio recordings already in the investigator's possession before the research begins
    - Identifiable private information obtained about an individual by interviewing other people
    - Identifiable biological specimens provided to the investigators from any source
    - Identifiable biological specimens already in the investigator's possession before the research begins.

A research project no longer involves human participants once the investigators have finished obtaining data through interaction or intervention with human participants or obtaining identifiable private information about the participants, which includes using, studying or analysing identifiable private information. Once all such activities described in the Committee-approved protocol are finished, the project no longer needs to undergo continuing review. For example, when the only remaining activity of a research project involves the analysis of aggregate data sets without individual participant identifiers, no further continuing review is necessary. At that point, the Committee can formally close its file for the project and advise the investigator of that action. Similarly, maintaining individually identifiable private information without using, studying or analysing such information is not human participants' research and thus does not require continuing review.

Study Closure or Final Report

A study is considered active or ongoing until a study closure or final report is submitted to the Human Research Ethics Committee. This is also consistent with FDA regulations (21 CFR 56.108) which require prompt reporting to the Committee of any changes in research activity, and completing a study is considered a change in activity.

The principal investigator can voluntarily close a study when completed and Human Research Ethics Committee approval is no longer required, when all participant accrual is completed and/or all data (including study follow-up data) pertaining to participants have been collected and when no further interaction with participants is planned for research purposes. In multi-centre commercial trials, the principal investigator must provide confirmation from the sponsor that all participants have completed their final visits and follow-up at the local site (i.e. University of Cape Town) is complete.

To formally close a study, the principal investigator must submit a final report specific to that study. Final reports will be reviewed and approved by an expedited process. The principal investigator will be sent written notification of the study's closure, including a signed original copy of the Final Closure Report (fhs010). If a study is not closed but is allowed to expire as a lapse in approval, an administrative suspension letter may be sent to the principal investigator.

If a principal investigator terminates employment with the University, he or she must submit a final report to the Human Research Ethics Committee or transfer the protocol to another principal investigator via an amendment which requires Committee approval. If the principal investigator is unwilling or unable to provide such an amendment, the Committee may choose to administratively close the study.

Verification of No Material Changes since Prior Human Research Ethics Committee Review

The Human Research Ethics Committee or other agents designated by the Committee may determine at any point during the period of approval for a particular protocol that the protocol requires verification from sources other than the investigator that no material changes have occurred since prior Committee review.

The nature of the study will determine from which source verification is to be requested. The decision will be made on a case-by-case basis using, among others, the following sources of verification:

- Pharmacy distribution records
- Data Safety Monitoring Boards
- Sponsors
- Research participants' records
- Hospital medical records

A request for verification that no material changes have occurred since prior Human Research Ethics Committee review may be made by, among others:

- The Human Research Ethics Committee based on information in the continuing review form.
- The Chair, a Committee member, the Committee's administrative staff.
- An investigative subcommittee or an independent audit team.

Examples of criteria which might alert the Human Research Ethics Committee to the need for such verification include:

- Randomly selected projects.
- A potential incident of non-compliance raises concern.
- Complex projects conducted by investigators who previously have failed to comply with research ethics guidelines or determinations of the Committee.
- Projects where concerns about possible material changes occurring without Committee approval have been raised based on information in the continuing review reports or from other sources.

References

1. Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, Republic of South Africa, 2024.
2. Office of Human Research Protections (OHRP). Guidance on Continuing Review of Research, November 10, 2010.
3. OHRP Guidance on Written IRB Procedures, July 1, 2011.

Protocol Amendments

Policy

Amendments to an approved protocol may become necessary as a study proceeds. Amendments may be minor or major. The Human Research Ethics Committee must review and approve all amendments to protocols involving human participants before implementation. All applications for an amendment must include the rationale or justification for the proposed change(s). The justification for an amendment must clarify how it will change the study, how it will affect risks to participants and what safeguards will be introduced to protect participants from additional risks. If the revision requires a change in the informed consent process, a revised consent form must be submitted with the amendment. Terms such as amendments, revisions, addenda, administrative changes, additions and modifications are used interchangeably to describe changes in an approved study.

Purpose

The purpose of this policy is to describe the procedures involved in applying for an amendment to an approved protocol. The policy also provides guidance on how to apply for a study exception (i.e. a temporary change or a change which affects only a few participants).

Definitions

Minor Amendments

A minor amendment is defined as a change that does not materially affect the balance of risks and benefits in a study or does not substantially change the specific aims or design of the study. Examples of minor amendments include:

- Administrative or informational amendments:
  - Changes in research staff.
  - Changing the study title or telephone numbers.
  - Addition or removal of qualified investigators, study sites.
  - Revision of format of consent documents, recruitment materials or questionnaires.
  - Correction of typographical errors.
- Procedural amendments
  - Drawing slightly different amounts of blood.
  - Changing frequency at which blood is drawn.

- An increase or decrease in proposed number of participants supported by a statistical justification.
- Narrowing the range of inclusion criteria.
- Broadening the range of exclusion criteria.
- Changing the amount of compensation, within reasonable limits.
- Revisions to the informed consent documents to improve clarity, to include missing elements or to revise lay language.
- Decreasing drug dosage or frequency of administration.
- Decrease in number of study visits provided such a decrease does not affect collection of relevant safety-related data.
- Minor adjustments in the duration of the study for retrospective reviews

Major Amendments

Such amendments involve significantly increased risk to participants and often reflect changes in the direction of a study that may substantially change its purpose or goal. Changes that alter the overall purpose or objective of a study may require a new study submission.

Examples of changes that may affect the balance of risks and benefits include:

- Adding a new activity that may increase risk to participants.
- Changing drugs or medications as well as dosages.
- Changing levels of radiation exposure.
- Adding a vulnerable population.
- Adding or changing invasive procedures.
- Adding a research arm to the study.
- Substantially extending the duration of exposure to the test material or intervention.

To obtain Human Research Ethics Committee approval for amendments, the principal investigator must submit an amendment application form describing all proposed modifications with a rationale for the changes (fhs006 and a synopsis of proposed changes). This applies to the protocol and the informed consent forms. In addition, all proposed changes must be indexed and highlighted in the revised protocol and consent documents. Major changes must be incorporated in the protocol and a revised protocol submitted. The approval of an amendment does not alter the original approval or expiry dates assigned to the protocol.

Amendments to Study Staff

The principal investigator must notify and obtain approval from the Human Research Ethics Committee for any staff changes by completing a study staff amendment form (FHS007). This includes the addition of students who are joining an active study for degree purposes.

Guidelines for Describing Potential Changes and Preparing a Synopsis

A concise description of potential changes is essential, and the Human Research Ethics Committee no longer accepts any research amendments that do not include a local PI-constructed synopsis describing planned changes. The Committee cannot rely on a study sponsor's description of the proposed revisions as it seldom provides adequate contextual detail to assess the changes. The degree of detail in the synopsis will depend on the nature and complexity of the proposed amendment. Researchers need to include enough information for Committee members to assess the amendment independently of any other protocol documentation. Any change in the risk-benefit ratio of the study must be defended. It is important to explain why changes are being made. For instance, there may be an overarching rationale for the changes (recruitment has been slow and the sample size, eligibility criteria and recruitment methods are being revised to increase the accrual rate and enable the study to be completed in a reasonable time frame); or each specific revision may be made for a different reason that needs clarification.

The amendment synopsis must:

- Be written in simple, non-technical and jargon-free language which is readily understood by Committee members who include non-scientists, non-experts in the PI's field and who represent the community. Acronyms must be spelt-out when used for the first time.
- Specify how the amendment will advance health and scientific knowledge in this population.
- Succinctly identify the amendment's purpose and objectives in the context of currently available and relevant knowledge.
- Provide a brief overview of inclusion and exclusion criteria, if applicable.
- Describe, if applicable, how participants will be recruited if different from the previously approved protocol. Specifically, address how, when, where and by whom participants will be identified and approached.
- Indicate whether any changes in design or sample size might affect a study's likelihood of achieving its objectives. If substantive changes in study design are intended, please provide a new statistical justification, and describe how data collected before this amendment will be incorporated into analyses.

- Describe the probability and severity of foreseeable harms (physical, psychological, social, and economic) that might occur in the amended protocol.
- Describe any changes in site-specific measures to protect participants' privacy and the confidentiality of the collected data.
- Explain how risks will be minimised and how safety will be protected.
- Describe expected benefits to individual participants and potential societal benefits within the local setting.
- Indicate whether post-trial treatment access will be affected by the amendment.
- Explain any changes to how, when, where and by whom consent and assent will be obtained.
- Clarify special protections for vulnerable participants such as children, cognitively-impaired, terminally or critically ill.
- Provide information on availability of compensation for research-related costs (e.g., travel) and inconvenience.
- Provide information on the on-going availability of insurance for research-related injuries.
- Where appropriate, briefly describe any changes to existing measures and protections for collection, storage and exchange of biological specimens.
- Identify and justify any aspects of the amendment that could reasonably be considered morally controversial.
- Please make sure that all amendments are highlighted with coloured track changes.
- Please provide updated informed consent and assent documents with track changes if applicable.

Amendments Requiring Full Committee Review

If the Chairperson or designee determines that an amendment requires review at a full committee meeting then, at least 7 to 10 days before the convened meeting, all members should receive and review an electronic synopsis of the proposed amendment and revised informed consent documentation (if applicable), and at least one member must receive the complete protocol.

The following materials are sent to the main reviewer. Amendments requiring full committee review will be assigned to a primary reviewer and will be placed on the agenda of the next scheduled meeting.

For reviews of amendments requiring full committee approval the following materials are sent to the main reviewer:

- Summary of proposed changes containing the relevant information required to determine whether the proposed changes increase the risks to human participants.
- New or revised study instruments that include but are not limited to:
  - New and/or revised informed consent and assent documents.
  - Data collection instruments.
  - Revised protocol.
  - Revised investigator's brochure, if applicable.

The complete Human Research Ethics Committee protocol file is available to all members prior to the scheduled meeting.

As part of the review, a decision will be made as to whether previously enrolled participants should be given information about the amendment when such information may impact their willingness to take part in the research. A written report of the final decision will be sent to the investigator, including a signed original copy of the amendment form (fhs006).

Unless proposed changes will significantly increase risk to participants or others, the Chair or designee will review amendments using an expedited procedure.

Guidelines for Reviewing Amendments

- Identify which part of the protocol is being reviewed:
  - Administrative details (e.g. study personnel, phone or fax numbers).
  - Inclusion or exclusion criteria.
  - Methods or procedures (e.g. adding a new questionnaire, increasing numbers of blood draws, adding extra visits).
  - Treatment parameters.
  - Stopping rules.
  - Consent documents.
  - Recruitments procedures (e.g. advertisements, posters, incentive gifts).
- Does the amendment increase risk for currently enrolled participants?
- Does the amendment increase risk for future participants?
- Should currently enrolled participants be re-consented?
- Is the amendment justified?

The Human Research Ethics Committee must review and approve all amendments to protocols involving human participants prior to implementation. The only exception is a protocol deviation that may be necessary to eliminate apparent immediate hazards to research participants. In this case, the principal investigator must notify the Chair in writing of such changes within seven calendar days of their occurrence. The Chair or a designee will review these changes as events that may represent unanticipated problems involving risks to participants or others and determine whether the change was consistent with ensuring participants' continued welfare.

Study Exceptions

Occasionally investigators want to make a temporary change or a change which affects only one or a few participants. These temporary or limited changes are defined as 'study exceptions'. Examples of study exceptions include:

- Enrolment of a participant who does not meet the eligibility criteria, for instance a participant whose age slightly exceeds the age inclusion criterion.
- Changing the dose of a study medication when justified.
- Changing a visit date.
- Adding an extra visit or omitting a visit.

All study exceptions must receive Human Research Ethics Committee approval prior to initiation and must be listed in the subsequent progress report. Submission and review of study exceptions must follow the policies defined for submission and review of amendments. The review must also determine whether the exception can affect participants' well-being, adversely or favourably, especially where an investigator repeatedly requests eligibility exceptions in the same study.

The following information should be included in a request for a study exception:

- Protocol title and investigator's name.
- The rationale for the exception – why is it the best choice for the participant.
- How the exception differs from the approved protocol.
- Whether the trial sponsor, if any, supports the exception.
- Whether data collected as a result of the exception will be analysed differently from the other data.
- Whether the exception changes the balance of risks and benefits.
- Whether an amendment to the study will follow.
- The only exception to this policy is when the eligibility exception is necessary to eliminate apparent immediate hazards to the participant.

If an eligibility deviation has occurred without prior Human Research Ethics Committee approval, the deviation must be reported as a protocol deviation or violation. The Committee cannot retrospectively approve the eligibility exception request and therefore must review the exception as a protocol deviation, following steps described in the policy on 'Protocol Deviations'.

References

1. Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, Republic of South Africa, 2024.
2. Office of Human Research Protections (OHRP). Guidance on Continuing Review of Research, November 10, 2010.
3. OHRP Guidance on Written IRB Procedures, July 1, 2011.

Unanticipated Problems Involving Risks to Research Participants and Others Including Adverse Events

Policy

In line with local and international ethical and regulatory requirements, the Human Research Ethics Committee must have written procedures to ensure timely reporting to the Committee, sponsors and appropriate regulatory agencies unanticipated problems, including serious adverse events, which might place human research participants at a greater risk of physical, psychological, economic or social harm.

Purpose

The purpose of this policy is to outline requirements and timelines for reporting and reacting to internal and external reports of unanticipated problems, including adverse events in research with human participants.

Procedures

Definitions

Unanticipated problems

An 'unanticipated' problem is any incident, experience or outcome that meets all the following three criteria:

- Unexpected in terms of its nature, severity or frequency, or the research population being studied; or if anticipated it is not fully addressed or specified in information provided to the Human Research Ethics Committee or to participants such as in initial protocol applications, any amendments, investigator brochures, scientific literature, product labelling, package inserts and Human Research Ethics Committee-approved informed consent documents or any existing documentation regarding the research conducted to date under the protocol;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places participants or others at a greater risk of physical, psychological, economic or social harm than was previously known or recognised.

In summary, an unanticipated problem is:

Unexpected – not in the consent form, investigator's brochure, protocol package insert or label; or unexpected in its frequency, severity or specificity;

Related to the research – caused by, or probably caused by, or associated with a device;

Harmful – caused harm to participants or others, or placed them at increased risk of physical, psychological, economic or social harm.

Examples of unanticipated problems include:

- Loss of a laptop computer containing confidential information about participants or others.
- A spouse physically abused by his or her partner for taking part in the study.
- Publication in the literature or a Data and Safety Monitoring Report that indicates an unexpected change in the balance of risks and benefits in the study.
- Finding that laboratory reports on blood or other samples were in error.

Adverse Events

An adverse event is defined as any untoward or unfavourable medical or psychological occurrence in a participant, including any abnormal laboratory finding, symptom or disease. An adverse event does not necessarily have a causal relationship with the research, or any risk associated with the research.

Unexpected adverse events

Unexpected adverse events are those in which any of the following applies:

- The specificity or severity is not consistent with the current Investigator's Brochure.
- The event is inconsistent with the risk information in the current protocol application.
- The event is occurring more frequently than anticipated.

For example, liver failure due to diffuse hepatic necrosis in a participant without any underlying liver disease if the protocol did not identify liver disease as a potential adverse event. In contrast, prolonged neutropenia and opportunistic infections in participants given an experimental chemotherapy regimen as part of an oncology trial would be examples of expected adverse events if the protocol described prolonged severe neutropenia and opportunistic infections as common risks for all participants.

Internal Adverse Event

Internal adverse events are those experienced by participants enrolled at a site under the jurisdiction of the Faculty of Health Sciences at the University of Cape Town (UCT).

External Adverse Event

External adverse events are those experienced by participants enrolled at other institutions or in a study for which UCT is not the coordinating centre.

Serious Adverse Event (SAE)

A serious adverse event is any adverse event in research that results in any of the following:

- Death.
- A life-threatening incident (places the participant at immediate risk of death from the event as it occurred).
- Hospitalisation (initial or prolonged).
- Disability.
- Congenital abnormality.
- Requires medical or surgical intervention to prevent permanent impairment or damage (e.g. allergic bronchospasm requiring intensive treatment in the emergency room or at home).
- Inadvertent disclosure of confidential information if this presents an immediate risk to a participant such as from spousal or child abuse.

Timelines for Reporting

Reporting Unanticipated Internal Problems or Adverse Events

Unanticipated Problems

Principal investigators must report to the Human Research Ethics Committee within seven calendar days after the investigator first learns of their occurrence all unanticipated problems that increase the risk of harm to participants or others.

Fatal and Life-threatening, Unexpected Adverse Drug Reactions

Principal investigators must report to the Human Research Ethics Committee as soon as possible but not later than seven calendar days after the investigator first learns of their occurrence all fatal and life-threatening adverse drug reactions in clinical trials.

Serious and Unexpected Non-fatal Adverse Drug Reactions

Principal investigators must report to the Human Research Ethics Committee as soon as possible but not later than fifteen calendar days after first learning of their occurrence all serious unexpected drug reactions that are not fatal or life-threatening.

Expected Adverse Drug Reactions

Principal investigators must notify the Human Research Ethics Committee within fifteen calendar days after the investigator first learns of their occurrence all adverse drug reactions that are expected but are judged to be occurring at a significantly higher frequency or severity than expected. The basis for these assessments must be included in the investigator's report.

