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STELLENBOSCH UNIVERSITY
HEALTH RESEARCH ETHICS COMMITTEE (HREC)

TERMS OF REFERENCE
and
STANDARD OPERATING PROCEDURES

Version 5
October 2019

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HREC SOP Version History

The latest published version of Stellenbosch University HREC SOPs are available at: http://www.sun.ac.za/english/faculty/healthsciences/rdsd/Pages/Ethics/SOP.aspx;

SOPs must be accessed only directly through the HREC website to ensure the correct version is used. NOTE: Do not "Google Search" as older, incorrect versions of the SOP document may appear in search results;

The onus is on research applicants to ensure they are working to the correct version of the SOPs.

HREC SOP Version Log

Version	Effective Date	Reason for change
5.0	October 2019	Revised following: 1) Internal HREC Executive Committee (EXCO) review to improve clarity and depth of guidelines for research applicants; 2) National Health Research Ethics Council (NHREC) Audit (November 2017); 3) new SOP on informed consent for research databases, registries and biobanks; 4) MTA requirements (NHREC communication, April 2019); new SOP on site monitoring.
4.3	June 2016	Revised following: 1) establishment of an Undergraduate Research Ethics Committee (UREC); 2) streamlining of HREC review fee process; 3) Introduction of a case report/series application form; 4) changes procedure for acquiring Stellenbosch University insurance for research participants; 5) delegation of review of non-therapeutic child research to HRECs by DoH (2015); and 6) updated guidelines for paediatric blood draw volumes
4.2	May 2015	Revised: 1) for inclusion of guidelines for paediatric blood draw volumes; 2) to align with the SA Department of Health (2015). Ethics in health research: Principles, structures and processes (2nd Ed.); and 3) following an AAHRPP benchmarking exercise.
4.1	May 2014	Revised: 1) following Internal HREC Executive Committee (EXCO) review to improve clarity and depth of guidelines for research applicants; 2) for inclusion of new guidelines on participant insurance, participant compensation, medical devices, and photographs in research; and 3) following National Health Research Ethics Council (NHREC) Audit (June 2013)

1. TERMS OF REFERENCE

1.1 Health Research Ethics Committees (HRECs)

1.1.1 Stellenbosch University is served by two, equivalent, Health Research Ethics Committees: HREC1 and HREC2, and by one subcommittee, the Undergraduate Research Ethics Committee (UREC):

1.1.2 HREC 1 and HREC 2 are full committees mandated by the National Health Research Ethics Council to review all research;

1.1.3 UREC is a subcommittee to HREC that was created specifically to review minimal risk undergraduate, Honours and BTech research in the Faculty of Medicine and Health Sciences. HREC is legally accountable for decisions taken by UREC. UREC has formally delegated authority to approve minimal risk undergraduate ethics applications, and to indicate that a UREC representative will serve as a member of HREC and attend, participate in discussions and vote at HREC meetings on a rotational basis.

Unless otherwise stipulated, these three committees shall hereafter be referred to as HREC (international equivalent titles: Research Ethics Committee (REC), Institutional Review Board (IRB), Independent Ethics Committee). These committees are mandated to fulfill their function by the Senate of Stellenbosch University through the Senate Research Ethics Committee, to which HREC reports at least annually in writing;

1.1.4 The **essential purpose of HREC** is to protect the dignity, rights, safety, and well-being of all human participants in health-related research. HREC will do this through independent, prospective and ongoing ethics review of all health research projects undertaken by members of staff, registered students and affiliates of the University;

1.1.5 The definition of health research used by HREC is in accordance with the SA National Health Act No 61. 2003;

1.1.6 HREC recognizes a distinction between a medical device and other medical products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. Medical devices can range from simple bed pans to pacemakers with micro-chip technology or laser surgical devices. They also include:

1.1.6.1 in vitro diagnostic products, such as general-purpose laboratory equipment, reagents and test kits, including monoclonal antibody technology;

1.1.6.2 certain electronic radiation emitting products with medical applications, e.g. diagnostic ultrasound products, X-ray machines and medical lasers;

1.1.7 a medical device is a product that is labelled, promoted or used in a manner that meets the following definition and is subject to pre- and post-marketing regulation: “An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is:

1.1.7.1 intended for use in the diagnosis of a disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or

1.1.7.2 intended to affect the structure or any function of the body and which does not achieve its primary intended purposes through chemical action within or on the body and which is not

dependent on being metabolized for the achievement of any of its primary intended purposes";

1.1.8 HREC may, at the discretion of the Chairperson or delegated member, except for review research protocols involving human participants submitted to it by researchers from other institutions who are not SU staff members, students or affiliates;

1.1.9 HREC is committed to the ethical principles laid down in the following documents and guidelines:

- The SA National Health Act. No. 61 of 2003;
- The SA Department of Health (2015). *Ethics in health research: Principles, processes and structures (2nd ed).* Department of Health: Pretoria, South Africa;
- The SA Department of Health (2006). *South African clinical trial guidelines: Good practice for clinical trials with human participants (3rd ed).* Department of Health: Pretoria, South Africa;
- World Medical Association (2013). *Declaration of Helsinki:* Ethical Principles for Medical Research Involving Human Subjects, United States;
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). *The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research* (Dhew publication, no. (os) 78-0012). Bethesda, Md.: Commission;
- The US Office of Human Research Protections 45 CFR 46[1] (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56;
- CIOMS (2002). *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Council for International Organisations of Medical Sciences and WHO: Geneva;
- ICH-GCP-E6 Sections 1-4; and
- The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite).

1.1.10 When strict compliance with the letter of a particular requirement of these declarations and codes is not possible, HREC will ensure that the proposed research is nonetheless in keeping with the spirit of the declarations and codes;

1.1.11 Ethics approval must be obtained before a study commences. HREC will not consider projects for approval if it is apparent that the research has already been conducted;

1.1.12 HREC has the authority, from time to time, to appoint a standing or *ad hoc* subcommittee to investigate or finalize certain matters under its jurisdiction, in compliance with applicable norms, rules and regulations;

1.1.13 The following mechanisms operate to ensure that the quality of ethics review is consistent across all committees, and specifically UREC as a subcommittee of HREC:

1.1.14 The Chairperson of UREC serves as an ex officio member of HREC;

1.1.15 At least the Chairperson, Vice Chairperson or Coordinator of UREC attends HREC 1 and HREC 2 committee meetings to report on reviews of undergraduate applications serving for HREC ratification;

[1] Common Federal Regulations (CFR) applies across all US states and abroad, when research is funded by the US federal government.

1.1.16 At least the Chairperson, Vice Chairperson or Coordinator of UREC attends HREC Executive Committee meetings; and

1.1.17 UREC members serve as HREC members and attend, participate in discussions and vote on review decisions at HREC meetings on a rotational basis throughout the year. This ensures cross-representation between HREC and UREC, over and above the existing representation of the UREC Chair, Vice Chair, and coordinator on the HREC Executive Committee;

1.1.18 UREC members may in addition be co-opted for review of HREC projects when expertise is needed;

1.1.19 Stellenbosch HREC is registered with the National Health Research Ethics Council (NHREC) and meets all the necessary compliance and auditory requirements;

1.1.20 The SU HREC complies with the Terms of the Federal Wide Assurance (FWA) when reviewing research covered by this Assurance and possess appropriate knowledge of the local context in which this Institution's research will be conducted. The SU HREC FWA Number is 00001372.

1.2 HREC Executive Committee (HREC EXCO)

1.2.1 Membership, Quorum and Officers

1.2.1.1 The HREC EXCO consists of the Chairpersons, Vice Chairpersons, Coordinators of both HRECs and UREC, and the Head of the Research Ethics Office;

1.2.1.2 The Chair of the HREC EXCO is the Head of the Health Research Ethics Office;

1.2.1.3 The Secretariat is provided by the Health Research Ethics Office;

1.2.1.4 Meetings are held no less than three times per year;

1.2.1.5 A quorum constitutes at least two representatives of each HREC and UREC, one coordinator and the Head of the Health Research Ethics office or his/her officially delegated representative;

1.2.1.6 Formal agendas and minutes are maintained that are distributed according to sound office practices;

1.2.1.7 Decisions are made by seeking consensus;

1.2.1.8 The Committee may extend rights of audience and debate on an ad hoc basis.

1.2.2 Purpose and scope

1.2.2.1 HREC EXCO reports on the work of the three Committees over time, reflects on the synergistic functioning and the meaningfulness of processes and arrangements in place;

1.2.2.2 Considers overarching matters identified or referred to the HREC EXCO;

1.2.2.3 Discuss and find solutions to pressing conceptual interpretations and concerns, if any; and

1.2.2.4 Provide opportunities for networking and mentorship;

1.2.2.5 Review and approve documents and processes pre submission to Stellenbosch University Senate Research Ethics Committee (SREC).

1.2.3 Organizational Relationship with HRECs and UREC

1.2.3.1 The outcomes of the deliberations and decisions of EXCO are communicated to HREC & UREC members during regularly convened monthly meetings where such decisions are discussed and confirmed;

1.2.3.2 Any and/or both of the HRECs may choose to debate, question and/or refer a decision back to the HREC EXCO for re-consideration and re-submission to the HRECs;

1.2.3.3 The implementation of an EXCO decision depends on HREC confirmation;

1.2.3.4 EXCO decisions will serve as part of the HREC meeting agenda for consideration by the full committee and will invite feedback to EXCO;

1.2.3.5 EXCO decisions will be communicated to UREC via email and will invite feedback to EXCO;

1.2.3.6 In cases of urgent or time sensitive matters, the HRECs may retrospectively confirm such a decision.

2. WRITING, REVISING AND MANAGING STANDARD OPERATING PROCEDURES

2.1 Policy

HREC Standard Operating Procedures are documents containing detailed written mandatory and/or advisory instructions and guidelines that relate to important tasks and practices associated with HREC functioning, the review and approval of health research protocols, and requirements for conducting and managing health research and continuing review.

2.2 Purpose

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

2.3 Scope and responsibilities

2.3.1 All SU researchers and their collaborators, SU HREC members and staff are responsible for working in accordance with approved SOPs;

2.3.2 All SU staff and affiliates to whom the HREC SOPs apply are responsible for identifying new SOPs that need to be written, or errors and omissions in current SOPs that need to be revised;

2.3.3 Requests to write or update HREC SOPs must be emailed to the HREC office via: ethics@sun.a.za;

2.3.4 The Head: Health Research Ethics Office is responsible for the oversight of HREC SOPs, as well as plans for writing and revising and implementation of HREC SOPs;

2.3.5 The HREC SOPs may be written by the Head: Health Research Ethics Office, the HREC Chairpersons or Vice Chairpersons or persons delegated to write or revise SOPs by the Head: Health Research Ethics Office or the HREC Chairpersons;

2.3.6 The Head: Health Research Ethics Office, the Chairpersons and the Vice Chairpersons, in collaboration with the Research Integrity Officer, are responsible for ensuring that the SOPs remain accurate, current and compliant with any changes to national and international research ethics guidelines and or regulatory requirements;

2.3.7 The HREC SOPs may be circulated to HREC EXCO and HREC committee members for expert advice and feedback;

2.4 The identification of need for a new or revised SOP

2.4.1 All HREC SOPs must be current and fit for purpose and must therefore undergo regular review;

2.4.2 A review of each SOP must be carried out at least once every three years;

2.4.3 New or revised SOPs may be necessary earlier and should be generated when:

2.4.3.1 The need has been identified by consensus amongst HREC EXCO or HREC committee members;

2.4.3.2 New or revised national or international research regulations, ethics guidelines or procedures are introduced;

2.4.3.3 Recommended by the National Health Research Ethics Council NHREC;

2.4.3.4 Clarification or additions are required to accommodate situations not well defined by the SOPs;

2.4.3.5 Gaps in procedures become apparent;

2.5 Review and approval of new or revised

2.5.1 **Minor new or revised SOPs**

2.5.1.1 Minor new or revised SOPs have no potential impact on participant safety, rights or welfare, integrity of data or regulatory compliance;

2.5.1.2 Minor new or revised SOPs are reviewed by the Head: Health Research Ethics Office and the HREC Chairpersons;

2.5.1.3 The HREC EXCO is responsible for final approval of minor new and revised SOPs;

2.5.2 **Major new or revised SOPs**

2.5.2.1 Major new or revised SOPs have a potential impact on participant safety, rights or welfare, integrity of data or regulatory compliance;

2.5.2.2 Major new or revised SOPs are reviewed by the full HREC committee and HREC EXCO;

2.5.2.3 Feedback from the full HREC committee and HREC EXCO is incorporated into the writing or revision of SOPs;

2.5.2.4 The full HREC committee and HREC EXCO are responsible for provisional approval of major new and revised SOPs;

2.5.2.5 The Senate Research Ethics Committee (SREC) is responsible for final approval of major new and revised SOPs;

2.6 SOP version control

2.6.1 **Modification history** must be detailed in an *SOP Version History Log* as a prefix to the HREC SOP content;

2.6.2 **Version numbers** in the format *x.x* must be assigned to every new issue of a SOP;

2.6.2.1 Minor new or revised SOPs result in an increment after the decimal point (e.g. 2.0 to 2.1);

2.6.2.2 Major new or revised SOPs result in a change before the decimal point (e.g. 2.2 to 3.0);

2.7 SOP distribution and record keeping

2.7.1 The Health Research Ethics Office will make finalised versions of all SOPs available on the Health Research ethics website: www.sun.ac.za/healthresearchethics;

2.7.2 The Health Research Ethics Office will **notify** SU researchers, HREC members and staff when a new or updated version of a SOP is published;

2.7.3 Paper copies are made available to HREC members and staff;

2.7.4 A paper copy of each finalised SOP version is stored in the 'SOP master folder' in the Health Research Ethics Office.

3 APPOINTMENT AND MEMBERSHIP

3.1 Policy

The Health Research Ethics Committee (HREC) has been established to oversee the safety, rights and welfare of human participants in research. The composition and functions of the HREC must meet the minimum standards and requirements, as set out in the Department of Health (2015) *Ethics in health research: Principles, structures and processes* and (2006) *South African Clinical Trial Guidelines*, and as specified in the US Federal Wide Assurance.

3.2 Purpose

The purpose of this policy is to outline the procedure for appointing the HREC Chairpersons and Committee members, and to describe their roles and responsibilities. The policy further defines HREC composition and describes the management of conflict of interest, confidentiality, and continuous professional development in research ethics and good clinical practice.

3.3 Chairperson: Appointment and Responsibilities

3.3.1 The Chairperson is appointed by the Senate Research Ethics Committee (SREC) of Stellenbosch University for a three-year renewable term on the recommendation of the Deputy Dean: Research and Internationalisation, Faculty of Medicine and Health Sciences in cooperation with the Head: Health Research Ethics Office;

3.3.2 The Chairperson may serve a maximum of three consecutive terms;

3.3.3 The Chairperson of the HREC performs a leadership, oversight and advisory role in the conceptualization, management and conduct of health research ethics initiatives at the institution. To be and to do such, the Chairperson needs to be a respected member of the medical and health care community, knowledgeable and experienced in operationalizing research ethics, research in medicine/ medical sciences/ health, legal frameworks and enabling sound committee leadership practices.