Serious and Unanticipated Adverse Device Effects

Principal investigators must report to the Human Research Ethics Committee and to the sponsor (if applicable) as soon as possible but not later than seven calendar days after first learning about their occurrence all unanticipated adverse device effects [21 CFR 812.150(a)(1)]. The sponsor shall immediately conduct an evaluation of the unanticipated adverse device effect [21 CFR 812.46(b)(1)].

New Information that might Impact the Conduct of a Clinical Trial

Principal investigators must report to the Human Research Ethics Committee within three calendar days of first learning about their occurrence other unexpected adverse events, regardless of severity, that may alter the balance of risks and benefits in a study and as a result warrant consideration of substantive changes in the overall conduct of a clinical trial. The report could include individual case reports or a major safety finding from other sources.

Reporting External Serious Unexpected Adverse Drug Reactions

Principal investigators must report to the Human Research Ethics Committee as part of the six-monthly progress report in a line listing format all serious unexpected adverse drug reactions originating from other South African or international sites.

NOTE:

In addition, the principal investigator or a designee must submit an executive summary or aggregate summary tabulation of all adverse drug reactions together with the line listings in order to provide an overview of the trial. Because of their overview of all study sites, sponsors are particularly well placed to provide investigators with these summaries. The Committee will not accept batches of unsummarised CIOMS or Medwatch Forms which will be returned unacknowledged to the principal investigator.

How are internal reports submitted?

Investigators typically learn about internal adverse events from participants, another collaborating investigator or the participant's health care provider. If the investigator judges that the event represents an unanticipated problem or adverse event that requires timely reporting as described above, the principal investigator shall use the standard SAE reporting form to notify the Human Research Ethics Committee and the sponsor and/or a central or independent monitoring committee (e.g. DSMB) as required under a monitoring plan described in the Committee-approved protocol. The standard internal reporting form must be completed regardless of whether other forms (e.g. sponsor, CIOMS, Medwatch) have already been completed. Information such as a summary of the event, or drug company reports may be attached and submitted with the form.

Reports of unanticipated problems, including serious adverse events, submitted to the Human Research Ethics Committee must include the following:

- Appropriate identifying information for the research protocol, such as title, investigator's name, and Human Research Ethics Committee reference number.
- A detailed description of the adverse event, incident, experience or outcome.
- An explanation of the basis for determining that the adverse event, incident, experience or outcome represents an unanticipated problem.
- A description of any changes to the protocol or other corrective actions taken or proposed in response to the unanticipated problem.

The investigator must independently determine and comment on whether the event was thought to be related, possibly related, unrelated or the relationship is unknown. The Human Research Ethics Committee therefore relies on the principal investigator's expertise to assess the causality of the problem or event, its seriousness and whether it was expected. Investigators must also recommend whether a change in the protocol is needed to minimise risks to participants, whether the consent form should be revised to reflect this risk and whether participants in the study should be re-consented in light of this risk.

All adverse event reports are acknowledged with an official Human Research Ethics Committee stamp and returned to the principal investigator. A copy of the stamped original is placed in the protocol file.

Investigation and Evaluation of the Reports

The Human Research Ethics Committee Chair or a designee is responsible for reviewing adverse events.

If there are immediate risks to participants, the Chair or designee may take one or more of the following actions:

- Suspend Human Research Ethics Committee approval to ensure the ongoing safety of participants.
- Call an emergency Human Research Ethics Committee meeting to act on the report.
- Request additional information from the principal investigator or others.

If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring body subsequently determines that the event does represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring body should report this finding to the investigator and such reports must be promptly submitted to the Committee.

Reportable events that are not serious and do not require immediate action are reviewed by the Human Research Ethics Committee Chair or designee using an expedited procedure. At the Chair's discretion, SAEs together with the corresponding DSMB report, if applicable, will be reviewed at convened Human Research Ethics Committee meetings. The Chair or full committee may request further information or require the following remedial actions:

- Revise the protocol.
- Modify inclusion or exclusion criteria to mitigate the newly identified risks.
- Suspend enrolment of new participants.
- Suspend procedures in currently enrolled participants.
- Modify informed consent documents to include a description of newly identified risks.
- Provide additional information about newly recognised risks to previously enrolled participants.
- Suspend approval.
- Terminate approval.

Any proposed changes to a research study in response to an unanticipated problem, including serious adverse events, must be submitted as amendments, and approved by the Human Research Ethics Committee before being implemented, except when necessary to eliminate apparent immediate hazards to participants.

At the time of continuing review, principal investigators must submit a summary of serious problems and serious adverse events that occurred at the investigator's site (i.e. internal), are study-related and that have occurred since the last continuing (or initial) review of the study.

In most cases, an appropriate summary would be a statement that there have been no unanticipated problems and that serious adverse events have occurred at the expected frequency and level of severity as documented in the protocol, the informed consent form and the investigator's brochure, where applicable. The principal investigator must also summarise in the continuing review report all internal non-serious adverse events that have occurred since the last continuing (or initial) review of the study. For multi-centre studies, the principal investigator shall include the following documents with the continuing report:

- Most recent copy of the sponsor's analysis of adverse event reports, if applicable.
- Most recent copy of the DSMB report, if applicable.
- Summary of all external serious adverse events presented in the context of the entire multi-centre study, if possible.

Reporting Unanticipated Problems to the Office for Human Research Protections (OHRP)

The regulations at 45 CFR 46.103(a) and (b)(5) do not specify a time frame for reporting, except to say this must be done 'promptly'. For a more serious incident, this may mean reporting to the OHRP within days. For a less serious incident, a few weeks may be sufficient. It may be appropriate for the Chair of the Human Research Ethics Committee to send an initial report, and indicate a follow-up or final report will follow by the earlier of:

- A specific date; or
- When an investigation has been completed or a corrective action plan has been implemented.

This reporting requirement applies to research that is:

- Conducted or supported by the US Department of Health and Human Services.
- Covered by a federal wide assurance (FWA) regardless of the funding source.

For unanticipated problems involving risks to participants or others, the report must include the following information:

- Name of the institution (e.g. University of Cape Town).
- Title of the research project and/or grant proposal in which the problem occurred.
- Name of principal investigator on the protocol.
- Human Research Ethics Committee reference number and the number of any applicable federal award(s) (grant, contract, or cooperative agreement).
- A detailed description of the problem.

- Actions the institution is taking or plans to take to address the problem (e.g. revise the protocol, suspend enrolment, terminate the research, revise the informed consent document, inform enrolled participants, increase participant monitoring).

When reviewing a report of an unanticipated problem, the OHRP assesses most closely the adequacy of the actions taken by the institution to address the problem. Likewise, when reviewing reports of non-compliance or suspension or termination of approval, the OHRP assesses whether the corrective actions will help ensure that the incident will not happen again, with the protocol or investigator in question, with any other investigator or protocol, or with the Human Research Ethics Committee. Therefore, the OHRP recommends that, when appropriate, corrective actions are applied institution wide.

After receiving and evaluating the incident report from the institution, the OHRP will respond in writing, accepting the report or requesting additional information. Reports must be sent to the Director of the Division of Compliance Oversight at the following email address: IRPT.OS@hhs.gov [3]

References

1. SAHPRA Publications. http://www.mccza.com/Publications/Index/8. Last accessed 10 July 2018.
2. Office for Human Research Protections. Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. January 15, 2007.
3. Office for Human Research Protections. Guidance on Reporting Incidents to OHRP. June 20, 2011.
4. WHO TDR. Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards, 2005.

Protocol Deviations

Policy

Research ethics and regulatory guidance requires that any changes to an approved protocol must receive prior Human Research Ethics Committee approval before implementation unless the change is to eliminate an immediate harm to a research participant. Sometimes changes are noted or recognised after they occur. All changes no matter how minor should be reported to the Human Research Ethics Committee whether they are planned or noted after the fact.

Purpose

The purpose of the policy is to define protocol deviations and to outline procedures for reporting deviations to the Human Research Ethics Committee. Protocol deviations will also be distinguished from other protocol modifications.

Definitions

Protocol amendment

A protocol amendment is a permanent, intentional action or process that amends or revises a previously approved protocol. There is documented approval from the Human Research Ethics Committee, sponsor and/ or the Data Safety and Monitoring Board. See 'Protocol Amendments' for further guidance.

Protocol or study exception

A protocol or study exception is a one-time intentional action or process that departs from the Human Research Ethics Committee-approved protocol. See 'Protocol Amendments' for further guidance.

Protocol deviation

A protocol deviation is an unplanned or unforeseen failure of the principal investigator or other study personnel to follow the specified procedures approved by the Human Research Ethics Committee. Protocol deviations differ from amendments because they usually apply to a single incident or participant and are not intended at the time to change the study.

It is the principal investigator's responsibility to categorise a protocol deviation as major or minor.

Major protocol deviations

Major protocol deviations are deviations which affect a participant's safety, condition or status, the integrity of the study data, pose a significant risk of harm and change the balance of risks and benefits and a participant's willingness to continue participation.

If a deviation meets any of the following criteria it should be classified as major (the list is not exhaustive):

- The deviation has harmed or posed a significant or substantive risk of harm to a participant:
  - A participant received the wrong treatment or incorrect dose.
  - A participant met withdrawal criteria during a study but was not withdrawn.
  - A participant received an excluded related medication.
- The deviation compromises the scientific integrity of the study data:
  - A participant was enrolled but does not meet the protocol's eligibility criteria
  - Failure to treat participants per protocol procedures that specifically relate to primary efficacy outcomes (if it involves participant's safety, it meets the category above)
  - Changing the protocol without Human Research Ethics Committee approval
  - Inadvertent loss of samples or data
- The deviation is a wilful or knowing breach of ethical or regulatory policies or guidelines:
  - Failure to obtain informed consent
  - Falsifying research or medical records
  - Performing tests or procedures beyond the investigator's professional scope
  - Failure to follow the safety monitoring plan
- The deviation involves serious or continuing non-compliance with institutional or regulatory policies:
  - Working under an expired professional license
  - Repeated minor deviations

Minor protocol deviations

Minor protocol deviations are deviations which do not affect a participant's safety, compromise the integrity of study data or affect a participant's willingness to continue taking part in the study.

Examples of minor deviations include:

- Missing pages of a completed consent form
- Inappropriate documentation of informed consent such as missing signatures
- Using an expired consent form that has not changed significantly

- Participant did not receive a copy of a signed consent form (but on discovery, a copy is given to participant)
- Study procedure conducted out of sequence

Often making a distinction between major and minor deviations is a matter of degree; for example, signing an expired/invalid consent form that has not changed significantly is likely to be categorised as a minor deviation, whereas signing an expired/invalid consent form which has since added or deleted study procedures to a new consent form would be considered a major deviation.

Documenting and Reporting Protocol Deviations

As soon as a protocol deviation is identified in a study, it must be reviewed, documented and categorised by the principal investigator. Documentation must include the following:

- Principal investigator's name and study title.
- Date deviation occurred.
- Date deviation identified.
- Has sponsor been notified, where applicable.
- Has sponsor agreed to allow participant to remain in the study, where applicable.
- Description of deviation.
- Explanation why deviation occurred.
- Corrective follow-up action taken.
- Preventive measures implemented, where applicable.
- Investigator's assessment of whether deviation is major or minor, with reasons.
- Principal investigator's signature and date.

Deviations may be recorded as a summary log or a note in the study records.

The principal investigator must report major protocol deviations to the Human Research Ethics Committee within seven calendar days of first hearing of the incident. The Chair or a designee will review all protocol deviations. As part of the review, the Chair will determine whether the deviation constitutes an unanticipated problem that involves risks to participants or others, or serious or continuing non-compliance which requires further action. Once the review is complete and the Chair is satisfied that appropriate follow-up action has occurred, an official acknowledgement will be sent to the principal investigator.

If the principal investigator determines the deviation is minor and has no impact on the study or welfare of participants, no further action is necessary, and the deviation can be reported in the next annual progress report.

References

1. Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, Republic of South Africa, 2024.
2. Office of Human Research Protections (OHRP). Guidance on Continuing Review of Research, November 10, 2010.
3. OHRP Guidance on Written IRB Procedures, July 1, 2011.

Non-compliance

Policy

The primary responsibility of the Human Research Ethics Committee is to protect the rights and welfare of human participants in research. The Committee is authorised to approve research which complies with national and international research ethics and regulatory guidance and institutional policies. The principal investigator must conduct his or her research using specific materials, forms and procedures approved by the Committee. Committee approval letters also specify any special conditions that accompany approval and provide a time limit on the approval period. The principal investigator and the study team are expected to comply with all ethical standards, regulations, laws and conditions placed on the conduct of the study. The Committee will investigate and address all reports or allegations of non-compliance.

Purpose

The purpose of this policy is to outline procedures for reporting and investigating non-compliance with human research ethical and regulatory requirements.

Definitions

Non-compliance

Non-compliance is defined as any violation of any regulation governing human research or any deviation from the Human Research Ethics Committee-approved protocol. Non-compliance varies in nature, severity and frequency.

Minor Non-compliance

Minor non-compliance is a non-compliant incident that does not affect participants' safety, compromise data integrity, violate participants' rights or welfare or affect participants' willingness to participate in the research. Examples include a missed deadline for a continuing review, inadvertent errors due to inattention to detail, misunderstanding or an oversight.

Serious Non-compliance

Serious non-compliance is an activity that jeopardises participants' safety, rights or welfare, or the integrity of the data. Examples include:

- Conducting clinical research without Human Research Ethics Committee approval.
- Research participants do not meet inclusion criteria but are still enrolled in an experimental study, potentially or actually increasing risk and adversely affecting their rights and welfare as research participants.
- Current Committee-approved consent form describing all potential risks and alternatives to participate is not used.
- Activities that compromise participants' privacy and confidentiality.
- Implementing substantive modifications to a Committee-approved protocol without prior Human Research Ethics Committee approval.
- Enrolment of research participants when Human Research Ethics Committee-approval has lapsed.
- Inadequate training and supervision of research staff.

Continuing Non-compliance

Continuing non-compliance is defined as a series of more than one non-compliant event in reasonably close proximity that, if unaddressed, may compromise the integrity of the human research protection programme. The pattern may reflect a lack of knowledge or a lack of commitment on the part of the investigator and study team to protecting participants' safety and welfare in research.

Examples include:

- Repeated failure to follow Human Research Ethics Committee policies and procedures particularly after the Committee has informed the investigator of the problem(s) and that corrective action needs to be taken.
- An investigator has a record of non-compliance over a long period or in a number of existing or previously approved studies.

Allegation of Non-compliance

Allegation of non-compliance is a report that represents an unproven assertion.

Finding of Non-compliance

Finding of non-compliance is a report of non-compliance that is true or an allegation of non-compliance that is determined to be true based on a preponderance of evidence.

Reporting Non-compliance

Allegations, observations or evidence of non-compliance in human research must be reported to the Human Research Ethics Committee Chair by:

- Principal investigators.
- Any member of the study team.
- Human Research Ethics Committee members.
- Study monitors, auditors or sponsors directly, or through the principal investigator.

Research participants and others not directly involved with conducting or overseeing the research may also report incidents of non-compliance.

The Human Research Ethics Committee will review all reports of non-compliance. The Chair may conduct the review alone or with designated individuals, empanel a reviewing subcommittee of Human Research Ethics Committee members or request an independent audit (See 'Compliance Audits' for further guidance). The Chair or subcommittee will review written materials, interview knowledgeable sources and collect relevant documentation. The Chair or subcommittee will compile a factual and objective written report of findings and evidence. During the process, the Chair will inform the principal investigator about the progress of the review and investigation. Findings which in the opinion of the Chair, subcommittee or auditor(s) are supported by the preponderance of evidence will be considered findings of non-compliance.

Human Research Ethics Committee's Responsibilities

The Human Research Ethics Committee is responsible for making a final determination as to whether serious or continuing non-compliance has taken place. This should occur as soon as possible which is usually at the next scheduled full-committee meeting. The Chair shall inform members about the actions taken thus far and advise regarding further actions to be taken.

In considering how to react to serious or continuing non-compliance, the Human Research Ethics Committee aims to:

- Correct the non-compliance.
- Institute corrective measures to help ensure the non-compliance does not happen again, either with the investigator or protocol in question, or with any other investigator or protocol.

- Attempt to mitigate any adverse effects on participants.

Possible Human Research Ethics Committee reactions include:

- Suspend or terminate the study if participants' safety and welfare are being jeopardised.
- Place the study on administrative hold pending the outcome of the investigation.
- Require periodic independent audits.
- Modify the research proposal.
- Modify continuing review timetable to include more frequent Committee reviews.
- Require that the principal investigator and study team receive additional education or training in research ethics and good clinical practice.
- Require oversight by a senior investigator.
- Limit the research of the investigator (by number of active protocols or number of active participants).
- Refer to other institutional entities if the non-compliance rises to the level of scientific or professional misconduct.
- Require that participants currently or previously on the study be notified of the non-compliance when such information might affect their willingness to continue to take part in the research.
- Require that participants be re-consented.
- Monitor the informed consent process.
- Conclude that the investigation served as an educational tool and that, based on the principal investigator's response to the investigation (such as an audit), no further action is necessary.

The Human Research Ethics Committee is responsible for ensuring that changes and other mandates are carried out by the principal investigator. To this end, the Human Research Ethics Committee may request appropriate documentation from the principal investigator and may perform confirmatory site visits.

Investigators' Responsibilities

Investigators:

- Must report non-compliance on their studies.
- May choose voluntarily to suspend or terminate a study until the potential issue is investigated and/or resolved.
- Are expected to cooperate with any fact-finding and subsequent investigation and to keep all records related to the investigation.

- Must respond promptly in writing to all issues and questions raised - this may include an explanation of the non-compliance and a plan of action to ensure that similar incidents will not occur in the future.
- Must comply with all recommendations resulting from the investigation.