3.3.4 The responsibilities of the Chairperson include but are not limited to:

3.3.4.1 **Play a Health Research Ethics leadership role in the institution:**

- 3.3.4.1.1 Providing courageous and respected leadership in research ethics;
- 3.3.4.1.2 Be a champion for the importance of ethics-in-context;
- 3.3.4.1.3 Cooperate and liaise with research ethicists and committees across SU campuses, the wider Western Cape and nationally, towards developing and promoting best practices in research ethics oversight and improving participant welfare and safety, particularly in multi-centre trials;
- 3.3.4.1.4 Advise and consult, as agreed, with researchers, HREC members and members of the HREC offices on research ethics issues;
- 3.3.4.1.5 Identify and support the enactment of research integrity cases where deemed necessary and the right thing to do;
- 3.3.4.1.6 Participate in non-compliance investigations;
- 3.3.4.1.7 Play a leadership role in the development and implementation of HREC policies and procedures;

3.3.4.1.8 Possess a comprehensive knowledge of national and international research ethics guidelines and regulations, institutional policies and relevant legislation;

3.3.4.1.9 Represent the HREC in the Executive Committee (EXCO) of the HRECs;

3.3.4.1.10 Represent the HREC in the Senate Research Ethics Committee (SREC);

3.3.4.1.11 Represent the HREC at the annual National Health Research Council (NHREC) meetings and other meetings at national level;

3.3.4.1.12 Promote a culture of respect within the research community for the Health Research Ethics Committee process and for research ethics more broadly;

3.3.4.1.13 Have an in-depth understanding of the ethical issues, HREC /SU research policies and the NHREC/Department of Health guidelines that are applicable to studies that are reviewed by the HREC. The HREC Chair is not expected to be the only, or ultimate authority on compliance issues – the Head of the HREC Office or other members of the HREC Office or Secretariat also take responsibility for compliance verification, but the HREC Chair is expected to be an active and knowledgeable partner in this aspect of the HREC system;

3.3.4.1.14 Represent the HREC in discussing HREC decisions and requirements with researchers and other stakeholders, and have the courage and confidence to uphold decisions that may not be popular with investigators, the research community, University officials and/or external stakeholders;

3.3.4.1.15 With the assistance of the coordinator, prepare an annual report for the National Health Research Ethics Council (NHREC) on the nature and volume of the HREC's activities;

3.3.4.1.16 Make inputs to ensure or support adequate resources (financial, human, knowledge development) to conduct health research ethics duties in line with national and international benchmarks;

3.3.4.1.17 Contribute to the development, review, enactment and monitoring of HREC policies, guidelines and SOPs;

3.3.4.1.18 Perform administrative duties such as the review and signing of letters, electronic communication, appointments and the preparation of directive documents.

3.3.4.1.19 Delegate their duties to HREC Vice Chairpersons on a case-by-case basis, where necessary;

3.3.4.1.20 Under exceptional circumstances, jointly with the Head: Health Research Ethics Office, conduct specific reviews and or review and provide input to specific research ethics issues.

3.3.4.2 Conduct and direct the proceedings of monthly HREC meetings;

3.3.4.2.1 Chairpersons are expected to attend a minimum of 70% of the HREC meetings scheduled for the year. 100% attendance is however preferable;

3.3.4.2.2 With the assistance of the coordinator, decide on review categorization, for example expedited, meeting assigned or excluded from review;

3.3.4.2.3 With the assistance of the coordinator, select reviewers with necessary expertise to perform initial and ongoing reviews;

3.3.4.2.4 With the assistance of the coordinator, prepare the agenda before meetings, and review the minutes after meetings;

3.3.4.2.5 Have respect for committee members from diverse backgrounds, perspectives and sources of expertise;

3.3.4.2.6 Facilitate sound ethical discourse, teamwork-with-integrity and the reaching of consensus at meetings;

3.3.4.2.7 Be a gatekeeper for the welfare and safety of the participant, their communities and vulnerable populations - carefully managing risk and benefit;

3.3.4.2.8 Where necessary, enact review decisions in line with national guidelines and with careful consideration of participant(s), researcher(s) and important scientific endeavors;

3.3.4.2.9 Conduct selected expedited and full committee reviews, as agreed, or delegate this task to suitably qualified individuals;

3.3.4.2.10 Preview all protocols presented to the full-committee and when necessary communicate with reviewers so that important HREC issues are identified ahead of the full-committee sitting;

3.3.4.2.11 Vote on protocols at the full committee meeting together with other HREC members;

3.3.4.2.12 Review and sign letters to researchers conveying HREC decisions and requirements relating to their protocols;

3.3.4.2.13 Manage complaints and concerns as communicated and support timeous solutions;

3.3.4.2.14 Delegate their duties to HREC Vice Chairpersons on a case-by-case basis, where necessary.

3.4 Vice-Chairpersons: Appointment and Responsibilities

3.4.1 Two Vice-Chairpersons are nominated and selected by members of the Health Research Ethics Committee for a three-year renewable term;

3.4.2 The Vice-Chairpersons may serve a maximum of three consecutive terms, preferably overlapping with the Chairperson for the purposes of continuity;

3.4.3 The Vice-Chairpersons' responsibilities are to:

3.4.3.1 Attend a minimum of 70% of the HREC meetings scheduled for the year. 100% attendance is however preferable;

3.4.3.2 Perform duties delegated by the Chairperson;

3.4.3.3 Act as Chairperson in the absence of the Chairperson;

3.4.3.4 Provide active in-meeting support, for example meeting management, timekeeping, and conceptual and psycho-social support to the Chairperson and members;

3.4.3.5 Vote on protocols at the full committee meeting together with other HREC members;

3.4.3.6 Act as a member of the HREC EXCO;

3.4.3.7 Advise and consult, as agreed, with researchers, HREC members and members of the HREC offices on research ethics issues;

3.4.3.8 Participate in non-compliance investigations;

3.4.3.9 Contribute to the development and implementation of HREC policies and procedures;

3.4.3.10 Represent the HREC in the Executive Committee (EXCO) of the HRECs;

3.4.3.11 Represent the HREC at the annual National Health Research Council (NHREC) meetings and other meetings at national level;

3.4.3.12

3.4.3.13 General responsibilities which accompany committee membership.

3.5 Committee members: Appointment and Responsibilities

3.5.1 Appointment to HREC will be by nomination and co-option;

3.5.1 All new members to HREC will undergo a formalized set of induction requirements, of which a minimum would include:

- 3.5.1.1 Successful completion of an online Research Ethics programme such as TRREE;
- 3.5.1.2 GCP training (if no evidence of a valid and current certification exists);
- 3.5.1.3 Orientation session to HREC SOP's, guidelines and processes as coordinated and offered by the Health Research Ethics Office;
- 3.5.1.4 Receive a full set of the HREC Guidelines and SOPs as well as the relevant National Guidelines and core reading material;
- 3.5.1.5 Training in the use of the relevant software application used (Infonetica) as arranged by the Research Ethics Office;
- 3.5.1.6 Attendance of at least one full HREC meeting as an observer.

3.5.2 HREC members are appointed, with a letter of appointment, by the Senate Research Ethics Committee (SREC);

3.5.3 HREC members may serve a maximum of three consecutive terms;

3.5.4 On appointment, HREC members sign a confidentiality and non-disclosure agreement;

3.5.5 HREC members will serve for a renewable term of three (3) years;

3.5.6 HREC members are expected to attend a minimum of 70% of the HREC meetings scheduled for the year. 100% attendance is however preferable;

3.5.7 Stellenbosch University obtains professional liability insurance to cover both affiliated and non-affiliated members when carrying out any professional duties under the auspices of HREC;

3.5.8 Committee members' responsibilities are to:

- 3.5.8.1 Perform reviews in a timeous fashion and meet review deadlines communicated by the HREC coordinator;
- 3.5.8.2 Provide timeous written notice if unable to take on a particular review (within 3 working days of receiving review allocations) to the HREC Chairperson and coordinator;
- 3.5.8.3 Attend meetings on a regular basis and not leave until meetings are adjourned;
- 3.5.8.4 Attend a minimum of 7 meetings per year (excluding sabbatical or other leave periods);
- 3.5.8.5 Provide timeous written apologies for meeting attendance to the Chairperson and HREC coordinator within 3 working days of receiving review allocations. It is crucial for the primary reviewer to be present at the meeting to present their review to the committee. If this will not be possible, the reviewer should make arrangements with the Chairperson to take over these review duties in order not to delay the review process;
- 3.5.8.6 Maintain strict confidentiality regarding protocol information, reviews and decisions, and all other matters discussed at committee meetings (see *Section3.9 Confidentiality* for more detail);

3.5.8.7 Disclose potential conflicts of interest to the Chairperson and committee coordinator, and where a conflict does exist, not review the protocol and leave the room during discussion of and voting on the protocol (see *Section 3.8 Conflict of Interest* for more detail);
3.5.8.8 Remain impartial and objective when reviewing protocols;
3.5.8.9 Respect each other's views and the deliberative process;
3.5.8.10 Serve as a primary reviewer for research in their area of expertise;
3.5.8.11 Serve as a general reviewer of all research discussed at full committee meetings;
3.5.8.12 Decide independently if the design and conduct of proposed studies will protect participants' safety, rights and welfare, and comply with relevant ethics guidance and regulations;
3.5.8.13 Decide by vote whether to approve, require revisions, defer or reject studies following deliberation at full committee meetings;
3.5.8.14 Perform expedited reviews of minimal risk research;
3.5.8.15 Keep up to date with national and international research ethics guidelines and regulations;
3.5.8.16 Take part in research ethics and good clinical practice (GCP) Continuous professional development and submit documented proof of such to the HREC office.

3.6 HREC Composition

3.6.1 The membership and composition of the HREC is reflected on the committee roster;

3.6.1 Towards its primary mandate to protect the rights and welfare of human research participants, HREC requires diverse membership to provide expertise in and sensitivity to a broad range of scientific and ethical considerations;

3.6.2 HREC members are appointed by the Senate Research Ethics Committee (SREC) on the recommendation of the Health Research Ethics Office for a renewable three-year term;

3.6.3 HREC composition is reported to and monitored by the HREC Executive Committee (EXCO), the Senate Research Ethics Committee (SREC) and the National Health Research Ethics Council (NHREC);

3.6.4 HREC membership composition is continuously monitored to ensure appropriate representation:
3.6.4.1 The Chairperson and the relevant coordinator monitor the ability of the Committee to review the range and specificity of protocols submitted to the Committee – both in terms of scientific discipline/ subject field(s) and research methodology/ies;
3.6.4.2 The Chairperson and the relevant coordinator identify expert needs to enable the Committee to review protocols as submitted by and within relevant medicine and health disciplines;
3.6.4.3 When a member resigns from the HREC, the choice of a replacement takes into account the overall balance of the committee and specific expertise that is needed;

3.6.5 At least annually HREC will submit documentation detailing current HREC membership and vacant appointments in specific expertise areas to the Vice Dean: Research, FMHS;

3.6.6 HREC may accompany this documentation with suggestions for specific nominees to fill vacant appointments, if these persons have already been identified;

3.6.7 Potential experts will be nominated by the Dean through a consultative process with relevant departmental heads in the Faculty and/or other relevant stakeholders;

3.6.8 Such nominated experts will undergo relevant induction training and preparation as outlined in *Section 3.10*).

3.6.9 In line with the Department of Health (2015) Ethics in Health Research: Principles, Processes and Structures (2nd ed), and (2006) Good Clinical Practice Guidelines, Department of Health, Pretoria: South Africa, Health Research Ethics Committee (HREC) membership composition must satisfy the following requirements:

3.6.9.1 Consist of members that collectively have the qualifications, experience and expertise to review and evaluate the scientific, medical, legal, psychosocial and ethical aspects of research applications;

3.6.9.2 Consist of members who are persons of good standing and who have a working knowledge of research ethics codes and guidelines;

3.6.9.3 Be representative of the communities it serves and, increasingly, reflect the demographic profile of the populations where research takes place;

3.6.9.4 Include members of both genders, although not more than 70% should be either male or female;

3.6.9.5 Have a Chairperson and 2 Vice-Chairpersons per committee in the case of HREC 1 and HREC 2, and a Chairperson and Vice Chairperson in the case of UREC;

3.6.9.6 Have at least 16 members per committee in the case of HREC, and at least 5 members in the case of UREC;

3.6.9.7 Include at least two lay persons who have no affiliation to the institution, are not currently involved in medical, scientific or legal work and are preferably from one of the communities in which research is conducted. UREC will be served by the same persons on an ad hoc basis;

3.6.9.8 Include at least one member with knowledge of, and current experience in, areas of research that are likely to be regularly reviewed by HREC;

3.6.9.9 Include at least one member with knowledge of, and current experience in, the professional care, counseling or treatment of people. Such a member might be, for example, a medical practitioner, psychologist, social worker or nurse;

3.6.9.10 Include at least one member who has professional training in both qualitative and quantitative research methodologies;

3.6.9.11 Include at least one member, on HREC 1 and HREC 2, who is legally trained. UREC will be served by the same person/s on an ad hoc basis;

3.6.9.12 Include at least one member with appropriate paediatric research expertise;

3.6.9.13 Include by invite or request, where applicable, *bona fide* students, researchers and other interested parties to attend meetings as non-voting observers, subject to the signing of confidentiality undertaking and subject also to being excluded from certain agenda items as determined by the Chair;

3.6.9.14 Include a UREC member (UREC members serve as a member of HREC and attend HREC meetings on a rotational basis);

3.6.9.15 Ensure that individuals who are responsible for business development in the HREC's institution (University of Stellenbosch) are prohibited from serving as members or ex-officio members on the HREC or carrying out day-to-day operations of the review process;

3.6.9.16 In special circumstances, at the discretion of the Chairperson, multiple members may be assigned to specific fields and put forward as alternative members when representing on the HREC roster. Alternate members only count towards a quorum if they are present as a replacement to the main member, not in addition to the main member.

3.7 Quorum and voting requirements

3.7.1 The HREC must review relevant new and continuing studies at a full committee meeting only when a quorum is present;

3.7.1 In accordance with Department of Health (2015) Ethics in Health Research: Principles, Processes and Structures (2nd ed), HREC considers a quorum present if:

3.7.1.1 33% of members are in attendance in the case of HREC, and 50% +1 in the case of UREC;

3.7.1.2 In the case of HREC 1 and HREC 2, this must include one non-affiliated member and one non-scientific member or lay person (this may be the same person); and

3.7.1.3 Alternate members only count towards a quorum if they are present as a replacement to the main member, not in addition to the main member.

3.7.2 The Chair and Vice-Chairs count towards the quorum;

3.7.3 Observers, guests and ex-officio members do not count as part of the quorum;

3.7.4 A quorum must be maintained for each vote. If the quorum fails, further studies cannot be reviewed and must be held over until the next convened meeting;

3.7.5 Members vote on each study using a secret ballot;

3.7.6 Voting by proxy is not allowed;

3.7.7 Consultants, ad hoc reviewers and ex-officio members may not vote;

3.7.8 Any member with a conflict of interest with respect to a specific study must leave the room during deliberations and decision-making and may not vote on the study.

3.8 Conflict of interest

3.8.1 HREC members are expected to make decisions and conduct their oversight responsibilities in an independent manner, free from bias and undue influence. HREC members and immediate family i.e. spouse or dependents may be involved in activities that could be perceived as conflicting with their HREC responsibility. The integrity of the HREC review process can be compromised if such conflicts of interests are not disclosed and where necessary, avoided. 45 CFR Section 46.107 (e) states that ”no IRB may have a member participate in the IRB’s initial and continuing review of any project in which the member has a conflicting interest except to provide information requested by the IRB.” These policies cover each type of review conducted by the HREC;

3.8.1 HREC members must disclose any relationship, interest or other circumstances, which could reasonably be perceived as creating a conflict of interest –including the following:

3.8.1.1 **Personal relationship:** The HREC member has a personal relationship with the principal investigator or key personnel of a research protocol under review by the HREC;

3.8.1.2 **Relationship to the research study:** The HREC member (his/her spouse or immediate family member) is the principal investigator or co-investigator of the research protocol under review by the HREC;

3.8.1.3 **Business relationship or affiliation:** The HREC member serves as a trustee, director, officer, owner or partner of a for-profit entity that could be affected by the outcome of the research protocol under review by the HREC;

3.8.1.4 **Financial interest:** The HREC member has a financial interest related to the research (financial interest in the sponsor, product, or service being tested) that could be affected by the outcome of the research protocol under review by the HREC. Included in the definition of financial interest are equity interests e.g. stock, stock options or other ownership interests, payment or expectation of payment derived from intellectual property rights (e.g. patent royalties); and payments received from a for-profit entity for consulting or other services;

3.8.1.5 Involvement of the HREC member, consultant, or their immediate family in the design, conduct, or reporting of research.