The principal investigator may submit a written request asking the Human Research Ethics Committee to reconsider its decision. The request should clearly indicate the facts or the interpretation in dispute and should provide supporting evidence where applicable. The Human Research Ethics Committee will decide either by consensus or vote to leave the decision unchanged or to reopen the investigation.

The final report shall include the following information:

- Name of the institution conducting the research.
- Title of research project and/or grant proposal in which the non-compliance occurred.
- Name of principal investigator on the protocol.
- Human Research Ethics Committee reference number and reference numbers for any applicable federal funding.
- A detailed description of the non-compliance.
- Actions the institution is taking or plans to take to address the non-compliance.

A copy of the final report may be sent to the:

- Dean of the Faculty of Health Sciences.
- Deputy-Dean of Research in the Faculty of Health Sciences.
- Principal investigator.
- Head of Department and/ or Chair of the Departmental Research Committee.
- Grants and Funding Office at the University of Cape Town, when research is funded by a grant or contract.
- Any external sponsors, where applicable.

US Federal Reporting Requirements

In keeping with Federal Wide Assurance requirements, the Human Research Ethics Committee Chair will promptly report the findings of serious or continuing non-compliance to the Office for Human Research Protections (OHRP), the FDA or both, where applicable. Administrative suspension or termination resulting from incidental non-compliance (for example, a missed deadline for continuing review) will not be reported to the OHRP or FDA unless considered serious or continuing non-compliance.

For more detailed guidance about procedures the Human Research Ethics Committee should take to file incident reports with the OHRP, see: Office for Human Research Protections. Guidance on Reporting Incidents to OHRP. June 20, 2011.

References

1. Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, Republic of South Africa, 2024.
2. Office of Human Research Protections (OHRP). Guidance on Continuing Review of Research, November 10, 2010.
3. OHRP Guidance on Written IRB Procedures, July 1, 2011.

Suspension and Termination

Policy

According to the Department of Health, where a research ethics committee is satisfied that such circumstances have arisen that a research project is not being conducted in accordance with the approved protocol and that, as a result, the rights and welfare of participants are not or will not be protected, the research ethics committee may withdraw approval. The research ethics committee shall also inform the researcher and the institution of its action and shall recommend that the research project be discontinued or suspended. Where ethical approval has been withdrawn, a researcher must discontinue the research and comply with any special conditions required by the research ethics committee.[1] For federally-funded research, the Human Research Ethics Committee also complies with US Common Rule regulations relating to suspensions and terminations. Consistent with this mandate, the Human Research Ethics Committee or Chair may suspend or terminate a study to protect participants' safety and welfare.

Purpose

The purpose of this policy is to outline the procedures for suspending or terminating research.

Procedures

The Human Research Ethics Committee may suspend or terminate a study based on a report or allegation of:

- Unanticipated problems involving risks to participants or others.
- Serious or continuing non-compliance.
- Findings in the continuing review or monitoring process.

Suspension

A suspension occurs when the Human Research Ethics Committee or Chair places a temporary hold on research that has been previously approved so that no new participants may be accrued, no research interventions may occur unless necessary for currently enrolled participants' safety and welfare, and no follow-up may be conducted unless it is in the best interest of participants and approved by the Committee.

Note: the term 'suspension' is often used to describe suspensions that occur 'for-cause' (as a result of a Human Research Ethics Committee decision) and suspensions that occur automatically due to a lapse of Committee approval.

For purposes of this policy, a suspension due to lapse of Committee approval will be referred to as an 'administrative closure' which will automatically occur when the Committee approval period expires.

Termination

Termination of a previously approved protocol occurs when the Human Research Ethics Committee withdraws approval and stops all research activity permanently. No new participants may be enrolled, and no further research interventions can occur. Where indicated, follow-up visits may be conducted with Committee approval to monitor participants' safety and welfare.

The Human Research Ethics Committee Chair will notify the principal investigator of the suspension or termination in writing, providing reasons. The Chair will inform the investigator of steps to be taken as a result of the suspension or termination of the research.

Steps could include:

- Drafting a plan to withdraw participants which protects their safety and wellbeing.
- Notifying current participants, by phone, email or in person, that the study has been suspended or terminated and providing reasons for the action.
- Notifying participants of any follow-up procedures, assessments or referrals which are necessary and permitted by the Human Research Ethics Committee for their safety. This may require a gradual withdrawal, if an abrupt discontinuation is likely to put participants at risk.
- Temporary or permanent transfer of responsibility for the study to another principal investigator.
- Reporting any adverse events or outcomes to the Human Research Ethics Committee and sponsor which happen during follow-up.

All written communication from the investigator to participants requires Human Research Ethics Committee approval prior to distribution.

The principal investigator may appeal against a decision to suspend or terminate a study within seven calendar days of receiving written notification. The written appeal to the Human Research Ethics Committee needs to include a plan for ensuring that the rights and welfare of currently enrolled participants are protected and a plan to ensure that future participants will be protected if the study receives Committee approval to continue.

Investigator-initiated Voluntary Suspension or Termination

An investigator may choose to voluntarily suspend or terminate some or all activities of an approved protocol. The investigator must notify the Chair of the Human Research Ethics Committee and provide reasons for the suspension or termination. The Committee may request any additional information in order to make an independent determination.

Records

The date that research is suspended, terminated, or voluntarily suspended or terminated must be noted in the protocol file and the database. All correspondence relating to these actions will be filed with the protocol.

Administrative Closure of a Protocol or Suspension due to Lapse of Human Research Ethics Committee Approval

If a continuing review of an active study is not approved prior to the expiry date, the Human Research Ethics Committee approval will automatically end, and the study will be suspended. It is the responsibility of principal investigators to monitor approval periods and to ensure that continuing review reports are filed in time to allow expedited or full committee review.

Whilst the Committee will try to send letters informing principal investigators of a suspension for lapse of approval, principal investigators remain responsible for suspending all research activities.

Reporting Human Research Ethics Committee Suspensions or Terminations

In keeping with Federal Wide Assurance requirements, the HREC Chair will promptly notify the Office for Human Research Protection (OHRP) and the Food and Drug Administration (FDA) when research under its jurisdiction is suspended or terminated. The report shall include the following information:

- Name of the institution conducting the research.
- Title of research project and/or grant proposal in which the non-compliance occurred.
- Name of principal investigator on the protocol.
- Human Research Ethics Committee reference number and reference numbers for any applicable federal funding.
- A detailed description of the reason for the suspension or termination.
- Actions the institution is taking or plans to take to address the suspension or termination.

Expiry of Human Research Ethics Committee approval will not be reported to the OHRP.

References

1. Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, Republic of South Africa, 2024.
2. Office for Human Research Protections. Guidance on Reporting Incidents to OHRP. June 20, 2011.

Compliance Audits

Policy

Auditing is an important mechanism for improving the ethical conduct of research and raising awareness of regulatory requirements. Authority for a research audit programme derives from the Department of Health Guidelines which mandate risk-related levels of monitoring, including 'random inspection of research sites, data and signed consent forms'[1]. Research audits in the Faculty of Health Sciences may be performed as part of a quality improvement and educational strategy or in response to a report or allegation of an unanticipated problem involving serious risks to participants, serious and continuing non-compliance, suspension or termination of a study, or a complaint from a third party such as a sponsor or a research participant. Depending on its purpose and value, an audit may include any or all of the following:

- Reviewing investigators' records
- Interviewing investigators, staff and research participants
- Observing the consent process from initiation to documentation of participants' consent

Purpose

The purpose of this policy is to outline procedures for conducting quality improvement audits or 'for-cause' audits of human participants research.

Quality Improvement Audits

Within the available time and resource constraints, the Human Research Ethics Committee, the Chair or a designee, or an independent auditor will undertake regular site visits as a continuing educational outreach initiative and an opportunity to:

- Hold roundtable discussions around site-specific ethical and regulatory issues.
- Meet investigators and other study team members in their workplace.
- Encourage face-to-face communication between researchers and Committee representatives.
- Share and promote best ethical practices in research.
- Identify and try to resolve any ethical problems the research team might be experiencing with Human Research Ethics Committee staff and/or the review process.

Ideally, routine site visits should be undertaken in a collegial spirit, be conducted with respect for all parties' privacy and confidentiality and with active involvement of all team members. Principal investigators will be given advance notice of a routine site visit and what it will entail.

The principal investigator needs to provide space to conduct the audit and must allow unimpeded access to any required documentation. The principal investigator must make available the following documentation:

- Regulatory and Human Research Ethics Committee documentation including:
  - All protocol submissions, Committee action letters, investigator's responses and final approval letters.
  - Progress reports and amendments.
  - Serious adverse event and protocol deviation reports.
  - Committee correspondence specific to the study.
  - All approved versions of the protocol, informed consent, recruitment materials and other tools such as surveys, questionnaires and case report forms.
  - Medical device records, if applicable.
  - Drug and pharmacy records, if applicable.
  - Participant medical records, if requested.

Site Selection

- Sites may be selected randomly for routine audits taking into account the following:
  - Investigators' research experience.
  - Nature of the research population, for example unconscious patients, children and adolescents, institutionalised participants.
  - Research involving greater than minimal risk.
- The Human Research Ethics Committee may request an audit.
- Principal investigators may request a routine site visit for educational and quality improvement purposes.

The audit team will use a standardised checklist to collect data relating to compliance with regulatory requirements and will conduct interviews with study team members, and occasionally participants. A final report will be compiled, focussing on strengths and recommendations on how shortcomings, if any, can best be addressed, with reference to national and international ethics and regulatory guidelines and best practices. If problems are identified, the final report will include appropriate follow-up measures to ensure corrective actions are implemented. This might include additional auditing and monitoring.

Once the principal investigator has reviewed the final report, addressed outstanding corrective actions and considered recommendations, the investigator will document these actions and return to the Chair or auditor. Once the investigator's responses are accepted, the audit is closed.

The final report is confidential and will only be shared beyond the Committee with the investigator's permission, unless the audit uncovers problems requiring further attention.

For-Cause Audits

Definition

A for-cause audit is an in-depth examination of all components of a research study, including all records and documents, observation of research procedures, and interviews with investigators, research staff members and participants to determine if participants' rights, safety and welfare are being upheld according to national and international ethical and regulatory standards.

Following a complaint or an allegation of a problem in a study, the Chair will decide whether the study should be:

- Suspended immediately due to immediate risks to participants or others
- Placed on administrative hold
- Allowed to continue until the for-cause audit is complete

If the Chair decides there are no immediate or serious risks to participants, an audit may be requested prior to placing immediate restrictions on the study. The Chair, in consultation with the Deputy-Dean of Research and/ or the Human Research Ethics Committee, may appoint a sub-committee or an independent auditor, on a per-project contract basis, to conduct the for-cause audit.

Pre-audit Preparation

The Chair will inform the principal investigator of the reasons for the audit, whether any restrictions have been placed on the study and relevant details relating to the auditing process.

A member of the audit team will ask the principal investigator to submit a list of participants (ID numbers) enrolled in the study or studies from which a percentage will be randomly selected for review. Only files of selected participants will be reviewed unless a more comprehensive review is called for based on the discovery of further problems. The principal investigator must ensure space is available for the audit team to conduct the review.

Document Review

Document review includes an in-depth review of the principal investigator's study file (also known as the study regulatory binder), source documents, consent forms and participants' records. Some or all of the following documentation will be examined depending on the nature and purpose of the audit:

- Investigator's Study File
- Regulatory Documentation and Study Staff
  - Delegated roles and responsibilities list:
    - Were delegated individuals qualified to perform tasks?
    - Did study staff receive adequate training on how to conduct delegated tasks?
    - Did study staff have an adequate understanding of the study?
    - Was there adequate supervision of delegated tasks?
    - Staff signature lists (provide an updated reference of research staff, past and present; useful for long studies, studies with a large number of staff, and/or high staff turnover).
    - Staff members' printed names, original signatures and signed initials, titles or roles (e.g. research nurse, study coordinator, PI).
  - Confirmation of regulatory approval (e.g. SAHPRA approval)
  - In FDA-regulated studies: signed FDA 1572 and clinical investigator financial disclosure forms for each listed investigator.
  - In NIH-sponsored studies: copy of NIH grant and progress reports.
  - Signed and dated investigators' CVs.
  - Investigator's brochure.
  - If an investigational drug or device study: device manual, package insert, dose administration guide.
  - Laboratory Certification:
    - Laboratory director's CV
    - Laboratory normal reference values, including updates
- Study Tracking Logs/Worksheets:
  - Human Research Ethics Committee tracking log
  - Screening log (which documents and tracks all potential participants that were considered and screened for the study)
    - Was informed consent obtained prior to screening?
    - How and where was participant recruited?
    - Reasons for exclusions/ineligibility
    - Was the Committee notified of study exceptions?

- Participant recruitment log:
  - Total contacted, total response, total enrolled.
  - Reasons for early withdrawals or exclusions.
  - How many participants is the site approved to enrol?
  - Are all recruitment methods and materials approved by the HREC?
- Monitoring log (offers a record of all monitoring visits and any corresponding letters, reports and changes resulting from the visit; also offers documentation of all outside persons who have had access to confidential study materials and when).
  - Have all monitoring reports, such as a DSMB reports, been submitted to the Human Research Ethics Committee?

- Study Standard Operating Procedures.
- Approved Protocol: current version and previous versions.
- Informed Consent Form: current version and previous versions:
  - Is there a consent form for each participant?
  - Who signed the consent form (participant, parent, legally authorised representative)?
  - When was the consent form signed in relation to when the first research activity began?
  - Was the correct version of the consent form used?
  - Is the content in the consent form current regarding the most recently approved protocol and amendments to the protocol?
  - Where the signed consent forms are stored and what measures are taken to protect the confidentiality of participants' signatures?
  - Where the consent process is conducted and by whom?
  - Did each participant receive a copy of the signed and dated consent form?
  - Should a copy of the consent form be included in the participant's medical record?
- Human Research Ethics Committee Documentation:
  - Initial submission.
  - Amendments.
  - Progress reports (on time? any lapsed approvals?).
  - Protocol exceptions and deviations:
    - Are there adequate explanations of why the event occurred?
    - Are there adequate descriptions of any follow-up corrective actions?
    - Were significant deviations (i.e. could affect participant's safety and/or data integrity) reported to the Human Research Ethics Committee in a timely fashion?
  - Closure reports.

- Reports of unanticipated problems and serious adverse events:
  - Have all adverse events (AEs) been reported to the Human Research Ethics Committee according to institutional and regulatory requirements?
  - Have any off-site AEs been received and reported to the Human Research Ethics Committee?
  - Is there evidence of follow-up for AEs?
  - Have appropriate regulatory bodies been notified of serious adverse events?
- Correspondence:
  - Description of document or submission.
  - Date sent to Human Research Ethics Committee.
  - Date approved by Human Research Ethics Committee.

- Are participants remunerated (e.g. cash, vouchers) and how is this tracked?
- Sponsor's correspondence and communication.
- Case Report Forms:
  - Source documents.
  - Participant eligibility checklist:
    - Is determination of eligibility by inclusion/exclusion criteria clearly noted in the record?
    - Who makes the eligibility decision? How is this communicated to the PI?
    - Are source documents, such as laboratory tests, diagnostic tests, physical examination results, available to verify that eligibility criteria were met?
    - Did all participants meet the eligibility criteria? If no, was a protocol deviation submitted to Human Research Ethics Committee?
  - Study visit checklist.
- Data Collection:
  - How data are captured (e.g. case report forms)?
  - Does case report form or data collection sheet include dated signature/initials of person collecting the information?
  - Is data collection complete for each participant?
  - Are source documents available to verify the data entries for each participant?
  - Do source documents include dated signature/initials of person obtaining the information?
  - Are changes/cross-outs routinely initialled and dated in participant's file?
  - Are the data collection tools the same or different from those that were approved by the Human Research Ethics Committee?

- If different, was an amendment submitted to cover the changes? Is a change in consent needed to cover the changes in the questionnaire?
- Are the data collection tools being administered within the timeframe specified by the protocol?
- If questionnaires are administered via interview, how is confidentiality maintained?

- Record Keeping:
  - Is there a binder or folder for regulatory documents?
  - Is there a binder or folder for Human Research Ethics Committee correspondence?
  - Is there a study file for each participant?
  - Are there consistent measures for documenting the research process?
  - Is there a system for writing narrative notes when a participant is seen for a visit or a phone call or mail contacts?
  - Where are records kept? How are they kept? Who has access to the records?
  - Who is responsible for training research staff on proper documentation?
- Drug or Device Oversight:
  - Is there documentation of drug or device use for each participant?
  - How are drugs sent to the principal investigator?
  - Who is responsible for shipping? If the site is responsible, are shipping receipts or packing slips on file?
  - Who is responsible for storage?
  - Who is responsible for drug dispensing to each participant?
  - Is there appropriate documentation for the return and/or destruction of drugs or devices?
  - Is there evidence of any drug or -device-related errors? If yes, have they been reported to the Human Research Ethics Committee?
- Storage of Specimens:
  - Is written consent required? If yes, does the consent clarify future uses of the sample?
  - Are/were participant identifiers collected? If yes, where are identifiers stored? How is confidentiality maintained?
  - Are samples coded? If yes, is there Human Research Ethics Committee approval for their re-use?
  - Are there procedures to withdraw individual samples? If yes, are these procedures described in the consent from?
  - Are samples being sent to third parties? If yes, is a material transfer agreement needed to cover the exchange?

- Is there any evidence of unintentional disclosures of participants' identity?

Additional Audit Procedures

- The audit team will also conduct individual interviews with the principal investigator and key research staff to determine if additional problems, not already examined during the record review, have occurred and to clarify any outstanding issues. It is also a useful opportunity to educate the principal investigator and staff.
- The audit team may visit locations where drugs or investigational devices are stored. The auditor may examine where and how drugs or devices are stored, the accountability records for use of the drugs or devices, the processes used to repair discard or return unused drugs or devices, and if and how a copy of the consent form is stored in the pharmacy.
- Likewise, the audit team may visit laboratories where biological samples are stored and analysed for the study.
- The audit team may observe the informed consent process:
  - Was the environment in which the consent process took place conducive to rational, thoughtful and unpressured decision-making?
  - Was the length of time devoted to the consent process sufficient?
  - Was the participant given adequate opportunity to ask questions?
  - Was the participant given an adequate explanation of the research using appropriate simplified language?
  - Did the participant show a reasonable level of understanding before signing the consent form?

Informed consent forms need to state that research may be audited by the Human Research Ethics Committee and other external monitoring agencies such as an independent auditor, the South African Health Products Regulatory Authority (SAHPRA) or the FDA. Further, participants need to be informed that their confidentiality will be maintained.

Preparation of Audit Report and Follow-up

Once the audit is complete, the audit team will compile a written report which is sent to the principal investigator, the Chair, the full committee at its next meeting and the Deputy Dean of Research. The principal investigator is required to respond in writing to each of the findings. The principal investigator's response is presented to the full committee and a final decision is taken based on its knowledge of the facts and the additional findings gathered by the audit team. The Human Research Ethics Committee may recommend a further follow-up visit(s) by the audit team to ensure corrective actions have been implemented and/or that the investigator and research staff undergo specific training in ethical and regulatory issues. The principal investigator will be notified of the final notice.

The principal investigator may submit a written request asking the Committee to reconsider its decision. The request must specify the facts or the interpretation in dispute and provide supporting evidence where applicable. A full committee will decide via consensus or vote whether to leave its decision unchanged or to reopen its review. The Committee may also use audit findings to decide if the protocol needs more than annual review.

If there is confirmatory evidence of an unanticipated problem or serious or continuing non-compliance which threatens the safety, rights and welfare of participants, the full committee may decide to suspend or terminate the study.

Additionally, in the case of federally-funded or -supported research, the Chair must report findings of serious non-compliance to the Office for Human Research Protection and/or the Food and Drug Administration. Reports of serious non-compliance leading to termination of a study will also be forwarded to the Dean of the Faculty of Health Sciences, the investigator's Head of Department, and funding bodies or sponsors. (See related policies on 'Non-compliance' and 'Suspension and Termination')

All documentation generated by the audit is filed with the protocol in the Human Research Ethics Committee office.

Investigators' Input to the Human Research Ethics Committee

Investigators may submit general comments, suggestions or concerns, including dissatisfaction with the Human Research Ethics Committee review process or operations, via the following mechanisms:

- The Dean of the Health Sciences Faculty
- The Deputy Dean of Research
- The Chair of the HREC

Principal investigators will be informed of the outcome of these submissions.

References

1. Ethics in Health Research: Principles, Processes and Structures 3rd Edition, Department of Health, Republic of South Africa, 2024.
2. OHRP. Guidance on Reporting Incidents to OHRP, June 20, 2011.
3. Prentice ED, Selwitz AS, Oki GSF, Kuhl J. Audit Systems. In: Bankert EA and Amdur RJ editors. Institutional Review Board, Second Edition. Jones and Bartlett Publishers, Canada, 2006. pp.53-56.
4. Stellenbosch University, Committee for Clinical Trials. Standard Operating Procedures and Guidelines: Guidelines for the Conduct of CPT Audits. February 2007.
5. US Department of Health and Human Services and the Food and Drug Administration. Guidance for Industry: Protecting the Rights, Safety, and Welfare of Study Subjects – Supervisory Responsibilities of Investigators, May 2007.
6. Wayne State University, Human Investigation Committee. For-Cause Audits of Human Research Studies, May 2006.

Informed Consent

Policy

The ethical principle of respect for persons requires that participants be given the opportunity to choose what may or may not happen to them. In the research context, the Human Research Ethics Committee views the informed consent process between the researcher and the potential participant as the primary mechanism for securing a participant's consent. For the informed consent process to be valid, participants must receive sufficient and relevant information about the research; must understand this information and must voluntarily choose whether to take part.[1 p.24-25] Adults, i.e. persons over the age of 18 years, may make independent decisions. The informed consent process for adults with diminished or no decision-making capacity (factually incapacitated) and for minors (legally incapacitated) is described in separate standard operating procedures: Research Involving Adults with Decisional Impairment and Children in Research respectively.

Consent documentation must be written in laypersons' language. The consent process is ongoing throughout a study and consent documentation should be revised when new information becomes available.

Purpose

The purpose of this policy is to provide ethical and regulatory guidance on the informed consent process and the format and content of informed consent documents.

Process and Documentation

Informed consent as an ongoing conversation

Informed consent is not simply a signature on a form but a process of interactive communication between the researcher and the potential participant. Depending on the nature and duration of the research, ongoing discussion with and education of participants may continue long after the consent document has been signed. Questions may arise well into the research experience; for example, a discussion of confidentiality may not be meaningful until participants are asked sensitive questions at which point, they must feel free to raise further concerns.

Informed consent involves educating potential participants, not merely disclosing information. Comprehension will vary from participant to participant.[2] Researchers need to distinguish comprehension (understanding the factual components of the information) from appreciation (what the information means for individual participants).

Whereas the written informed consent document emphasises factual information, interactive communication is able to focus on what the factual information means for a particular participant; for instance, how an individual participant interprets 'risk' or 'benefit' is likely to depend on that participant's specific circumstances. As an example, studies show that many participants, particularly from poorer communities, enrol in studies to access better health care even though there is meant to be a clear distinction between research and treatment. In certain cultures, it is common for potential participants to bring family members with them to assist with decision-making.[3-6] Accounting for participants' customs and circumstances can also improve the informed consent process.[7-11]

The emphasis should be on effective communication with adequate opportunity for asking questions, achieving clarity and understanding, and making reasoned decisions. In addition to the written consent form, researchers need to consider other creative methods of conveying information:

- Videotapes, photographs or diagrams of research procedures.
- Pre-visits to the research site to see equipment, such as MRIs.
- Group discussions.
- Web sites.
- Comics that explain the nature of the research.
- Distributing participant-oriented material about clinical and other research, for example cancer trial pamphlets, brochures and guidance on participants' rights in research.

Setting

- Conduct the discussion in a private and quiet place although this will be a challenge in busy outpatient clinics and community health centres. Researchers may need to delay the consent process if potential participants' privacy and confidentiality cannot be protected.
- Be prepared to accommodate potential participants with disabilities. For example, visually-impaired people may benefit from documentation with large font and high contrast. Hearing-impaired people may need sign language interpreters.

Who should obtain consent?

The principal investigator is responsible for ensuring that participants understand what it means to enrol in a study. The principal investigator can delegate this task to suitably qualified team members. The protocol must list the names, positions and experience of those who will obtain informed consent. The decision will depend on the following:

- The technical details of the protocol and who can best explain them.

- Who is most capable of answering participants' questions? It is possible that this function could be shared between the principal investigator and another staff member such as a research nurse, social worker or counsellor.
- Multilingualism – is a well-trained interpreter needed to facilitate the consent process?
- Minimising the possibility of undue influence and ensuring the person obtaining the consent is appropriately trained, independent and bias-free. For instance, if the investigator is also the treating doctor, is the participant able to distinguish the different roles and will the participant not feel he or she must agree to take part in order to 'please' the doctor and guarantee continued treatment?

  Other settings where the presence of authority figures may influence a potential participant's voluntary decision include prisons, schools or work environments.

Written consent

In line with the National Health Act of 2003,[12] the Committee has limited latitude to waive the legal requirement for written (signed) informed consent in prospective research with human participants, including research which carries no or minimal risk. However, in some circumstances, for example where a signed consent form is the only link between the participant and the research and the main risk is potential harm to privacy, the investigator may request and justify a waiver of written consent. The Committee will consider such requests on a case-by-case basis.

Signatures on consent forms, including witnesses

- The signature of the participant or legally authorised representative on the informed consent form indicates that the study has been explained to the person and he or she agrees to participate.
- The HREC does not require the signature of a witness when the participant reads and is capable of understanding the consent document.
- The signature/date of the witness, in the case of illiterate participants, indicates that another, preferably impartial, person has observed the consenting of the participant and attests to the accuracy and apparent understanding of the participant.

Translation of informed consent documents

The signed informed consent document is the written record of the consent interview. The informed consent document also serves as reference material to reinforce a participant's understanding of the study. The informed consent document must therefore be in a language the participant understands. When a study intends to enrol participants who are unlikely to understand English or who might prefer to be interviewed in their home language, the HREC expects the informed consent document to be translated into participants' first language. In the Western Cape, the most common spoken languages are Afrikaans, English and Xhosa.

The English version of the informed consent documents and any other written/audio/video materials should be submitted to, and approved, by the Committee prior to translation. Unless required by funders or sponsors, the Committee does not expect researchers to use certified translation services to translate informed consent documents. However, if not formally certified, translators should have extensive experience of research and medical terminology. In addition, a second person should back translate the consent document into English to verify accuracy and to ensure all information from the English version is included.

The Committee will approve only the English version and will acknowledge receipt of Afrikaans and Xhosa versions and certificates of translation.

Other points to consider:

- In order to protect privacy and to prevent pressure or bias, the Committee prefers interpreters not to be related to potential participants.
- If the member of the research team obtaining informed consent is not fluent in the participant's home language, an interpreter fluent in English and the participant's language should be available to address the participant's questions and assess their comprehension.
- How transparent and authentic will the interpreted conversation be? With three people communicating (participant, researcher and interpreter), will everything said by each person be translated?
- How will the interpreter incorporate cultural considerations into the consent information?
- Informed consent is an ongoing process. Will an interpreter be present at future meetings to ensure participants understand ongoing study-related communication and to address ongoing questions?

Allow enough time for decision-making

Discussions with potential participants should take place with enough time for them to think carefully about participation. Participants may want to take the consent document home to discuss participation with their family, friends, a religious advisor or a community elder. According to national research ethics guidelines: 'No person should be *required* to make an immediate decision.'[1 p.24]

Ensuring readability[13-18]

The consent document should be written in non-technical terms at a level which potential participants will understand:

- Direct it no higher than a 6th to 8th grade reading level.
- Check the Flesch-Kincaid Reading Level using Microsoft Word: Highlight portions of the text to be analysed and click on Tools; Click on Spelling and Grammar > Options and tick 'Spelling and Grammar' and 'Readability Statistics '. The grade level, reading ease score and percent of passive sentences appear when the spell-check feature has ended. Many formulas are available for determining rough estimates of reading levels, but they must be interpreted with caution and researchers are urged to keep in mind their shortcomings which are well-described in freely downloadable literature.[14 pp.13-14, 15]
- Use simple and short sentences.
- Avoid technical language, medical jargon and acronyms.
- Use common, everyday words instead of jargon, for example 'medical check-up' instead of 'clinical examination'.
- Be careful of common words used in uncommon ways; for example, health workers may refer to 'positive' test results which may not be good news in the customary sense of the word whereas 'negative' results may be good news.
- Be careful of homonyms which are words with different meanings that sound alike. The words may or may not be spelt in the same way. For instance, participants may misinterpret homonyms such as 'stool', 'gait', 'dressing', 'tissue', and 'shots' (injections). During the consent process, make sure to clarify what words really mean in the research context.
- Avoid large blocks of printed text. Break the text into short sections.
- Use reader-friendly headings to format consent documents:
    - Why is this study being done?
    - Why are you being asked to take part?
    - How many people will take part in the study?
    - How long will the study last?

- What do we do to decide if you are eligible to be take part?
- What will happen if you decide to take part in the study?
- What are the risks and discomforts of this study?
- Are there any benefits to you for being in the study?
- What other choices do you have?
- What will happen when the study is over?
- Will your test results be shared with you?
- Will the results of the research be shared with you?
- Will any of your blood, tissue or other samples be stored and used for research in the future?
- Will you receive any reward (money or food vouchers) for taking part in this study?
- Who will see the information which is collected about you during the study?
- Who do I speak to (or contact) if I have any questions about the study?

- Use at least 12-point font or larger, depending on the study population.
- Use the second person (you) not the third person (the participant) to enhance personal identification.
- Use active rather than passive verbs, for example 'We will need to collect a blood sample from your child' rather than 'A blood sample will be needed from your child'; 'We will ask you questions about your health' rather than 'You will be asked questions about your health'.
- Give fluid volumes in equivalent teaspoons or tablespoons rather than in mls.
- Avoid words that do not add value to your text such as 'very', 'actually, 'really'.
- Break up dense chunks of content. Convert long lists embedded in sentences into bulleted lists with one point per line (for example, eligibility criteria for enrolment). Use numbered lists if the order of items is important.
- Don't decrease margins and white space to fit content onto one page. One page crammed with content can be more off-putting than several well-spaced pages.
- To the extent possible, given regulatory requirements, limit the content in the consent form to what the reader truly needs to know.
- A useful rule of thumb is to tailor the amount of information in the consent form to the level of risk involved in a study.

Informed consent form summary

Consider including a simply written one-page summary, which is clearly titled 'This is a summary only'. Participants can refer to the main consent document for complete, more –detailed information. The summary must include, in lay language (i.e. understandable to the people being asked to participate) the following elements:

- Why is this research being done – what is it trying to find out?
- Why are you being invited to take part?
- How long will you take part in this research – how much of your time will be needed – will you need to take time off work?
- What procedures, drugs or other treatments are involved in this research?
- What are the risks and discomforts of taking part in this research?
- Are there any benefits to you if you take part in this research?
- What other choices do you have?
- What happens if you do not want to take part in this research?
- What happens at the end of this research?

Answering participants' questions

Before reaching a decision, participants must have an opportunity to ask questions about the research. (See also Assessing Understanding)

Some questions participants should consider before taking part in research:

- Who is doing this study and what is it trying to find out?
- Will this research help in understanding my condition? If so, how?
- What could happen to me, good or bad, if I take part?
- What will I be asked to do?
- What tests or procedures will be done during the study?
- How will my treatment be decided?
- Is it possible I'll receive a placebo?
- Could my condition get worse during the research?
- What will happen if it does?
- Could I stay on my ordinary treatment?
- What other choices do I have if I decide not to be in this study?
- What happens if I say no?
- If I'm hurt or get sick during the research, who will pay the costs that may result?

- If this is a new medicine, will I be insured if things go wrong?
- Who will pay for extra costs related to the research?
- Will I be charged anything or be paid for being in the study?
- If I decide to take part in the research, how will it affect my daily life?
- Will I have to visit the hospital/clinic more often? If so, how much more often?
- Who will be in charge of my care? Will I still be able to see my own doctor?
- How long will the study last?
- What will happen if I change my mind and want to leave the study?
- What must I do if I want to stop being in this study?
- Will I be told the results of the study?
- What will happen to my personal information?
- Who will see my study results and medical records?
- If I have any questions, who should I call?
- Who reviewed or approved this study?
- What is a Research Ethics Committee?

Inclusion of this or a similar list of questions at the end of the informed consent document might encourage participants to raise issues they do not fully understand or are hesitant to ask.

Assessing Understanding[13]

Teach-Back[19]

Teach-Back is a way to confirm that you have explained what a potential participant needs to know. It is not a test of the participant but rather a test of how well you explained a concept.

Investigators should ask questions through-out the consent process to make sure potential participants understand what they are consenting to. For example, start by saying:

- 'It's my job to explain things clearly. To make sure I did this properly I'd like to hear what you understand about this research. Please tell me about this study in your own words?'

Make sure potential participants have understood all the important elements of the study:

Purpose of the Study

- Could you explain to me what we are going to ask you to do in this study? This will help me be sure you understand the research instead of Do you understand the research and what will happen?

- Why are we doing this study – tell me in your own words?
- How would you explain this research to your husband/wife/friend?
- Tell me in your own words what will happen to you if you agree to be in this study?

What is required of participants?

- What are you expected to do if you decide to be in this study?
- How long will this research last?

Risks

- Can you tell me the possible good and bad things which may happen to you if you take the experimental drug?
- What worries you most about choosing to be in this study?
- What is the worst thing that could happen to you if you take part in this research?
- Tell me about some of the side effects we talked about.
- What are some of the side effects that you need to keep an eye on and report to your doctor/ the investigator/ the research nurse?

Benefits

- What chance do you think there is that your condition will get better if you take part in this research?
- What do you expect to gain by being in the study?

Voluntariness

- Will anything happen to you if you refuse to be in the study?

Stopping Participation

- What happens if you say you don't want to be in the study?
- What should you do if you agree to be in this research but later change your mind?
- What options do you have if you choose not to be in this research?

Privacy

- Who will be able to see the information you give us?

No Fault Insurance

- What happens if you get sick or hurt during this study?

Compensation

- What about the costs of being in this research?

- Will you be paid to take part in the study?

Contact Information

- Who should you contact if you have a problem or a question about the research /your rights/ or a complaint?

When participants' answers are unclear the researcher should ask follow-up questions to determine if participants' understanding is correct. The idea is not to quiz potential participants but to foster an open exchange of information and encourage them to ask questions, including some they might not have thought of. Tell participants that the need to ask these questions is due to the complexity of the content rather than the 'fault' of potential participants. Ask potential participants if they have any further questions.