3.8.2 HREC members are required to disclose only those interests that may be affected by the research, which is the subject of the research proposal and that might otherwise reasonably be perceived to affect their independent unbiased judgment with respect to the HREC's review of the protocol or related matters;

3.8.3 All HREC members who identify a potential conflict of interest are required to sign the conflict of interest declaration form (Appendix #: HREC Conflict of interest declaration form) and submit to the HREC coordinator prior to, or during the meeting. The Chairperson and committee shall determine whether a conflict exists, and these members recuse themselves from the discussions of, and voting on, these protocols. The determination of whether or not a conflict exists shall be reflected in the minutes;

3.8.4 The Chairperson may similarly become involved in a situation of potential conflict of interest. In this case he/she should discuss the matter with the Committee, or the Chairperson of the Senate Research Ethics Committee, whichever is seen to be most appropriate.

3.8.5 **Recusal:** HREC members who have a conflict of interest related to any research protocols that the HREC is about to consider will refrain from participating in any discussion of the protocol or related matters, except to the extent necessary to provide relevant factual information requested by the chair. Unless requested by the chair to provide such information to the HREC, the HREC member with a conflict of interest will leave the meeting during the discussion and voting process i.e. will not be counted toward the quorum. The HREC member's absence will be documented in the minutes with the indication that a conflict of interest was the reason for the absence. The outcome of the committee decision in the absence of the recused member will not be discussed upon return of the member concerned but may be conveyed after closure of the meeting;

3.8.6 All reviewers will sign a COI declaration which is part of the protocol review form. HREC members assigned as a primary or secondary reviewer for a protocol or related matters, with respect to which a conflict of interest has been identified, will notify the chair so that the protocol can be reassigned;

3.8.7 In the event that the conflict of interest involves the Chairperson, he or she will appoint the Vice-Chairperson, or another member as acting Chairperson (with approval of the committee). The acting Chairperson will conduct the meeting, for the remainder of the discussion, of the item in question.

3.9 Confidentiality

3.9.1 **Confidential Information** shall mean certain proprietary, personal, clinical or protocol-specific information, which the HREC member acknowledges to be confidential. Such information includes all protocols relating to research with human participants and associated documentation. The Confidential Information may be conveyed in written, graphic, oral or physical form including (but not limited to) scientific knowledge, skills, processes, inventions, techniques, formulae, products, business operations, patient requirements, biological materials, designs, sketches, photographs, drawings, specifications, reports, studies, findings, data, plans or other records, and/or software

3.9.2 All HREC members and support staff shall sign a standard confidentiality and non-disclosure agreement on appointment to HREC.

3.10 Continuous professional development in research ethics and good clinical practice (GCP)

3.10.1 All members undergo an HREC orientation and research ethics training pre appointment to HREC;

3.10.2 To stay abreast with recent development in the broad area of research ethics and science, HREC members are supported through the HREC office for;

- 3.10.2.1 TRREE training: New HREC members are required to complete 3 modules and submit certificates to the HREC office. (Module 1: Introduction to research; Module 2.1: Research ethics evaluation; and National Supplement: South Africa);
- 3.10.2.2 Western Cape REC Workshop: HREC encourages and funds registration and attendance by HREC members at the annual Western Cape research ethics training workshop;
- 3.10.2.3 Research ethics training: HREC members are encouraged to attend research ethics training workshops and seminars offered at Stellenbosch University and/or by other agencies. Our HREC office regularly updates members on course offerings and covers the cost of this training for interested members;
- 3.10.2.4 In-meeting training: HREC meetings are also used as a training platform for members since discussions and debates on relevant research ethics issues are encouraged. Chairpersons will in addition offer targeted discussions on pertinent ethics topics for the first half hour of each HREC meeting;
- 3.10.2.5 In-house research ethics training: The Health Research Ethics Office will arrange for at least one in-house research ethics training workshop by an ethics expert for committee members within the first year of each three-year appointment cycle;
- 3.10.2.6 Continued GCP training: HREC members are required to keep their GCP training up to date and submit certificates to the HREC office. The HREC office regularly updates members on course offerings and covers the cost of this GCP training for all members.

3.11 Consultants and ad hoc reviewers

3.11.1 The HREC Chairperson may seek expert opinion in the interests of time or to protect of research participants;

3.11.1 The HREC full committee may defer to another meeting or obtain consultation if there is not at least one person on the HREC with appropriate scientific or scholarly expertise or other expertise or knowledge to conduct an in-depth review of the protocol. Reasons for seeking additional or special competence may include but are not limited to the need for:

3.11.1.1 Additional ethical, scientific, clinical, statistical or scholarly expertise;
3.11.1.2 Particular knowledge about potentially vulnerable populations;
3.11.1.3 Broader understanding of gender or cultural issues;
3.11.1.4 Greater sensitivity to community perceptions;

3.11.2 Consultants and ad hoc reviewers:
3.11.2.1 Must have access to all documents submitted to the HREC relevant to the specific study under review;
3.11.2.2 May take part in deliberations and may make recommendations concerning the study;
3.11.2.3 May not vote unless required by a particular protocol and such voting status is confirmed by the HREC in advance on a case by case basis;
3.11.2.4 Must affirm that they have no conflict of interest with respect to the specific studies that they are invited to review;
3.11.2.5 Must maintain strict confidentiality with respect to the specific protocol and the meeting's proceedings;
3.11.2.6 May provide information about a specific study by written reports and/or by attending the meeting.

3.12 Evaluation of HREC Members and Chairpersons

3.12.1 The HREC Chairperson, Vice-Chairpersons and members will be evaluated annually. This will be done by means of both an objective and subjective assessment;

3.12.2 **Objective assessment:** At the end of each academic year, the REC coordinator of each HREC will provide the following metrics for each HREC member:
3.12.2.1 Number of meetings attended and chaired out of the total number of meetings;
3.12.2.2 Number of exempt determinations made;
3.12.2.3 Number of minimal risk protocols reviewed;
3.12.2.4 Number of protocols reviewed that went to the convened HREC meeting;
3.12.2.5 Number of reviews completed as the primary reviewer;
3.12.2.6 Number of reviews completed as the secondary reviewer.

3.12.3 **Subjective assessment:** At the end of each academic year, each HREC member will complete a self-evaluation form (see attachment).

3.12.4 The results of the HREC member assessments are shared with HREC Chairpersons and are used to make determinations regarding training development and the composition of the HREC itself;

3.12.5 The results of the HREC member assessments and HREC Chairperson and Vice-Chairperson assessments are presented at the HREC Executive Committee (EXCO) meeting and are used to make determinations regarding training development, the composition of the HREC itself, and overall improvement of the HRPP.

3.13 Institutional recognition of HREC membership

3.13.1 The Health Research Ethics Office will inform the Dean and the Head of Research Development and Support, SU, of the titles, names and affiliation of all HREC members on an annual basis or earlier as necessary. This information will also be available on the relevant SU website;

3.13.1 HREC members may indicate such committee membership (and portfolio if any, within the Committee) in their Curriculum Vitae and profile such membership when applying for, for example promotion or a new position;

3.13.2 Heads of Departments and affiliated units will consider the workload of HREC members in the organization and work distribution of departmental members where possible;

3.13.3 SU will recognize the membership and work of an HREC member in the institutional annual performance review as a positive and worthy endeavor;

3.13.4 SU will strive to put mechanisms in place to recognize and support members of Committees for the work they do. Such could include funding research ethics networking and training opportunities and appreciative events;

3.13.5 The workload and responsibilities of HREC Chairpersons will be specifically considered – equitable financial and other resources as agreed to be put in place by the institution to support the needs, time and effort of Chairpersons.

4 HREC APPLICATION REQUIREMENTS AND REVIEW PROCESS: EXEMPTION

4.1 Policy

4.1.1 Certain types of research may be exempt from HREC review. These include:

4.1.1.1 Systematic reviews using information that is available in the public domain;

4.1.1.2 Research involving the collection or study of existing data, documents, records and/or pathological specimens that are publicly available;

4.1.1.3 Research on commercial cell lines;

4.1.1.4 Undergraduate educational activities (no intention to publicly present or publish (See *Section 7.3.3: Undergraduate, Honours and BTech research* for detailed requirements and see *Appendix VII*: *Guidance on educational exercises and health research*);

4.1.1.5 Quality assurance audit (no intention to publicly present or publish).

4.2 Policy

The purpose of this policy is to define and describe the application requirements and review process for exemption from HREC review.