The best questions are non-directive and open-ended. Avoid questions which require a 'yes' or 'no' answer:

- 'What more do you want to know?' instead of 'Do you have any questions?'
- 'What else would you like to know?'

Remember that participants may say they don't have any questions simply because they don't know what to ask.

'Written Tests'

Researchers may also 'test' participants' understanding using a written test, especially when studies are technically complex and involve difficult scientific concepts. Written tests usually include multiple choice or true/false questions, or questions that can be answered in one or two words. Although written tests provide a permanent record of participants' understanding, they are less flexible than oral questioning.

Researchers must also ensure that participants receive the correct answers, with verbal explanations if necessary, after completing a written test.

Unwittingly, 'Tests and quizzes' tend to put the responsibility for understanding on the patient. What distinguishes teach back from a test or quiz is that it puts the onus on us, the investigator or study coordinator, and not the patient. If the patient is unable to teach back the information correctly, then it is because we did not do a good enough job of explaining it.' [19 p. 114]

Patients Highly Dependent on Medical Care[1] pp.38-39, 46-47

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, fearing this may compromise his medical treatment. Characteristic features of intensive care research include difficulties in communicating with patients receiving ventilation assistance and impairment of cognition in heavily sedated individuals. For planned intensive care research and if possible, researchers should obtain informed consent from potential participants before admission to that care.

Delayed consent

In particular circumstances, the REC may approve delayed consent. The HREC should ensure that the researcher provides a clear and full justification for the proposed delay. The HREC may approve a delay in obtaining informed consent for research participation by patients highly dependent on medical care if:

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

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

Context-specific, Required Information in Informed Consent Forms

Contact details for the Human Research Ethics Committee

Informed consent forms must include the following statement (required wording):

'The UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.'

Care after research (also known as post-trial access)

The Declaration of Helsinki (2024)[25] recognises that researchers have an ethical responsibility to research participants and provides the following interpretation of post-trial provisions:

> *"In advance of a clinical trial, post-trial provisions must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or governments for all participants who still need an intervention identified as beneficial and reasonably safe in the trial. Exceptions to this requirement must be approved by a research ethics committee. Specific information about post-trial provisions must be disclosed to participants as part of informed consent."* (Paragraph 34, Declaration of Helsinki 2024).

This interpretation of post-trial provisions emphasises the importance of post-trial access to proven interventions as well as access to other care or benefits.

Investigators should aim to secure the provision of a care after research package, including the investigational product where appropriate, before the initiation of the trial. The lack of such arrangements should be justified to the HREC. The proposed care after research package must be described in the informed consent document.

If a sponsor does not intend to provide post-trial access, the informed consent document must explain the following in large, bolded text:

- Even if a participant's condition improves on the study drug, it will not be provided by the sponsor after the end of the study.
- How participants/patients will be managed at the end of a clinical trial, for example will they resume their previous treatment regimen?

Insurance cover in interventional studies

In interventional clinical research and trials, the consent form must include a simply-worded statement that reasonable medical expenses imposed by research-related injuries will be paid for by the sponsor's insurer according to the SA Good Clinical Practice Guidelines 2020.

In the case of interventional research that is not sponsored by a commercial entity, the University has no-fault insurance cover. (Cross Reference: SOP for Insurance against Research-related Bodily Injury for recommended wording.)

Exculpatory language

Written and oral informed consent must not include any exculpatory language which implies that a participant will waive his or her legal rights or releases or appears to release the investigator, the sponsor or the institution from liability or negligence. 'OHRP and FDA consider exculpatory language to be language which has the general effect of freeing or appearing to free an individual or an entity from malpractice or negligence, or from blame, fault or guilt. Therefore a waiver in an informed consent document of any legal right a participant may have may be permissible so long as that waiver does not have the general effect of freeing or appearing to free an individual or entity from responsibility for malpractice or negligence, blame, fault, or guilt' [20]

Practically-speaking, exculpatory statements are statements in which a participant is asked to agree to or accept something, usually unfavourable to the participant. On the other hand, a statement which provides simple facts is unlikely to be viewed as exculpatory.

Permissible

'As part of the research, the investigators will remove some cells from the blood you donated. The University may commercialise some of these cells. The university will not share any profits with you'.

'Tissue donated by you in this study may be used to establish a cell line that could later be patented. There are no plans to provide financial compensation to you should this happen'.

Exculpatory

'I understand that the institution will not share any profits received from the sale or commercialisation of any cells developed in this study. By consenting to participate, I authorize the use of my bodily fluids and tissue samples for the research described above.'

'I understand that I will not sue the sponsor or investigator for any negligence'.

In short, simply state the factual situation and avoid any statement which requires prospective participants' agreement.

Mandatory reporting and disease notification

If an investigator is planning a study that is designed or likely to produce information that may generate mandatory reporting obligations (such as physical abuse of a child or elder), the permission/assent/consent form(s) must disclose mandatory reporting requirements and how finding such information will be handled. If the investigator is planning a study that requires home visits, the permission/assent form(s) must disclose the obligations of the investigator if such information is discovered unexpectedly (i.e., not anticipated given the study design or participant population) and how discovery of such information will be handled.[21-22] (Cross Reference: SOP for Research Involving Children)

Consent form: The researcher(s) may not be able to maintain as confidential, information about known or reasonably suspected incidents of abuse or neglect of a child, dependent adult or elder, including, but not limited to, physical, sexual, emotional, and financial abuse or neglect. If the researcher is given such information, he or she may report it to the authorities.

Likewise, where indicated, researchers must inform participants about mandatory reporting of notifiable conditions (e.g. tuberculosis) (http://www.sastm.org.za/Home/DiseaseNotification).

Focus groups and participant observation

In the context of focus groups, the informed consent document must include a statement indicating that the researcher cannot guarantee that participants' confidentiality will be maintained as other participants in the group may disclose what was discussed with persons outside the group. The researcher can request that focus group members respect each other's confidentiality by not speaking to others about matters raised in the group.

In the context of participant observation, the researcher should:

- Ensure that participants are aware of the researcher's identity and purpose among the group.
- Disclose and disseminate as broadly as possible through general announcements or other informal means the researcher's purpose, research topic, and data gathering methods. Participants should be aware that any of their interactions with the researcher may constitute some form of data gathering.
- Obtain permission from group leaders or spokespersons, where appropriate, but especially if they can help communicate to a community the researcher's identity, purpose and methods. At the same time, researchers must be careful to avoid situations where such public endorsements or

announcements to the community create pressure to participate. Participants must remain free to avoid all interaction with the researcher.

- To the extent possible, the researcher must try to obtain informed consent from each individual participant with whom the researcher interacts.

Recommended Wording for Consent Forms in Clinical Trials

There are sections of consent forms for clinical trials which are often too legalistic or include excessive medical terminology. To address this problem, the HREC has formulated sample text for clinical trials; specifically, for sections on Study Procedures, Possible Side-Effects of the Study Medicines and Confidentiality. (Similar recommendations for Sample Storage and Future Use, and Insurance Clauses are provided in the relevant SOPs.)

Study procedures/schedule

Many consent forms for clinical trials describe the study procedures in detail over numerous pages, and procedures which are repeated in the study during different visits are described repetitively. The HREC proposes that such detailed descriptions, if necessary, be provided in an appendix to the main consent form.

In the main consent form procedures can be summarised, for example:

'*If you agree to participate in this study, you will then have certain tests and procedures. These include:*

- *Recording your personal information, including for example your name, age, gender, ethnicity;*
- *Physical examination including your height, weight, blood pressure and heart rate;*
- *Blood tests. Blood will be taken from a vein in your arm for testing of your general health and to check your medical condition/disease. We will take XXX ml from your arm XXX times in the course of this study. This is the same as XXX table/teaspoons. The most we will ever take at once is XXX ml (XXX table/teaspoons);*
- *CT Scan. This means that a picture is taken of your internal organs. You will need to lie on a bed and the bed will be moved into the scanning machine. The procedure is painless, but you could feel a bit anxious about being inside the machine;*
- *Questionnaires: you will be asked to answer questions about how you have been feeling, about how your condition/disease has affected your daily activities, your diet and any worries that you have had about your health.*

We give details on each of these procedures and when they will happen in the section called 'Study Procedures' (Appendix 1). In this section we will give information about what taking part in this study will mean to you. For example, you will be given information on:

- *How often you have to come and see the doctor/study nurse;*
- *How long each visit will take;*
- *Which tests and procedures will be performed at each visit;*
- *What samples are being collected and how they will be used*.'

Possible side-effects of the study medicines

'*All medicines can cause unwanted effects. We call these 'side-effects' of the medicine. Because this is research, we do not yet know all the side effects of the medicine that we will ask you to take. Part of the reason for doing this study is to find out if it is safe. It is possible that some of the side effects of the medicine in this study will be harmful for your health – now or in the future. There is also a small chance that you may experience a serious or permanent side effect from the study medicines. This is why it is important that you tell your study doctor or nurse about any side-effect that you have. Please tell them all your symptoms, even when you do not think they are related to the medicine you are taking for this study.*

Because we do not yet know all the side effects of the medicines you are taking, we are careful to monitor your health during this study. This is why we take so many blood samples. For this reason, it is also very important that you come to all the study visits.

The most common side effects that we know about so far are:'

- Give a short list of the known side effects of the drug in plain language. Examples are 'headache', 'diarrhoea', 'skin rash', 'vomiting', 'weakness'.
- Please do not use any medical terms for symptoms.
- Also give an indication of relative severity of these side effects.
- Also give an indication of the known incidence e.g. These types of side-effects occur in one in 5 people.
- (There is considerable variation about what constitutes 'common' side effects vs. rarer side effects. 'Common' varies between 5% and 20%, 'rare' side effects can occur in 1%-5% of people who take the drug.)

'*The most severe side effects that we know so far about are:'*

- Give severe side effects even if they are uncommon. Examples are severe blistering, organ failure, bone marrow suppression, death.
- Again, please use common language to describe these effects.
- Also give an indication of the known incidence, including whether serious side-effects are rare or common for the drug or drug class.

'*A detailed description of all the possible side effects of the medicines in this study is given in Appendix 2 of this form.*'

Confidentiality

'*The sponsor will use the information collected about you for the purposes of this study and for scientific research such as the study of your disease. The sponsor may also use this information to apply for permission to sell the drug in some countries. The information will be stored both on paper and on computer. To protect your privacy, the information will be labelled in a way that will not identify you. The study doctor will give a code to you and your information and samples will be known only by that code. If the results of this study are published, your identity is kept confidential. The information collected may be sent to other members of the sponsor companies, to contractors working for them and to regulatory authorities. By signing this form, you are allowing this use of the study information.*

Your study doctor will keep your personal medical records and a list that links each patient's name to his or her code number for at least XXX years in a secure place. Regulatory authorities, members of the research ethics committee, employees at the study site and of the sponsor will have access to this list. These persons are able to compare and check the study information collected about you with information on your medical records. They will do this to check that the study has been done properly. As far as the law allows, your medical records will not be made public.

You can arrange with your study doctor to see the information collected about you, and you can ask for any mistakes to be corrected.

The sponsor may delay your access to this information if the study is not yet complete. If you decide to leave the study at any time, the sponsor may still use your information collected up to that point.

You will find information about this trial at (give web address), e.g., www.clinicaltrials.gov. This website will not include any information that can identify you.'

Regulatory Frameworks for Informed Consent

South African Department of Health (DoH)[1]

Adults, i.e. persons over the age of 18 years, may make independent decisions about research participation.

The DoH requires the HREC to assess the adequacy and readability of the following elements of information in consent documentation:

- That the person is being asked to participate in research.
- That the choice whether to participate is voluntary.
- That refusal to participate will not be penalised.
- That choosing to participate can be reversed, i.e. the person may decide to terminate participation at any time without explanation or prejudice.
- The purpose and nature of the research procedures and components.
- The research-related activities and procedures that the participant is being asked to consent to.
- The expected duration of participation.
- The nature of the participant's responsibilities.
- The nature of the researcher's responsibilities.
- The anticipated risks of harm or discomfort.
- The measures to minimise risk of harm.
- The extent to which confidentiality is possible.
- Whether reimbursement for expenses is available. Additionally, the informed consent documentation should indicate whether reimbursements are pro rata if the participant does not complete the study; i.e. whether only some of the offered reimbursement is available if participation is stopped before the anticipated end of the study.
- That sponsors of the research and regulatory authorities may inspect research records.
- Who the researchers are and the nature of their expertise.
- The potential benefits, if any, for participants both during and after the research.
- That the research may be terminated early in particular circumstances.
- That the research has been approved by a registered REC (include identifying details).

The DoH guidelines also require researchers to assess potential participants' level of understanding of the information, particularly when 'very vulnerable' participants will be recruited.

South African Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants 2020 (SA GCP, 2020 Guidelines)

NOTE: SA GCP Guidelines state that the informed consent procedure must be 'tailored to local conditions'.[23 pp.32, 57] This implies that, at a minimum, the documentation must be appropriately translated and adapted to meet the levels of comprehension and language needs of local participants. It is therefore incumbent on the Human Research Ethics Committee to ensure that investigators comply with these standards in clinical trials.

SA GCP Guidelines require the following information/explanations in consent documents to be used in clinical trials:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment, where appropriate.
- The trial procedures to be followed, including all invasive procedures.
- The participant's responsibilities.
- Participation in the trial is voluntary and refusal to participate or withdraw from the trial will not prejudice the ongoing care of the person in any way.
- Those aspects of the trial that are not experimental.
- The foreseeable risks of harm or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.
- The expected benefits. When there is no clinical benefit to the participant, the participant must be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the participant and their potential benefits and risks.
- The compensation and/or treatment available to the participant in the event of trial-related injury.
- The anticipated payment, if any, to the participant in the trial.
- The anticipated expenses, if any, to the participant for taking part in the trial.
- Allow access of sponsor, SAHPRA, National Health Research Ethics Council, relevant research ethics committees and/or other regulatory authority to participant records.
- Provide a contact name and number for the principal investigator and directly responsible investigator.
- The identity of the sponsor and any potential conflict of interests.
- The requirement to preserve the participant's confidentiality.
- Expected duration of participant's participation.

- Foreseeable circumstances and/or other reasons under which the participant's involvement in the trial may be terminated.
- Approximate number of participants in the trial.

Once consent is obtained, the investigator must:

- Place a copy of the signed consent form and a source document identifying the study and recording the dates of participation in the participant's medical record.
- Keep the original signed consent form with the trial records.
- Offer a copy of the signed consent form to the participant. (Researchers should remind participants that the consent form includes important contact details, especially phone numbers, in case they have questions or concerns during the study.)

US federally-funded or supported research

Consent requirements

The following eight basic elements are legally required under the Common Rule Regulations: 45 CFR 46.116(a)[24] and FDA 21 CFR 50.25(a):

1. Research statement
   - A statement that the study involves research.
   - An explanation of the purposes of the research.
   - The expected duration of participants' participation.
   - A description of procedures to be followed.
   - Identification of any procedures that are experimental.
2. A description of any reasonably foreseeable risks or discomforts.
3. A description of any benefits to participants or others.
4. Disclosure of appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the participant.
5. A statement describing the extent, if any, of confidentiality and who has access to data.
6. For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what this consists of, or where further information may be obtained or who to call. This is not limited to physical injury. (Note: SA investigators must apply SA GCP Guidelines and, where applicable, UCT's No Fault Insurance Policy.)
7. An explanation of who to contact for answers to pertinent questions about the research (usually the principal investigator and other members of the study team), participants' rights as research

participants (usually the chairperson of research ethics committee) and research-related injuries (usually the principal investigator and emergency numbers).

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits, to which he or she is entitled.

The following six additional elements are legally required under the Common Rule 45 CFR 46.116(b) and FDA Regulations 21 CFR 50.25(b) if appropriate:

1. A statement that the particular treatment or procedure may involve risks to the participants, embryos or foetuses which are currently unforeseeable
2. Investigator-initiated termination of participation.
3. Additional costs to participants of taking part in the research. (Note: The Human Research Ethics Committee does not allow researchers to impose extra research-related costs on participants. Any additional costs must be covered by the investigator, funder or sponsor).
4. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination.
5. A statement that significant new findings developed during the course of the research which may affect a participant's willingness to continue taking part will be provided to the participant.
6. The approximate number of participants in the study.

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Insurance against Research-Related Bodily Injury

Policy

Research participants should not have to bear the financial cost of remedying harms that occur when something goes wrong during a study. Consequently, the University of Cape Town (UCT) requires researchers or sponsors to provide compensation to participants who suffer research-related bodily injuries during clinical studies conducted under its auspices. Although insurance is not a requirement for all research, when research-related bodily injury is foreseeable, researchers, industry and the HREC must ensure insurance cover is available.

UCT carries a No-Fault Insurance Policy to cover non-commercially sponsored interventional clinical research. No Fault compensation implies that participants incurring a research-related injury are not required to prove wrong-doing to be compensated.

Purpose

The purpose of this policy is to explain insurance requirements for industry- and investigator-led clinical research at UCT.

Definitions

Injury is defined as bodily harm. The term does not include:

- Impairment of mental processes or emotional distress
- Injuries from normal diagnostic or therapeutic procedures or interventions which are performed as part of patient management
- Injuries from the normal course of a disease or condition
- Injuries resulting from non-compliance with study procedures.

The argument that a sponsor should pay for pain and suffering, loss of income and other possible claims 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 researcher has been professionally negligent and caused harm. A more detailed account of the legal and moral basis of research-related health insurance in South Africa is provided in Section 3.4.2 of the South African Department of Health's research ethics guidelines[1].