4.3 HREC application and review process: Exemption

4.3.1 **To submit an HREC application for exemption:** submit an electronic copy of the HREC exemption application package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

4.3.2 The HREC office accepts new exempt research applications at any time, on a rolling basis;

4.3.3 HREC front office administration reviews the application for completeness and may request additional information from the applicant;

4.3.4 The Health Research Ethics Coordinator reviews the exemption application and makes a recommendation to the HREC Chairperson;

4.3.5 The exemption application and review outcome are approved, at the discretion of the HREC Chairperson, and ratified at the next available convened HREC meeting;

4.3.6 The University of Stellenbosch HREC deems that FDA studies do not qualify for exempt review and will be reviewed under the procedures of a convened HREC meeting as discussed in point 4.6 below;

4.3.7 Once the decision is made that the research is exempt from review, an HREC official notification will be sent to the investigator.

4.4 Documents required for HREC application: Exemption

The application for an HREC exemption letter requires submission of the following documents:

4.4.1 Completed electronic HREC Exemption Application Form submitted via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

4.4.2 Cover letter;

4.4.3 Protocol synopsis (max 2 pages); and

4.4.4 For those cases in which the HREC letter is required for publication purposes, a copy of the submitted manuscript.

5 HREC APPLICATION REQUIREMENTS AND REVIEW PROCESS: CASE REPORTS AND CASE SERIES

5.1 Policy

Case reports and series can sometimes reveal very personal information about patients and may even lead to their recognition by readers of the report, particularly if photographs or other visual media are used. In general, informed consent should be obtained from each patient before publishing or presenting a case report or case series.

5.2 Purpose

The purpose of this policy is to define and describe the application requirements and review process for case reports and case series.

5.3 HREC application and review process: Case reports and case series

5.3.1 **To submit an HREC application for Case reports and case series:** submit an electronic copy of the HREC case report and case series application package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

5.3.2 The HREC office accepts new case report and case series applications at any time, on a rolling basis;

5.3.3 HREC front office administration reviews the application for completeness and may request additional information from the applicant;

5.3.4 The Health Research Ethics Coordinator reviews the application and makes a recommendation to the HREC Chairperson;

5.3.5 The application and review outcome are approved, at the discretion of the HREC Chairperson, and ratified at the next available convened HREC meeting;

5.3.6 Once a decision is made, an HREC official notification will be sent to the investigator.

5.4 Documents required for HREC application: Case reports and case series

5.4.1 The application for HREC review of a case report or case series should include:

- 5.4.1.1 Completed electronic HREC Case Report and Case Series Application Form submitted via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;
- 5.4.1.2 Cover letter;
- 5.4.1.3 Signed consent from each patient or their legally appointed representative, or **a clear and adequately motivated justification for a waiver of informed consent**, for HREC consideration; **and**
- 5.4.1.4 The case report or draft article/presentation.

6. HREC APPLICATION REQUIREMENTS AND REVIEW PROCESS: NEW RESEARCH

6.1 Policy

This policy covers all new research protocols and prescribes investigator responsibilities for submitting documents to the HREC.

6.2 Purpose

The purpose of this policy is to define and describe the application requirements and review process for new research reviewed by the HREC.

6.3 HREC application and review process: New research

6.3.1 **To submit an HREC application for new research:**

6.3.1.1 As far as possible before a submission deadline, submit an electronic copy of the HREC application package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za; **and**

6.3.1.2 *All health and student research*: **No hard copies** are required; **or**

6.3.1.3 *Clinical Trial:*[1] Submit **two (2) hard copies** of the HREC application package to the HREC Office, Research Development and Support Division (RDSD), Room 5007, Education Building. The contents of the two hard copy application packages must exactly match the contents of the electronic application package submitted via https://applyethics.sun.za in order for the application to be considered complete;

6.3.2 Guidelines for submissions are available from the Health Research Ethics Office website at www.sun.ac.za/healthresearchethics, see *Forms & Instructions*;

6.3.3 HREC applications can be submitted on a rolling basis, but must be received by the published HREC submission deadline in order to be considered for the agenda of that meeting;

6.3.4 UREC applications for new *minimal risk* Undergraduate, Honours and BTech research can be submitted on a rolling basis, but must be received by the published UREC submission deadline;

6.3.5 The dates for HREC meetings and submission deadlines are available from the Health Research Ethics Office website at www.sun.ac.za/healthresearchethics;

6.3.6 **Submission of a research application by the HREC submission deadline does not guarantee that application will be incorporated into a specific meeting agenda and/or review cycle.** If the number of research applications submitted by a particular submission deadline is too large for one committee meeting to accommodate, the research application will appear at the next available meeting.

[1] *Definition of a Clinical Trial for HREC application purposes:* Research study or investigation intended to test safety (not harmful or dangerous to human health), quality (ingredients are of good quality), effectiveness (working to diagnose, treat, prevent or cure a disease condition) and efficacy (better/ best when compared with other treatment or medicine for a similar condition) of new and/or existing or old medicines, medical devices and/or treatment options, using human participants (South African National Clinical Trials Register, South African Department of Health, see:http://www.sanctr.gov.za/Resources/Whatisaclinicaltrial/tabid/175/Default.aspx)

6.4 Minimal risk review (expedited review)

6.4.1 A new research application may be considered suitable for *minimal risk (expedited) review* if the risk level of the proposed research meets the criteria outlined in the following definition;

6.4.2 **Minimal risk research:** the probability and magnitude of harm or discomfort anticipated in the research, is not greater, in and of itself, than that ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests;

6.4.3 A "**minimal risk**" review process may be used, at the discretion of the HREC Chairperson, or another experienced member delegated this responsibility by the Chairperson;

6.4.4 UREC has formally delegated authority to review and approve *minimal risk* Undergraduate, Honours and BTech ethics applications (see *Section 7.3.3: Undergraduate, Honours and BTech research* for detailed application requirements and review process);

6.4.5 An experienced member of HREC is defined as an individual with the necessary qualifications as suggested in *Section 3: Appointment and Membership* and with at least 1-year experience as an HREC member;

6.4.6 The criteria used to approve an expedited procedure is the same as the criteria used for review by a convened HREC;

6.4.7 See *Appendix VI: US Federal OHRP guideline: Expedited review procedure* for projects considered suitable for minimal risk review according to US-HHS requirements. HREC broadly adheres to the requirements stipulated in this document, except for those related to clinical trials;

6.4.8 The HREC member responsible for review of a minimal risk study may not reject a study classified as minimal risk by the Chairperson;

6.4.9 The following projects are considered by HREC **not** suitable for minimal risk review and should (except in exceptional circumstances) be reviewed in a convened HREC meeting:

6.4.9.1 All clinical trials involving drugs/medical devices or other therapeutic interventions;

6.4.9.2 Multi-institutional and/or multi-site collaborative research projects;

6.4.9.3 International grant funded research.

6.4.10 The HREC office accepts new minimal risk research applications at any time, on a rolling basis;

6.4.11 The applicant submits the application via https://applyethics.sun.ac.za;

6.4.12 HREC front office administration reviews the application for completeness and may request additional information from the applicant;

6.4.13 The HREC Coordinator allocates the application to one HREC reviewer;

6.4.14 An HREC member reviews the minimal risk research application and submits their proposed review outcome to the HREC office;

6.4.15 The research application and review outcome are approved, at the discretion of the HREC Chairperson, and ratified at the next available convened HREC meeting;

6.4.16 Once a decision is made, an HREC official notification will be sent to the investigator;

6.4.17 After review, the HREC member can recommend that the research, or components thereof, represent more than minimal risk and refer the review to the next available convened HREC meeting.