Template for Insurance against Research-Related Bodily Injury

In clinical studies that involve risk of bodily injury, the informed consent form **must** include a simply-worded statement explaining the scope of insurance cover, which includes what a participant is agreeing to and specifies that the participant does not forfeit his or her legal rights.

The template below is based on the SA GCP Guidelines 2020, the Department of Health Ethics in Research Guidelines and *Venter v Roche Products (Pty) Ltd et al* (12285/08) [2013] WCHC 7 May 2013 and on appeal (A11/2014) 22 October 2014.

Notes for researchers (i.e. not for inclusion in the consent form):

i. *Research study insurance does not substitute malpractice insurance.*
ii. *ABPI guidelines on compensation apply only to unlicensed substances used in Phase II and III clinical trials. Therefore, 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.*

'What happens if I get hurt taking part in this study?' (*or an equivalent heading*)

This research study is covered by an insurance policy taken out by the University of Cape Town (or *sponsor's name)* if you suffer a bodily injury because you are taking part in the study.

The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2020 (*or latest version*), which are based on the Association of the British Pharmaceutical Industry Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines.

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 straightaway if you have a side effect from the study medicine.

References

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Privacy and Confidentiality

Policy

Protocols must describe provisions to protect participants' privacy and to respect their right to be free from unauthorised intrusion. Investigators must be particularly vigilant when accessing personal or sensitive information without participants' knowledge or consent, for instance when reviewing medical records or databases solely for research purposes.

All information relating to human participants in research studies must be kept secure and confidential to the extent permitted by law. This is to protect participants from potential harms, including stigmatisation, embarrassment and loss of insurance or employment. Researchers must provide a detailed plan of how participants' private and personal information will be collected, stored and shared with others.

Purpose

The purpose of this policy is to outline minimum requirements to protect participants' privacy and confidentiality when taking part in research.

Definitions

Privacy

Privacy in research is defined as having control over the extent, timing and circumstances of sharing oneself – physically, behaviourally or intellectually – with others. This means respecting an individuals' right to be free from unauthorised or unreasonable intrusion relating to the individual's private information, including control over the extent, timing and circumstances of obtaining such information. Privacy is concerned with participants or potential participants as 'people' in terms of access to personal information from or about them.

Confidentiality

Confidentiality relates to the use of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways inconsistent with the original intent of the disclosure, without that individual's permission.

Sensitive Information

Sensitive information is a sub-set of personal or private information and includes:

- Sexual attitudes, preferences and practices.
- Use of or treatment for alcohol, drugs or other addictive substances.
- Illegal conduct.
- Private information such as genetic information, financial affairs, such as earnings, sources of income.
- Psychological well-being and mental health.
- Stigmatising medical diagnoses such as HIV positivity, psychiatric illness.

Investigators must provide a detailed plan in the protocol and the informed consent documents of how they will protect privacy and confidentiality:

- How will researchers identify and approach potential participants about enrolling in a study? How participants are identified may be an invasion of their privacy and confidentiality; for example, identifying potential participants from medical records to which researchers would not normally have clinical access, or searching databases such as disease registries or pharmacy records which contain personal information about patients.
- How will researchers protect participants' privacy during interaction and data collection in sub-optimal circumstances; for example, recording physical measurements of pre-teens in a school setting, eliciting private medical or financial information in a quasi-public setting?
- What happens to information collected during screening interviews or telephone calls? Will the names of ineligible participants be maintained in a register in case they are eligible for future studies or will the data be destroyed?
- Will members of the research team, including fieldworkers, data capturers and transcribers, sign a confidentiality agreement that they will not discuss or share research information with anyone other than the principal or other named researchers?
- How will data be stored: in locked offices, in locked filing cabinets, on password-protected computers, or on computers that are not linked to a network?
- Will data be coded to remove identifying details? Who will be able to link the code back to the participant's identifying details? Will the key to the code be kept in a separate location or on a separate computer?
- How long will data be stored for?
- How will electronic or paper records of personal/sensitive information be disposed? Will audio or video recordings be destroyed and after what time span?

- Is there an option and is it scientifically acceptable to collect data anonymously without any identifying details?
- Under what circumstances may the coding system be broken?
- Who will have access to participants' personal information?
    - Researchers
    - Regulatory authorities (e.g. SAHPRA, FDA)
    - Sponsors
    - Research Ethics Committee
    - Health Professions Council of South Africa

Written informed consent must be obtained for any public use of audio or videotapes, video recordings, photographs or other images (such as MRIs or CT scans) or verbatim quotations which show participants' faces or disclose unique or identifying details.

Data gathering methods, including interviews, inventories, questionnaires, should include only essential personal information and should be administered using procedures and in circumstances that will protect participants' privacy. Some participants may not want to be seen entering a facility which might lead to stigmatisation (for example, facilities known to treat illnesses such as HIV and tuberculosis or known to provide termination of pregnancies).

If a study involves a focus group:

In the case of focus groups, the informed consent document must state that the researcher cannot guarantee confidentiality as participants may disclose information shared during the focus group session outside the research setting. The researcher can ask participants to respect each other's confidentiality. Participants may also prefer to use pseudonyms in place of their own names.

Suggested wording in an informed consent form:

Taking part in the focus group may involve some loss of privacy; however, we will keep your records as confidential as possible. We will ask you and the other people in the focus group to use only first names during the group sessions. We will also ask group members not to tell anyone outside the group what any particular person said in the group. However, we cannot guarantee that everyone will keep the discussions private. Only the researcher and assistant will have access to your study records and the tape-recordings. After the group discussions have been copied from the tapes, the tapes will be destroyed. Your individual identities will not be used in any reports or publications that may result from this study.

Legally-required release of personal information

If observed or disclosed during a research study, researchers have a legal obligation to report the following:

- Child physical or sexual abuse or neglect.
- Family violence.
- Notifiable diseases, e.g. tuberculosis.
- Information sought under a warrant or subpoena, e.g. criminal or civil litigation.
- In FDA-related research, incidents involving medical devices [21 CFR 803].

When protocols are able to identify in advance that there is a possibility researchers' might need to disclose legally-mandated information, this needs to be stated in the informed consent form so participants can factor any risks to their privacy into their decision to take part in a study. See the policy 'Research Involving Children' for further guidance on mandatory reporting requirements.

Protocols may require researchers and other parties such as transcribers and observers to sign a confidentiality agreement.

Examples of clauses in confidentiality agreements might include the following:

For the researcher(s):

- I/we will maintain patients' confidentiality and wherever possible data will be recorded anonymously.
- I/we will not disclose individually-identifiable information except to researchers who sign this agreement, and members of the Human Research Ethics Committee, which is responsible for monitoring, auditing and reviewing the activities of researchers engaged in human research.
- I/we will store the information in a secure place (e.g. locked cupboard or password-protected computer).
- I/we will destroy any identifiable information as soon as the purpose of data collection has been achieved.
- I/we will report and publish research findings in a way that protects participants' identities.
- I/we the undersigned acknowledge and accept these commitments.

For fieldwork assistants/transcribers:

- I/we will keep all the research information shared with me/us confidential by not discussing or sharing the information in any form or format (e.g. tape or audio recordings, transcripts, field notes).

- I/we will keep all the research information in any form or format (e.g. tape or audio recordings, transcripts, field notes) securely in a locked cupboard while it is in my/our possession.
- After I/we have reported to and discussed my/our findings with the researcher(s), I/we will destroy all research information in any form or format (e.g. tape or audio recordings, transcripts, field notes, information stored on a hard drive) that I/we do not return to the researcher(s).
- I/we the undersigned acknowledge and accept these commitments.

Databases, Registries and Repositories

Databases and tissue banks are exclusively concerned with obtaining, maintaining and accessing participant health information, often including personal health information, for research, over long periods of time. This may pose particular risks to participants' privacy and confidentiality. The Human Research Ethics Committee requires researchers to explain in the initial repository protocol and informed consent form:

- What information will be collected.
- How it will be stored.
- Who will have access for research purposes.

The Committee also requires that new protocols be submitted for each future use of stored data or specimens which include personal identifying details. See the related policy on 'Databases, Registries and Repositories' for more detailed guidance on maintaining confidentiality when collecting, storing and sharing information in studies which use databases, registries and repositories.

Collection and Storage of Data or Biological Specimens for Research Purposes

Policy

Research involving the collection of data and/or biological specimens may need added protections; for instance, genetic studies where findings may carry psychological, social or economic risks for an individual, a family or a community will require a detailed plan of how confidentiality would be protected. In studies using anonymous specimens and perceived risks are lower, the protocol would need to state what measures will be taken to de-identify samples to render them anonymous.

Purpose

The purpose of this policy is to outline specific ethical issues and regulations, including informed consent requirements, in research which involves the collection and storage of data and biological specimens.

Additionally, this policy aims to harmonise its recommendations with existing and future ethical guidelines and consent templates developed by the Human Heredity and Health in Africa (H3Africa) Initiative http://h3africa.org/ . "The vision of H3Africa is to create and support a pan-continental network of laboratories that will be equipped to apply leading-edge research to the study of the complex interplay between environmental and genetic factors which determines disease susceptibility and drug responses in African populations. Data generated from this effort will inform strategies to address health inequity and ultimately lead to health benefit in Africa." http://h3africa.org/about/vision

Definitions

Biological Material

'Biological material' 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.[1]

Donor

'Donor' means a person from whose body human biological material has been removed or withdrawn for the purpose of genetic testing, genetic training, genetic health research and therapeutics.[1]

Anonymous Samples or Data

Data or biological specimens obtained by a researcher without any identifying information and without a link to a specific participant or donor.

Identifiable Samples or Data

Data or biological specimens obtained by the researcher with identifying details such as name, folder number or address.

Identifiers

Information that could be associated with a specific research participant such as name, address, medical folder number, phone or fax number or biometric identifier (e.g. finger print).

Coded Data or Samples

Identifiers have been replaced with a number, symbol or a letter and a key exists to decipher the code, allowing linkage of the code to a specific individual.

Broad Consent

Broad consent refers to a process by which individuals donate their samples for a broad range of future studies, subject to specific restrictions such as approval by a human research ethics committee.[2]

Blanket Consent

Blanket consent refers to a process by which individuals donate their samples without any restrictions. This standard operating procedure does not support blanket consent for future storage of samples.

Retrospective Study

A study which uses specimens that already exist when Human Research Ethics Committee approval is requested. This includes tissue collected for diagnostic purposes and then stored; for example, pathology samples or the secondary use of specimens previously collected for another research proposal and subsequently stored in a tissue bank.

Policy on the Use of Biological Specimens in Retrospective Studies

Use of existing or archived specimens collected for clinical or diagnostic purposes, including waste and left-over samples, requires expedited review. The Chair or designee must determine whether consent was obtained at the time of collection and the nature of that consent.

If subsequent use falls within the scope of the original informed consent, then additional informed consent is not required. Researchers wishing to use information or specimens for research that differs in any way from that described in the original informed consent form must submit a new or amended consent document for approval before initiating the new activity. The Chair or designee will decide on a case-by-case basis whether a protocol requires expedited or full committee review.

As a general principle, written informed consent is not needed if:

- Samples will be used anonymously, and the results will not place an individual, family or community at social, psychological or economic risk.
- If the link to identifiers exists but is not provided to the research team and the results will not place an individual, family or community at social, psychological or economic risk. The investigator holding the code or link must sign a written agreement that he or she will not release the identifiers to the research team. This written confirmation must be included in the submission to the Human Research Ethics Committee.

If the samples can be linked to identifiers, the Chair or designee will decide on a case-by-case basis whether a protocol requires expedited or full committee review.

Removal or Withdrawal of Biological Samples from Living Persons

'A competent person may not remove any biological material from the body of another living person for purposes of genetic testing, genetic training, genetic health research or therapeutics, unless it is done with written informed consent of the person from whom such biological material is removed'.[1]

Removal of Biological Samples from Deceased Persons

'Any organisation or institution or person that intends to use tissue from a deceased person for purposes of genetic testing, health research and therapeutics, where no consent has been given by the deceased person before her or his death and where there is no evidence that the removal of the tissue or cells would be contrary to a direction given by the deceased before his or her death, must take steps … to locate the spouse, partner, major child, parent, guardian, major brother or major sister of a deceased person, in the specific order mentioned, in order to obtain consent.'[1]

Research Utilising Embryonic Stem Cells and Umbilical Cord Blood Stem Cells

'Excess embryos obtained from in vitro fertilisation may be used to produce embryonic stem cell lines for the purpose of research, provided that the competent person obtains written informed consent from embryo donor or cord blood donor'.[1]

Research Utilising Primordial Germ Cells

'Research on primordial germ cells obtained from aborted foetuses may be carried out provided that the competent person (e.g. registered medical practitioner or nurse) obtains prior written informed consent from the donor of the aborted foetus.'[1]

Human Biological Material Registers

'An authorised institution that performs genetic research or generates embryonic stem cells, must have separate registers to record such genetic research or generation of embryonic stem cell lines. The authorised institution must submit details of the registers … to the Minister by the end of March of each year.'[1]

'An authorised institution that keeps or discloses genetic material records or other individually identifiable or related health information in any form … must ensure the:

- Information is used for the purpose for which it was originally intended.
- Written informed consent of the user or donor is obtained for long term storage of genetic material, stem cells or research findings.
- The records are destroyed after the purpose for which they were created has been served.
- The information is treated as anonymous if used for research purposes.'[1]

Considerations for Research Involving Genetic and/ or Genomic Material

Depending on the scope or nature of the research, complex ethical issues may arise when conducting studies involving genetic material and/or genetic testing:

- Participating in research using genetic material may involve psychosocial risks to individual participants, their families and communities. For example, social risks may include a breach of confidentiality which could affect family relationships, lead to stigmatisation or loss of insurability; and psychological risks may include the impact of learning a genetic diagnosis, and the impact if no effective therapy exists.
- On the other hand, where genetic research is conducted using anonymous samples, there may be minimal risk of psychosocial harm to individuals or groups from whom samples are acquired, for instance, anonymous samples of tumour cells analysed for specific genetic information.

For studies which carry distinct psychosocial risks, investigators need to consider the following ethical issues in their protocols:

- Are clear guidelines in place for disclosure of information to participants, including interim or inconclusive research results?
- Will participants be protected against disclosure of medical or other personal information about themselves to other family members?
- Will participants be given the option not to receive information about themselves?
- Will limits on such protections be clearly communicated to participants, including obtaining advance consent should such disclosures need to be made, for example, when family members will be warned about risks to their health?
- Will participants receive counselling as part of the process of communicating test or other findings to participants?
- Will participants be told about possible incidental findings such as paternity, a disease or condition other than the one under study?
- Will the data be protected from disclosure to third parties such as employers and insurance companies?
- Will participants be informed of potential risks of a third party becoming aware of the study findings?
- Will data be stored in a secure manner? Describe measures.
- Will data be coded to protect participants' identity? Describe measures.
- Are there adequate provisions for protecting against misuse of tissue samples, for example, obtaining consent for any use other than specified in the study?
- Have participants consented to future use of stored specimens in new studies?
- Are there adequate provisions to manage data or specimens if a participant withdraws from the study?
- Does the researcher plan to disclose research findings to a participant's personal physician for clinical purposes? Is this appropriate? Will participants have an option to refuse?
- In the event of publication, will participants' privacy be protected? Have participants been informed about how findings might be published?
- If research involves family members has the appropriateness of different strategies for recruitment been evaluated? If a researcher wishes to contact relatives of an index case, the index case or proband must be asked whether this contact is acceptable. If the index case declines to allow contact of relatives, the study may not proceed. If consent is given, the following recruitment strategies are recommended:

- The researcher may provide the proband with a packet of information about the study and ask that he or she distributes the information to eligible relatives. The packet should include instructions about how to contact the researchers if the relative has further questions. Researchers can include postcards for relatives to return indicating their interest in being contacted about the study.
- The researcher may ask the proband to provide limited contact information (name, address, phone number) for relatives who are eligible for the study. Researchers may send information to the named relatives about whom to contact for further information if they are interested in taking part.
- The researcher could ask the proband which option he or she feels is the more appropriate.

- If a researcher wants to collect information about relatives from the proband, the researcher must collect the least identifiable information necessary to meet the scientific goals of the study. If the researcher plans to collect personal information about family members, strong confidentiality protections need to be in place. Alternatively, the researcher should obtain Human Research Ethics Committee approval to recruit family members into the study and collect information from them directly with informed consent.
- The informed consent form should explain the following:
  - The kind of information researchers will feedback to participants (e.g. only information the researcher feels is reliable, or no genetic information will be disclosed), a justification for either decision, and at what point in the study they will receive that information.
  - The risks associated with taking part in genetic/genomic research.
  - Participants may learn things about themselves or their family that they did not really want to know, or that they may be uncomfortable knowing.
  - If participants want information, precautions must be in place to minimise the potential harm of receiving bad news and to preserve the confidentiality of the results. Ideally, genetic findings should be communicated in a clinical rather than a research relationship with the participant.
  - Information about participants may be learned by others in their family.
  - The extent to which findings will and are able to be kept confidential.

Guidelines for Information Sheet for Storage and Future Use of Biological Samples

- The information sheet and consent form for *future* storage of genetic and/ or genomic information should not be longer than two pages and must be separate from the ICF for the main study.
- Explain that the researcher is seeking permission to store participants' unused samples for possible future use in either his or her own research or for someone else's research.
- Explain that participants need to decide about the future use of their blood, tissue, sperm or sputum sample because they have given consent only for the study they are presently taking part in.
- Explain that sometimes people do not want their samples used for research into areas they do not agree with, for example research into birth control. Use lay terms to explain different research possibilities.
- State that participants can choose if they don't want their sample used at all.
- If genetic and/ or genomic research is a possibility, explain what this is and any implications for participants or their families.
- Inform the participant that at present, the researchers can trace which blood, tissue, sperm or sputum sample belongs to the participant. Participants must choose whether they want to let researchers keep the sample but remove the identifiers, or whether they would not mind if the researchers know whose sample it is. Explain the risks and benefits of each option.
- Inform the participant of a researcher's obligations in cases where the sample remains linked; for example, an obligation to inform a participant of results which have immediate clinical relevance such multi-drug resistant tuberculosis.
- Explain that any research which uses participants' samples must be approved by the Human Research Ethics Committee.
- Explain that the participant may refuse to allow samples to be stored with no loss of benefits and that participation in the current study will not be affected in any way.
- Inform participants that they may withdraw permission at any time and provide the necessary contact details of the researcher or institution.
- Explain how confidentiality will be maintained including any limitations.
- Inform participants of no direct benefit, if applicable; inform of other potential benefits as appropriate: advancement of knowledge, clinical relevance to individual, family or society as a whole and long-term benefit if researcher plans to re-contact participants to disclose clinically relevant information.

Consent Guidelines on Storage Options [3, 4, 5]

If any of the (TYPE of SAMPLE i.e. blood, tissue) I have provided for this research project is unused or left over when the research is completed (tick ONE choice from each of the following boxes):

☐ I do not give permission for my [TYPE of SAMPLE] sample to be stored for future research.

☐ I give permission for my [TYPE of SAMPLE] sample to be stored indefinitely and used in future research of any type which has been approved by a registered or accredited HREC.

AND

☐ I want my identity removed from my [TYPE of SAMPLE] sample

☐ I want my identity kept with my [TYPE of SAMPLE] sample.

I have read the information, or it has been read to me. I have had the chance to ask questions about it and I am satisfied with the answers I was given. I consent voluntarily and understand that I have the right to withdraw my consent without this affecting the research I am currently taking part in or my medical care.

NOTE: H3Africa-funded studies must comply with the informed consent guidelines developed by its Ethics Working Group.[5] For instance, H3Africa has developed specific consent guidance for sharing stored data for secondary analyses by other investigators not directly involved in the research, as well as the development of cell lines.

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3. Department of Human Genetics has developed DNA consent forms in Afrikaans, English and Xhosa which can be adapted for research purposes. These are available at: http://web.uct.ac.za/depts/genetics/ under Genetic Testing Protocols and Policy Guidelines.
4. World Health Organization. Informed Consent Templates. Consent for Storage and Future Use of Unused Samples. Available on the HREC's website: http://www.health.uct.ac.za/research/humanethics/forms/
5. H3Africa Guidelines for Informed Consent. Developed by the H3Africa Working Group on Ethics and Regulatory Issues for the Human Heredity and Health (H3Africa) Consortium, August 2013. http://h3africa.org/ethics/17-ethics/71-informed-consent

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Databases, Registries and Repositories

Policy

Databases, registries (data banks) and repositories (tissue banks) all involve the collection of information and/or biological specimens over time. Databases, registries and repositories may be created for research, diagnostic or clinical purposes or both. With advances in molecular techniques and information technology, data and tissue banks constitute a valuable resource for researchers to address questions extending far beyond those envisaged when the data and/or specimens were first collected. To ensure that participants' privacy and confidentiality are protected, databases, registries and repositories must develop procedural mechanisms for secure collection, receipt, storage and sharing of information and specimens.

Note: data banks, registries and tissue banks are all considered 'repositories' for ethical and regulatory purposes. Any reference to repositories in this policy applies equally to data banks, registries and tissue banks.

See related policy on 'Collection and Storage of Data or Biological Specimens for Research Purposes'.

Purpose

The purpose of this policy is to outline ethical requirements for establishing databases, registries and repositories for research purposes.

Definitions

Databases

Databases are collections of information elements (i.e. data) arranged for ease and speed of search and retrieval. Databases may be maintained electronically or as paper-based systems. Examples of databases include:

- A set of observations (i.e. data) from a longitudinal research study.
- An electronic file of a clinic's patients.
- A collection of diagnosis, treatment and follow-up information on a sub-set of hospital patients, for example patients with diabetes or admissions to an intensive care unit.
- A file of outcomes information compiled for quality assurance activities.
- Names, diagnosis and contact information of potential research participants in specific research fields; for example, HIV prevention research.

Registries

Registries or data banks are collections of information or databases whose organisers:

- Receive information from multiple sources.
- Maintain the information over time.
- Control access to and use of the information by multiple users or for multiple purposes which may change over time.

Registries often contain codes that link information and specimens to their donors' identity. Examples of South African registries include the National Cancer Registry, the Hereditary Colorectal Cancer Registry and the South African Bone Marrow Registry.

Repositories

Repositories collect, store and distribute human materials for research purposes. Human biological material may include blood, urine, faeces, bone marrow and cell aspirates. In research protocols, human biological materials are usually referred to as 'tissues' or 'specimens'. Repositories usually include demographic and/or medical information about the individuals from whom the specimens were obtained, and often contain codes that link the information and specimens to the donors' identity.

Human Research Ethics Committee Oversight of Databases, Registries or Repositories

The role of the Human Research Ethics Committee varies with the intent and use of a repository:

- Committee approval and oversight are not required for repositories created and operated for non-research purposes. Such purposes may include diagnosis, treatment, billing, quality assurance and quality improvement, and public health surveillance. These data cannot be used for research unless the repository or database is registered with the Human Research Ethics Committee, or specific research ethics approval is sought prospectively on a study-by-study basis. Human Research Ethics Committee approval of a protocol wishing to use identifiable information from a repository created for non-research purposes will be made on a case-by-case basis. An example might include use of a clinic's patient database to identify and recruit potential research participants.
- Repositories created, maintained and used for present or future research purposes must obtain Committee approval. Researchers can apply to establish a repository for research purposes, or to convert an existing research or non-research database into a research repository, by completing Form FHS020 available for downloading at: http://www.health.uct.ac.za/research/humanethics/forms/

Principal investigators do not need to include a protocol when they submit an FHS020 form. However, they need to submit:

- An annual progress report (FHS017) which must reflect all new research undertaken by PIs or named co-investigators which uses data from the repositories.
- A full application form (FHS013) for approval of all new studies undertaken by researchers who are not named co-investigators on the FHS017 form.
- A full application form, including a departmentally-reviewed protocol, for research undertaken for degree purposes. In the case of research for a master's or doctoral degree, the student in question should submit the application form and protocol. The study will receive its own HREC reference number which will be linked to that of the registry.

Informed Consent

Since a repository with linked or identifiable information may be used by many researchers and for many studies over time, donor-participants' informed consent should include the following information in simple language:

- The general concept and purpose of repositories:
  - Name and purpose of specific repository for which consent is requested.
  - How the repository works.
  - Types of research the repository supports.
- Conditions and requirements under which data/specimens will be shared with researchers.
- How participants' privacy and confidentiality will be protected.
- Specific risks related to use and storage of data/specimens, particularly if personal identifiers are retained.
- When human genetic research is anticipated, information about potential consequences of genetic testing (e.g. paternity determinations, insurance risks, reproduction decisions) and associated confidentiality risks.
- Potential benefits, if any:
  - Inform participants if there is no direct benefit.
  - Include other potential benefits such as societal benefit through the advancement of knowledge.
- Where applicable, the fact that specimens may be:
  - Used for future research not yet identified.
  - Shared with or transferred to other institutions.

- A statement that participants may withdraw their consent at any time either by requesting that data or tissue be destroyed or that all personal identifiers be removed.
- Information about the length of storage.
- When consent to use information or specimens will expire.
- Information about possible secondary use of stored tissue or the possible creation of an immortalised cell line based on the specimen.
- Obtaining informed consent to use data or specimens stored in a repository created for non-research purposes may be problematic since research was not intended at the time of collection. Where feasible, the Committee may require a researcher to obtain informed consent. However, the Committee may approve a waiver of consent requirements if:
- The research involves no more than minimal risk (e.g. anonymous use of samples); and
- The waiver will not adversely affect participants' rights and welfare; and
- The research could not practically be carried out without the waiver.

When information and/or specimens are provided to researchers outside UCT's Faculty of Health Sciences and its affiliates, use of the data and/or specimens must comply with any additional requirements of the recipient institution and its Human Research Ethics Committee or Institutional Review Board. Likewise, the recipient institution must agree to comply with all terms stipulated by the donor institution. These inter-institutional agreements should be confirmed in writing.

References

1. Sobel M, Hansen K. Banking of Human Biological Materials for Research. In: Bankert EA and Amdur RJ editors. Institutional Review Board, Second Edition. Jones and Bartlett Publishers, Canada, 2006. Pp.434-437.

Children in Research

Policy

Since research is vital to improve the health and wellbeing of children, the Human Research Ethics Committee (HREC) faces a delicate balance between protecting children, widely considered a vulnerable group *from* research, and protecting children *through* research. Legal, regulatory and ethical guidance offers added safeguards to protect children who participate in research. Importantly, children should not bear more risk than absolutely essential to answer questions that can only be addressed in research with them. The HREC must determine that research involving children is scientifically necessary and ethically sound; for instance, research-related risks to minors must be minimised and within permissible levels, parental permission and assent must be appropriate and privacy and confidentiality protections adequate. The HREC should include members with sufficient expertise and experience to evaluate the distinctive features of neonatal, child and adolescent research.

Purpose

The purpose of this policy is to outline general and specific ethical, regulatory and legal requirements for conducting research with children and adolescents.

Central Ethical Issues in Research with Children

Children are vulnerable in the research context

- Their physical, cognitive and emotional development is incomplete.
- They are dependent on others for their wellbeing.
- Young children typically defer to adult authority and power which may compromise voluntariness.
- They are legally unable to make independent decisions about whether to take part in research.
- Children living in poverty are particularly vulnerable; for example, parents may have a poor understanding of research and may be more susceptible to pressures of enrolment, such as access to better health care.[1 2]

Generally, children ought not to bear the burdens of research unless absolutely necessary; yet, if they are to benefit from health-related advances then children must take part in relevant health research

- Researchers face the ethical dilemma of how to balance protection and access: fairness demands protection and opportunity for inclusion.

The extensive off-label use of diagnostic and therapeutic interventions to treat children has led to the conclusion that children are already being used as research participants without the benefit of ethical and regulatory oversight, or a systematic commitment to discover what works best. Some argue that off-label use of diagnostic and therapeutic interventions has become the standard of care for many children. If new interventions are only tested in adults but are used in children, then children are exposed to risks from interventions not specifically proven safe and effective in this population. Clinicians face difficult choices when treating children. If they use untested interventions they face dangers of under-dosing, over-dosing or prescribing unsuitable paediatric formulations. If, on the other hand, clinicians use only proven interventions, they are severely limited in their diagnostic and therapeutic options. So, in our efforts to protect children from research-related harm, we may actually deprive them of the benefits of health-related research.

Researchers must resolve the tension between advancing knowledge to benefit future children and limiting potential harm to individual children

- The most intractable ethical issues arise in non-beneficial research where there is no prospect of direct benefit to individual child-participants but there is risk of harm. Is it a greater wrong to use individual children where there is no prospect of individual benefit (i.e. to serve societal rather than the child's own interests) or to fail to obtain vitally important information that may benefit all children, such as vaccine or pharmacokinetic (PK) studies? Researchers and the HREC face dual obligations to protect individual child-participants and to protect children as a class. Community engagement is important to gauge whether the research is consistent with societal and parental values, is broadly viewed as a valuable paediatric project and has the community's support.

Determining the minimal risk standard in research with children

- Minimal risk is a useful sorting mechanism which draws attention to riskier research and acts as a threshold limiting the amount of non-therapeutic risk in research. Research involving more than minimal risk that does not offer a child-participant the prospect of direct benefit must not exceed the threshold of a 'minor increase' over minimal risk. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in research are not greater than the harms or discomfort ordinarily encountered in daily life in a stable society or during the performance of routine physical or psychological examinations or tests. This is also called the 'everyday risks standard' or the 'routine examination' standard.

The 'everyday risks standard' raises the ethical question of what risks count as the risks of daily life: should risks of daily life be measured against the risks healthy children typically face in everyday life (i.e. an absolute interpretation) or against actual risks in the background of children who take part in research (i.e. a relativistic interpretation). Arguments against a relative standard of minimal risk claim that it would impose a disproportionate burden of research on sick or disadvantaged children. According to this view, children with a specific disease or condition face certain risks such as extra lumbar punctures or venipunctures because they have a specific disease or condition. Hence these risks are already part of their daily lives, that is to say they are already risks of daily life. This raises the ethical question of how a relativistic argument could be justified without violating the principle of justice. Justice demands that research not unduly involve groups unlikely to benefit from research; but in this case children with a specific disease or condition may benefit from the research. If the only way to provide some benefit is to conduct research among these groups of children, then a relative standard may be justified by the prospect of future benefits among those most likely to gain from the findings of the research. In short, reasonable differences exist regarding the interpretation of the minimal risk standard in research involving children. (Binik and Weijer offer an incisive critique of this highly ambiguous, yet central, concept underpinning research with children.[3])

Definitions

For purposes of this SOP:

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

Assent means a minor's affirmative agreement to participate in research. Mere failure to object should not be interpreted as assent.

Best interests means significant decisions affecting a minor's life should aim to promote, amongst others, the minor's physical, mental, moral, emotional and social welfare.[4]

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

Child means a person under the age of 18 years (s 28 Constitution; s 1 Children's Act 38 of 2005). See the Children's Institute website for up-to-date information on the Children's Act http://www.ci.org.za/index.php?option=com_content&view=article&id=546&Itemid=30

Child-headed household means a household per s 137 Children's Act 38 of 2005. **Condition** means physical and psychosocial characteristics understood to affect health.[4] **Dissent** means a child's refusal to take part in research and must be respected. **Guardian** means a person appointed by a court to look after the financial and welfare interests of a minor, or a person appointed by a parent with sole responsibility for the minor in terms of the parent's Will.

Harm means physical, emotional, psychological, social or legal harm. **Minor** is a person under the age of 18 years (Section 17, Children's Act No. 38 of 2005). The terms minor and child are used interchangeably. Minors are legally incapable of performing legal transactions without assistance from a parent or guardian. In the research context, this means that, in principle, anyone under the age of 18 years may not choose independently whether to participate in research; a parent or guardian must give permission for the minor to choose. **Minimal Risk** means the probability and magnitude of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in daily life in a stable society or in routine medical, dental, educational or psychological tests or examinations.[4] **Neonate** means a new-born child, including an infant less than a month old. **Non-therapeutic research** means research that includes interventions that do not hold the prospect of direct health-related benefit to the participant but may produce results that contribute to generalisable knowledge.[4]

Orphan means a child who has no surviving parent caring for him or her (s 1 Children's Act 38 of 2005). **Parent** includes an adoptive parent (s 1 Children's Act 38 of 2005). **Therapeutic research** means research that includes interventions that may hold out the prospect of direct health-related benefit for the participant.[4]

Vulnerable persons means those persons at increased risk of research-related harm, or who are limited in their freedom to make choices, or relatively incapable of protecting their own interests.[4]

Minimal Conditions for Research Involving Minors

The following considerations are critical when researchers develop and the HREC reviews proposals to involve child-participants:[5]

a. Children should participate in research when their participation is scientifically indispensable to the research. Research should investigate a problem relevant to children. The protocol should provide sufficient information to justify clearly why children should be included as participants.
   Clinical research, in particular, is only justified when it addresses an important paediatric health need and necessary information cannot be extrapolated from research using consenting adults.

For example, a condition or disease does not occur among adults or important safety and dosing information cannot reliably be extrapolated from adverse event information obtained in equivalent adult research. In the case of clinical interventional research, equipoise should exist; in other words, in the research context uncertainty prevails amongst health care experts about whether a particular treatment or intervention is better than another.

b. Children should participate in research only where such research poses acceptable risks of harm. That is, research involving minors should be approved only if:
    i. The research, including observational research, is not contrary to the best interest of the minor;
    ii. The research, including observational research, places the minor at no more than minimal risk of harm (i.e. the 'everyday risks standard' which means the risk of harm is commensurate with daily life in a stable society or routine medical, dental, educational or psychological tests or examinations – referred to as 'negligible risk' in some guidelines); or
    iii. The research involves greater than minimal risk of harm but provides the prospect of direct benefit for the minor. In a clinical study, direct benefit generally means a health benefit to an individual participant that results from the research intervention being studied and not from other clinical interventions included in the protocol such as increased health monitoring or compensation for participation. The degree of risk of harm should be justified by the potential benefit; or
    iv. The research, including observational research, involves greater than minimal risk of harm, with no prospect of direct benefit to the minor, but has a high probability of providing significant 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.
    vi. Where appropriate, the minor will assent to participation.

c. Research involving children must be reviewed appropriately. The National Health Act distinguishes research with children as 'therapeutic' and 'non-therapeutic' research. The intention is to ensure HRECs give due consideration to the degree of risk of harm posed by a proposal and the likelihood of benefit to the child-participant.

This distinction is of little practical import since most research involves a mix of 'therapeutic' and 'non-therapeutic' interventions or components and reviewers usually assess the proposal as a whole. (In its Paediatric Section, the FDA provides examples of ethical considerations when reviewing non-therapeutic research, including components analysis: http://www.fda.gov/scienceresearch/specialtopics/pediatrictherapeuticsresearch/ucm106601.htm.