6.5 Full committee review (convened HREC meeting)

6.5.1 A new research application posing more than minimal risk to potential research participants requires review at a convened (full) HREC meeting;

6.5.2 A new research application is considered suitable for *full committee review* if the risk level of the proposed research meets the criteria outlined in the following definition;

6.5.3 **More than minimal risk**: the probability and magnitude of harm or discomfort anticipated is greater, in and of itself, than that ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests;

6.5.4 HREC convenes on a monthly basis, except December, to review and consider:

6.5.4.1 Continuing Review Reports: *Progress Reports* for active research and *Final Reports* for closing/finalised research, amendment applications, SAE reports, etc.;

6.5.4.2 New research applications requiring a full committee review i.e. research that poses more than minimal risk to participants;

6.5.4.3 New research applications approved via minimal risk review by HREC, for ratification of approval;

6.5.4.4 New research applications approved via minimal risk review by UREC, for ratification of approval;

6.5.4.5 Major protocol amendments;

6.5.4.6 Adverse events reported in previously approved studies;

6.5.4.7 General and policy matters; and/or

6.5.4.8 Allegations of misconduct in research or other complaints.

6.5.5 **Pre-meeting process**

6.5.5.1 New research applications must be received by the HREC office by the published agenda due dates (usually 3 weeks prior to the upcoming HREC meeting) in order to be considered for the agenda of that meeting;

6.5.5.2 Agenda closure dates are published in conjunction with meeting dates but do not guarantee that applications will be incorporated into a specific agenda. If the number of research applications submitted by the agenda due date is too large for one committee meeting to accommodate, the research application will appear at the next meeting;

6.5.5.3 The applicant submits the application via https://applyethics.sun.ac.za;

6.5.5.4 The HREC Coordinator allocates each research application to two members of the relevant committee, at least three weeks prior to the meeting for evaluation and review;

6.5.5.5 The Chairperson reviews all research prior to review allocations to committee members and may, at her/his discretion, co-opt an external consultant for a particular review, if s/he feels the committee does not have the necessary expertise to adequately evaluate all aspects of a particular research application;

6.5.5.6 Committee members submit their completed reviews one week prior to the meeting;

6.5.5.7 The HREC coordinator collates all the available reviews into the meeting agenda and distributes the agenda, via Infonetica, to the full committee at least 3 days prior to the meeting. Electronic links to the application materials are available to all committee members as part of the meeting "Agenda" file;

6.5.5.8 Reviewers make written comments available to the Chairperson, prior to each meeting, if they are unable to attend the meeting.

6.5.6 **Convened HREC meeting**

6.5.6.1 Each member of the committee receives a hard copy of the agenda outlining any announcements and all reviews to be discussed;

6.5.6.2 The Chairperson opens the meeting;

6.5.6.3 A quorum must be present for all decision making (see detailed quorum requirements in *Section 3.7);*

6.5.6.4 The secretary records those present and also notes apologies;

6.5.6.5 The minutes of the previous HREC meeting are corrected and accepted;

6.5.6.6 New Agenda Items are generally discussed in the following order, but this may be subject to change depending on volume and type of items received at each meeting:

- 6.5.6.6.1 Matters arising from the previous meeting;
- 6.5.6.6.2 General items;
- 6.5.6.6.3 Project progress reports/re-approvals;
- 6.5.6.6.4 New applications;
- 6.5.6.6.5 Resubmission of “deferred” projects;
- 6.5.6.6.6 Ratification of projects approved by minimal risk review by HREC members;
- 6.5.6.6.7 Ratification of projects approved by minimal risk review by UREC members;
- 6.5.6.6.8 Discussion and review of projects referred to the full committee after minimal risk review;
- 6.5.6.6.9 Major amendments for discussion. (A major amendment is one that may alter the risk-benefit ratio of the study or result in significant change in study procedures);
- 6.5.6.6.10 Ratification of minor amendments approved via the minimal risk review process. (A minor amendment is one that does not alter the risk-benefit ratio of the study). Amendments that involve only minor changes to ICFs; administrative protocol changes; do not need to be ratified by the committee;
- 6.5.6.6.11 Serious adverse events (SAEs);
- 6.5.6.6.12 Other documents/submissions for noting/approval;

6.5.6.7 New applications are introduced by the Chairperson. The primary reviewer presents a summary and review of the study to the committee. The second reviewer adds comments. Discussion is then opened to the full committee. Throughout the discussion the research documents pertaining to the study are projected by the secretary onto a screen for review by the convened committee;

6.5.6.8 If the investigator is a member of the committee s/he may answer any specific queries that members wish to address but should voluntarily recuse her/himself prior to discussion and decision-making. This recusal is recorded in the minutes;

6.5.6.9 Investigators will not attend the meeting routinely unless requested to do so by the Chairperson. Investigators may request to present information to the committee that will

assist with decision making and attendance at the meeting is at the discretion of the Chairperson;

6.5.6.10 The Chairperson facilitates discussion and summarises the perceived viewpoint(s) of the committee;

6.5.6.11 The HREC votes on a proposal as summarized by the chair (the chair and vice-chair take part in the vote)

6.5.6.12 One of the following decisions must be made:

6.5.6.12.1 **Approved:** The proposed research is approved in its current form, with no changes required. The date of approval is considered the date that all conditions were determined to be met;

6.5.6.12.2 **Approved with stipulations:** The proposed research is approved with minor alterations required. The onus is left on the research applicant to meet these stipulations prior to the start of any research related activities;

6.5.6.12.3 **Modifications required:** The proposed research has no major ethical concerns, but a number of clarifications or methodological changes are required. The research applicant must resubmit the revised research application. The review can be finalised by an expedited review process i.e. without having to serve before the full committee again;

6.5.6.12.4 **Deferred:** The proposed research has major methodological and/or ethical concerns and requires considerable revision. The research applicant must resubmit the revised research application. The revised research application will be reconsidered at a convened (full) committee meeting;

6.5.6.12.5 **Rejected:** The proposed research may not be resubmitted;

6.5.6.13 Once a decision is made, an HREC official notification will be sent to the investigator;

6.5.6.14 The HREC will defer the proposed research to another meeting, or obtain consultation if there is not at least one person on the HREC with appropriate scientific or scholarly expertise or other expertise or knowledge to conduct an in-depth review of the protocol;

6.5.6.15 Voting will be recorded as number for, against and abstaining;

6.5.6.16 The secretary records all decisions, and the method by which they were made, in the minutes. All discussion points, issues of controversy and reasons for decisions are documented in the minutes. The secretary also documents any member leaving or entering the room during the meeting, in order to record recusls and ensure that a quorum is always present;

6.5.6.17 In the event that a clear decision cannot be established by the committee, the HREC the Chairperson (or acting Chairperson) will have the final deciding vote;

6.6 Documents required for HREC application: New research

HREC requires the following documents as part of the application package for review of applications for new research:

6.6.1 Completed electronic HREC Application Form submitted via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

6.6.2 **Cover letter,**

6.6.3 **PI-generated protocol synopsis.** The synopsis must:

6.6.3.1 Be between 750 and 1500 words;

6.6.3.2 Be readily understood by committee members who include non-scientists and community members. Write in simple, non-technical language and spell out acronyms on first use;

6.6.3.3 Contain sufficient information for committee members to evaluate the proposal independently of any other protocol documentation. Aside from the primary reviewers, all other committee members rely heavily on only the synopsis and supporting documentation (recruitment adverts, informed consent forms, data collection tools etc.) to review, discuss and vote on a proposal in the meeting;

6.6.3.4 Be specific to the local principal investigator's site (particularly important for multi-site studies). Sponsor-produced synopses are, as a rule, too general and lack enough relevant detail specific to the local site. Given familiarity with the local setting, the principal investigator is well placed to prepare a contextually relevant and ethically reflective synopsis, to allow the committee to undertake a thorough review:

6.6.3.4.1 Specify how the research will be conducted at the local site. Indicate, where necessary, how this might be different from what is stated in the international protocol;

6.6.3.4.2 Describe the local study site, including the available infrastructure, and the roles and responsibilities of study staff;

6.6.3.4.3 Detail the specifics of participant selection, socio-demographic and educational background of participants, and any risks and benefits that might be unique to local participants;

6.6.3.4.4 Describe the recruitment and informed consent processes proposed for the local site;

6.6.3.5 Situate the study's purpose and (local) social value in the context of currently available and relevant literature;

6.6.3.6 Describe the research objectives and any hypotheses being tested;

6.6.3.7 Describe the design of the study and research methodologies. In the case of clinical research, carefully distinguish experimental interventions from standard of care;

6.6.3.8 Detail inclusion and exclusion criteria;

6.6.3.9 Describe how participants will be selected and recruited, with specific detail on partcipants' soci-demographic and educational background; how, when, where and by whom participants will be identified and approached;