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, the HREC has permission to exercise the Minister's delegated power to approve research with children that includes non-therapeutic components. The HREC must ensure that its deliberations on these components are properly minuted and recorded as required by the Regulations.[6] This includes the review of the researcher's detailed explanation and justification for the proposed non-therapeutic study. A template of 'Conditions for Approval of Non-therapeutic Research with Minors' is provided at the end of this SOP and in the New Protocols Applications Section on the HREC's website. The HREC must include members with appropriate paediatric research experience.

e. Children should participate only where the proper written permissions have been obtained. The general principle is that minors cannot agree to research participation without assistance of a parent or guardian (exceptions to the general principle are discussed in the section Minors' Independent Consent). This principle holds despite exceptions in the Children's Act 38 of 2005 for consent to medical treatment and surgical operations (s 129); consent to HIV-testing (s 130); and the exception for female minors created in the Choice on Termination of Pregnancy Act 92 of 1996 (s 5(2)). Consequently, in principle, the consent process for a minor's participation in research requires

- Permission in writing from parents or legal guardian for the minor to be approached and invited to participate (in accordance with s 10 of the Children's Act 38 of 2005);
- Assent from the minor in writing (i.e. agreement to participate) if he or she chooses to participate.

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

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

Parental Permission[5]

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

Parental permission and the minor's decision must be consistent, i.e. if the minor decides not to participate, the parent may not override this decision. If the parent is reluctant for the minor to

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

Orphans without Guardians[5]

Introduction

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

Justification

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

Pragmatic parental substitutes

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

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

This guidance takes its lead from the Constitution, the Children's Act, the National Health Act, the Criminal Law (Sexual Offences) Amendment Act; the South African Good Clinical Practice Guidelines (2020)

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

1. The risk standards set out in 'Minimal conditions for research involving minors(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 relevant to minors.

NOTE: if the proposed research holds more than a minimal risk of harm, there must be a compelling justification for why orphans should be included as participants, e.g. the research focus is particularly relevant for orphans without guardians and cannot be studied without their enrolment.

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

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

Minors' Independent Consent[5]

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

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

Mandatory Reporting Obligations[5]

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

i. **Reporting obligations for abuse and neglect**

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

Depending on the nature of a study, researchers need to inform children and parents or legal guardians in the assent and consent documents of researchers' obligations to report ill-treatment. Based on this information, parents and minors may choose not to take part in a study.

ii. **Reporting obligations for under-age sexual activity**

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

The Sexual Offences Act differentiates between adolescents (12 - <16 years) and older minors (16 and 17 years). In the case of children younger than 12 years, sexual activity is unlawful even with consent. For adolescents, the situation is as follows. The *Teddy Bear Clinic* case[7] found criminalisation of consensual sexual acts between adolescents aged 12 – <16 years to be unconstitutional, on the basis that adolescents should not be subjected to criminal sanctions when they exercise their entitlement to determine their personal relationships in light of their rights to autonomy, dignity and privacy. The Constitutional Court imposed a moratorium on action against adolescents in terms of ss 15 and 16 of the Sexual Offences Act.[8] This moratorium of 18 months is to give Parliament time to revise the offending legislative provisions by April 2015. Consensual sexual acts between adolescents aged 12 - <16 years are not criminal and are not reportable. Sexual acts with adolescents aged 12 - <16 years by an adult or a person >16 years, *even if consensual*, are criminal and reportable. Sexual acts with children <12 years are criminal and reportable.

iii. **Sexual and reproductive health research with minors**

Research with minors that focuses on their sexuality and reproductive health is likely to encounter instances of abuse and underage sexual activity. The dilemma for researchers is whether to ignore the strict letter of the law or to report as indicated in terms of the Sexual Offences Act and the Children's Act.

The clash of interests is obvious, e.g. using the law to protect the minor from abuse may have the unintended consequence of increased harm (physical and social) for that child.

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

Examples of wording in the informed consent and assent forms:

Consent form

The researcher(s) may not be able to keep confidential, information about known or reasonably suspected incidents of deliberate neglect or physical, sexual or emotional abuse of a child. If a researcher is given such information, he or she may report it to the authorities such as child welfare or the police.

Assent form

We will not tell anyone what you tell us without your permission unless there is something that could cause harm to you or someone else. If you tell us that someone is or has been hurting you, we may have to tell that to people who are responsible for protecting children so they can make sure you are safe.

General Pointers for Protocol Review

a. Children may be included in research only if their participation is necessary to answer the scientific question being investigated and cannot be obtained from consenting adults. This means that researchers must always justify the inclusion of children in a study.

b. Consider potential benefits, harms and discomforts from the child's perspective:

   i. The research environment should be child-friendly with age-appropriate furniture, play equipment and food.

   ii. Where possible, coordinate the collection of clinical and research samples. If this is not possible, the HREC needs to consider the *cumulative effect* of discomfort caused by a number of blood draws over the duration of a study.[9]

   iii. Only research staff with paediatric expertise and/or experience should perform research-related procedures.

   iv. Where possible, use topical anaesthesia such as EMLA during potentially painful procedures.

   v. Researchers may not make more than two attempts to draw blood intended solely for research purposes.

   vi. Where appropriate, protocols must include data monitoring mechanisms that allow rapid termination in the face of unexpected problems or adverse events.

   vii. Where possible, use laboratories experienced in handling small volumes of blood.

   viii. Consider less invasive alternatives to blood samples for research purposes, such as saliva for extraction of genomic DNA.[9]

   ix. Where possible, consider using population PK studies involving larger numbers of children but a reduced number of blood samples from individual participants.[9]

   x. A recent review article notes that existing guidelines relating to blood sample volumes in research with children are not evidence-based, pointing to a need for further research '… designed to more clearly define safe limits of blood loss over appropriate periods of time relevant to different clinical trial settings'.[9 p. 1010]

c. Interpreting and clarifying regulatory language can be daunting and can lead to inconsistent review of paediatric protocols. The Committee should consider using an *age-indexed* interpretation of minimal risk standard.[10] This would introduce a measure of flexibility when evaluating the risks of daily life and routine examinations. For example, questions about sexuality, substance use and depression are (or at least, should be) part of routine medical and psychological examinations of children beginning in early adolescence. Likewise, the Committee needs to be flexible in its interpretation of assent and dissent.

The earliest age at which assent is recommended is arbitrarily set at 7 years. However, the assent process should be developmentally appropriate depending on a child's age, maturity and experience with a disease or condition. The child must agree whether the research as he or she understands it is an activity which he or she wants to take part in. Researchers must be sensitive to a child's non-verbal cues reflecting his or her willingness or unwillingness to take part. The older the minor, the more an assent form will mirror a parental consent form. Dissent means a child's refusal to take part and must be respected. In practice, reasonable people may disagree as to exactly when (predictably) resistance such as crying becomes dissent.[11] Arguably, most infants and toddlers are likely to protest (dissent) to venipunctures, generally viewed as a minimal risk procedure.

d. The Committee views informed consent as a process of communication between the researcher, parent and child-participant. The Committee should bear in mind that "… the amount of information that a child must comprehend to provide meaningful and developmentally appropriate child assent (or dissent) should be allowed to vary with the age and maturity of the child. By understanding child assent together with the important protections of parental permission, child assent does not need to be burdened with the same informational and process requirements ... Further research needs to be done on how best to obtain truly informed and voluntary parental permission and child assent for research participation."[12 p. 291] Consent and assent need to be *culturally-sensitive*.[13] The protocol must indicate:
    i. Who will request assent and consent (preferably someone with paediatric expertise or experience).
    ii. How and when assent and consent will be requested. This is particularly important when children with a serious and/or critical condition and their parents are approached to enrol in research. If standard therapy has failed, parents may see a trial as the only option for survival. In such a situation, the informed consent document must describe possible burdens of participation and alternative forms of care such as palliation.
    iii. If a parent or guardian will be present when assent or consent is obtained.
    iv. Sometimes it may be appropriate for the researcher to spend time alone with a child or adolescent. This may make it easier for a child or adolescent to ask questions and not feel pressured or inhibited by a parent or guardian.
    v. How the researcher will assess a child-participant's decision-making capacity.
    vi. How the researcher will assess the child-participant's understanding of information exchanged during the assent or consent process.
    vii. The weight of ensuring that parents, guardians and child-participants understand what will happen during a study rests with the investigator.

viii. Researchers need to explore innovative and creative approaches to obtain assent or consent from minor-participants.[14] Examples might include:

- Videotapes or photographs of research procedures.
  For example: http://www.childrenandclinicalstudies.nhlbi.nih.gov
- Pre-visits to the research site to see equipment such as MRIs.
- Designing comics or illustrated assent/consent forms that explain the nature of the research.
- Using the Teach-Back Method
  For example: http://www.gillettechildrens.org/blog/gillettes-teach-back-method/

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8. Draft Criminal Law (Sexual Offences & related matters) Amendment Act Amendment Bill [B-2014].
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12. Roth-Cline M, Nelson RM. Parental permission and child assent in research on children. Yale Journal of Biology and Medicine 2013;86: 291-301.
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Template for Mandatory Reporting of Abuse[5]

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

NOTE *that arrangements and negotiations e.g. with Childline South Africa or other agencies, should be made before the application for research ethics review. The applicant should be able to assure the HREC about the referral arrangements.*

1. Disclosure by any adolescent under 16 years of sexual or other abuse, or on whose behalf abuse is reported by a peer, caregiver, guardian or family member or other relevant person, should trigger an immediate termination of further interviews with the respondent and members of the household.

2. If there is a clear statement that the parties involved in the abuse include an adult (anyone 18 years or older) or anyone who is more than two years older than the adolescent (s 56(2)(b)), the interviewer should report the matter to Childline South Africa at toll free: 0800 055 555 [or another child protection agency]. Childline should contact a registered social worker in the area who should investigate and inform the South African Police Service (SAPS) accordingly. The interviewer should record details of the child's name, physical address and the name of the school the child attends. As proof of complying with the statutory reporting obligation, the interviewer should insist on a Childline reference number.

3. Any secondary reporting of abuse, e.g. where a child indicates that she has reported the abuse to a teacher or another adult but that no action has been taken, the matter should be brought to the attention of Childline, who should deal with the matter. Again, the interviewer should insist on a Childline reference number, as proof of reporting.

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

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

Template for Conditions for Approval of Non-Therapeutic Research with Minors

The HREC has Ministerial permission to approve research with children that includes non-therapeutic components provided the research meets all the conditions listed below. Non-therapeutic research means research that includes interventions that do not hold out the prospect of direct health-related benefit to the participant but may produce results that contribute to generalisable knowledge.

Please complete and submit with all new protocol applications involving minor-participants.

Condition 1: The research objectives cannot be achieved except by the participation of minors
Describe the scientific justification for the enrolment of minors. Explain why this research must be done with minors as participants:

Condition 2: The research is likely lead to an improved scientific understanding of certain conditions, diseases or disorders affecting minors

Describe how the research might, or aims to, advance knowledge affecting the health and welfare of minors as a class. Note that 'condition' is defined as 'physical and psychosocial characteristics understood to affect health' meaning this research does not only involve children with an illness.

Condition 3: Any consent given to the research is in line with public policy
Consent given by authorised persons must be in line with public policy considerations. Describe how consent to the research will be in line with public policy or would be acceptable, for example, show how the research poses acceptable risks and promotes the rights of minors.

Condition 4: The research does not pose a significant risk to minors; and if there is some risk, the benefit of the research outweighs the risk

Describe how the potential risks from the research procedures and/or intervention to minor participants will be minimized and describe any possible benefits from the research to society in the form of knowledge.

Research Ethics Guidance for Elective Students

Where do I begin if, as part of my elective experience, I decide to conduct a research project involving human participants or their personal medical records?

First, you need to make contact with a local UCT-based supervisor who is willing to oversee all aspects of your research during your elective placement. You need to organise this in advance of your visit – ask your co-supervisor in your home institution to help you with these arrangements.

Your local supervisor will help you to identify a suitable research project which can be completed within the timeframe of your elective. Your research project must be feasible and within your level of expertise. Alternatively, your local supervisor may place you in an existing research project.

Will my research proposal need some kind of review?

Your research proposal must undergo two separate review processes. First, the departmental research committee where you are doing your elective will review the scientific and scholarly merit of your proposal. Second, the Human Research Ethics Committee in the Faculty of Health Sciences will review ethical aspects of your application. Your local supervisor will assist with these applications. Even if your proposal has ethical approval in your home institution, it still needs local research ethics approval. If you are joining a study that already has research ethics approval, your local supervisor still needs to obtain Human Research Ethics Committee approval to include you in the existing research.

You also need to ask your local supervisor if you must obtain additional administrative approval or authorisation from medical superintendents or managers to conduct your research, including accessing personal medical records, in specific settings such as hospitals, community-based health centres and non-governmental organisations.

For more information about how to apply for research ethics approval contact the Human Research Ethics Committee Administrative Team via email hrec-enquiries@uct.ac.za.

How long does it take to get research ethics approval?

Because it is time-consuming, we advise you to initiate contact with a local supervisor at least 6 months before your elective begins. In general, the length of time it takes to obtain ethics approval depends on the ethical issues inherent in your study. For example, ethical concerns may relate to the methodology, the study population or the level of risk in your proposed study. By anticipating the ethical issues and receiving proper guidance and supervision in the planning stages of your study, you are likely to reduce turn-around times between submission to the Committee and obtaining final

ethics approval. Therefore, before submitting your proposal to the Committee you need to make sure it complies with the ethical principles laid down in the Declaration of Helsinki 2024 and the South African Department of Health's: Ethics in Health Research: Principles, Structures and Processes, 2024.

Your research must also comply with South African law, for instance the requirements for informed consent and special considerations when undertaking research among minors (<18 years of age). These are described in the standard operating procedure entitled Research with Children on our website.

Wherever possible, the Human Research Ethics Committee tries to review student proposals through an expedited process. This means that if your research project involves no more than minimal risk to potential participants, it may be reviewed by the Chairperson of the Committee or someone designated by the Chairperson with expertise in the area in which you plan to undertake your study. However, the Chairperson reserves the right to decide if a full committee review is necessary.

For record-keeping purposes, please notify Ms Paschaline Jacobs, the Elective Officer in the Faculty of Health Sciences, when you receive ethical approval for your research. Her email address is Paschaline.Jacobs@uct.ac.za

Once your study is complete, or within six months of Human Research Ethics Committee approval, you need to submit a detailed report of your findings to your local supervisor, the Committee and relevant stakeholders. This is important because your findings may directly or indirectly benefit the participants and communities who formed part of your research.

If you intend publishing your findings, in the early stages of planning, you need to discuss with your local and home-based supervisor any matters relating to authorship and acknowledgement.

Some general points:

- Become familiar with the cultural and socioeconomic influences in your participants' lives. Find out about literacy levels in the areas where you will undertake your research.
- Bear in mind that many potential participants might not understand English or might prefer to be interviewed or answer questions in their home language which might be Afrikaans, English or Xhosa.
- Ascertain from your local supervisor whether your information sheets and informed consent forms need to be translated into the local languages and who might be able to assist you with this task.

- Remember that informed consent is a process and not simply signing a form. This is particularly important in an environment where participants might not readily understand the meaning of 'research' or the difference between treatment and research.
- Whenever you are 'on-site' doing your research ensure that you carry your Human Research Ethics Committee letter of approval with you, in case anyone questions who you are and what you are doing in a particular setting.
- Finally, keep in mind that all research involving human participants requires ethical approval by the Human Research Ethics Committee at UCT before you can begin piloting your study or recruiting participants.

Postgraduate Candidates – Applying for Human Research Ethics Approval

Policy

The Faculty of Health Sciences requires all postgraduate degree candidates who undertake research with humans to have a substantive and procedural understanding of human research ethics.[1] To this end, each candidate must independently submit to the Human Research Ethics Committee a full research ethics application for review. This must follow scientific review and approval of the research proposal by the relevant Departmental Research Committee. University-wide guidelines for a doctoral degree are available on UCT's website:

Purpose

The purpose of this policy is to describe the research ethics requirements for candidates wishing to register for a postgraduate degree which involves human participants research. See related Standard Operating Procedure: Definition of Human Research and Human Participants.

Procedure

1. Each candidate must prepare and submit to the relevant departmental research committee (DRC) a fully developed research proposal for scientific review. The supervisor is expected to play a central role in assisting the candidate to develop a scientifically and ethically sound proposal which meets the University's standards for a doctoral degree.
2. Following approval by the DRC, the candidate must submit the proposal for review by the Human Research Ethics Committee. The ethical requirements for human research, and the submission process for research ethics approval, are fully described on the Committee's website. Candidates can also seek guidance with ethical issues from the Chairperson and/or members of the Human Research Ethics Committee, prior to submission, and during the study. Commonly, low-risk research with humans will undergo an expedited review by the Chairperson or a designee. Alternatively, the application may require review by a full Committee at a monthly meeting. Submission and meeting dates are posted on the website.
3. If the proposal is a sub-study of a larger, existing project which already has a HREC reference number, the postgraduate study, if approved, will receive its own reference number which will be linked to the main project. In order to facilitate and coordinate annual approvals of the main project, the candidate, supervisor or overall Principal Investigator can request that the postgraduate sub-study be given the same annual re-approval date as the main study.

4. The postgraduate candidate is personally responsible for submitting the human research ethics approval letter to the Post-Graduate Office. This is not the supervisor's responsibility.
5. **NOTE**: The Human Research Ethics Committee does not give retrospective research ethics approval for completed research.

References

1. Faculty of Health Sciences Handbook 2013: Section FGP8.