6.6.3.10 Describe the frequency, severity, duration and reversibility of foreseeable harms, including physical, psychological, social and economic. Describe site-specific measures to minimize the potential for these harms and protect participant welfare;

6.6.3.11 Describe expected benefits to individual participants and/or potential societal benefits in the local setting;

6.6.3.12 Describe site-specific measures to protect participants' privacy and the confidentiality of their collected data;

6.6.3.13 Describe what measures and protections will be in place for collection and storage of biological specimens;

6.6.3.14 Indicate, with appropriate justification, whether post-trial treatment will be available for local participants; and

6.6.3.15 Identify and justify any aspects of the study that could reasonably be considered ethically controversial, for example, the use of placebo, withholding standard of care, deception, commercial drug or device trials where the intervention is unlikely to be accessible or affordable in the local setting. Detail how these ethical issues will be addressed and any extra protections that will be implemented;

6.6.4 **Research protocol;**

6.6.5 For multi-site studies, a **protocol addendum** that should at a minimum:

6.6.5.1 Specify how the research will be conducted at the local site. Indicate, where necessary, how this might be different from what is stated in the international protocol;

6.6.5.2 Describe the local study site, including the available infrastructure, and the roles and responsibilities of study staff;

6.6.5.3 Detail the specifics of participant selection, socio-demographic and educational background of participants, and any risks and benefits that might be unique to local participants;

6.6.5.4 Describe the recruitment and informed consent processes proposed for the local site;

6.6.6 **Informed consent and assent forms** OR motivated request for a waiver of informed consent:

6.6.6.1 Submit drafted informed consent and assent forms in either English or Afrikaans. Once the HREC-required changes, if any, have been made, submit translations in English, Afrikaans and Xhosa, along with a translation certificate or letter of authenticity;

6.6.6.2 If translated consent forms are not necessary for the particular study, specifically justify this in the protocol under "Ethical considerations";

6.6.6.3 For **multi-site trials**, the informed consent and/or assent forms should be adapted by the principal investigator for the local site. Submit only those forms relevant to the local site;

6.6.6.4 Informed consent and assent templates for child research, genetic research, case reports, and online research can be found on the HREC website www.sun.ac.za/healthresearchethics under *Forms and Instructions*)

6.6.7 **Participant recruitment materials** (e.g. adverts, flyers, posters etc.);

6.6.8 **Data collection tools** (e.g. survey, questionnaire, interview guide);

6.6.9 **Material for participants** (e.g. diaries, patient identification cards);

6.6.10 **Letters of authorization from institutions** (e.g. hospital, clinic, school);

6.6.11 **Budget** (and financial contract, if external funding)**;**

6.6.12 **Post-trial care**/care after research justification;

6.6.13 For studies that intend to send or receive data or samples to or from another location, a **Material Transfer Agreement (MTA) Term Sheet** (see *Section 18: Material Transfer Agreements* for details on MTA review requirements);

6.6.14 **Proof of insurance for participants**;

6.6.15 **Two-page CV for each investigator and research supervisor**. The CV must:

6.6.15.1 Demonstrate experience relevant to the proposed research; and

6.6.15.2 Include: MPS number, HPCSA number and category of registration;

6.6.16 **Signed investigator declaration and conflict of interest forms for each investigator and research supervisor.** Complete and sign an "investigator declaration" and declare any conflict of interest for each principal investigator, co-investigator, sub-investigator and research supervisor;

6.6.17 **HREC payment instruction form and Proof of payment for HREC review fee:**

6.6.17.1 **Clinical trial:** submit only a Payment Instruction form for clinical trials;

6.6.17.2 **All other health and student research:** Submit both a Payment instruction form for health research AND Proof of payment through internal requisition or external bank deposit;

6.6.17.3 Non-sponsored student research conducted for degree purposes at Stellenbosch University, research funded solely from an SU departmental budget, Harry Crossley research, and self-funded research is exempt from HREC fees. Submit only a completed Payment instruction form for health research;

6.6.18 For studies using REDCap as the data management tool:

6.6.18.1 Data dictionary of the REDCap database;

6.6.18.2 List of users assigned to have access to the database;

6.6.19 For studies that require submitted documents with version numbers and version dates to be listed in the HREC response letter, a **cover letter** listing all submitted documents with version numbers and version dates;

6.6.20 **For industry- or sponsor-driven studies and HREC clinical trial[1] applications:**

6.6.20.1 Sponsor synopsis;

6.6.20.2 Proof of GCP training for investigators;

6.6.20.3 Investigator's brochure;

6.6.20.4 SA approved package insert(s) of registered comparators;

6.6.20.5 A summary of Phase III efficacy and safety data if this is an application for an open label or extension study;

6.6.20.6 SAPHRA letter of approval or proof of application;

6.6.20.7 If an application has been submitted to SAHPRA, a copy of Section 13 (Ethical Issues) extracted from the CTF1 application form;

6.6.20.8 NHREC approval or proof of application;

6.6.20.9 Letter of legal indemnity, extended to Stellenbosch University and Tygerberg/Stikland Hospital (if applicable);

6.6.21 Other relevant documentation.

[1] *Definition of a Clinical Trial for HREC application purposes:* Research study or investigation intended to test safety (not harmful or dangerous to human health), quality (ingredients are of good quality), effectiveness (working to diagnose, treat, prevent or cure a disease condition) and efficacy (better/ best when compared with other treatment or medicine for a similar condition) of new and/or existing or old medicines, medical devices and/or treatment options, using human participants (South African National Clinical Trials Register, South African Department of Health, see:http://www.sanctr.gov.za/Resources/Whatisaclinicaltrial/tabid/175/Default.aspx)

7. HREC APPLICATION REQUIREMENTS AND REVIEW PROCESS: STUDENT RESEARCH

7.1 Policy

This policy covers all new student research protocols and prescribes student and supervisor responsibilities for submitting documents to the HREC.

7.2 Purpose

The purpose of this policy is to define and describe the application requirements and review process for new student research reviewed by the HREC and/or UREC.

7.3 HREC application and review process: Student research

7.3.1 PhD research

7.3.1.1 PhD projects will usually (preferably) be reviewed by a full HREC. However, if there is a well-motivated reason why minimal risk review is required, then a covering letter of motivation requesting minimal risk review should be submitted along with the project;

7.3.1.2 Phd applicants must follow the HREC application requirements and review process as detailed in *Section 6: HREC Application requirements and review process: New research;* **and**

7.3.1.3 All PhD projects **must have undergone a scientific review process first** before being submitted to HREC for ethics review and approval. The **final** version of the protocol, as approved by the scientific committee, should be submitted to HREC.

7.3.2 Postgraduate research (degree and diploma)

7.3.2.1 All postgraduate student health research for degree and diploma purposes (with the exception of Honours and BTech projects) must be submitted to HREC for review prior to the start of study related activities;

7.3.2.2 Postgraduate research applicants must follow the HREC application requirements and review process as detailed in *Section 6: HREC Application requirements and review process: New research;*

7.3.2.3 Honours-and BTech projects will be reviewed by the Undergraduate Research Ethics Committee. Please refer to *Section 4.7.3* below;

7.3.2.4 Given the time limitations for many postgraduate students, it is recommended that postgraduate students either:

7.3.2.4.1 Pursue research that poses no more than minimal risk. This research can be reviewed using the minimal risk review process, which generally offers a shorter turnaround time by the HREC; **or**

7.3.2.4.2 Pursue research that poses more than minimal risk, but plan for this in advance, and submit to the HREC with plenty of time for adequate convened (full) meeting review prior to the expected research start date;

7.3.3 Undergraduate, Honours and BTech research

7.3.3.1 Many Undergraduate, Honours and BTech students are required to complete small research projects or educational exercises during the course of their studies. Only some of these projects will require Undergraduate Research Ethics Committee (UREC) review;

7.3.3.2 It is the supervisor's responsibility to establish, within the applicable laws and regulations relating to research ethics, whether or not the project requires UREC review;

7.3.3.3 Supervisors are advised to seek further guidance and confirmation from the UREC Chairperson, UREC coordinator or a delegated member;

7.3.3.4 Supervisors of Undergraduate, Honours and BTech projects should note the following:

7.3.3.4.1 The scope and ethical sensitivity of the project should be carefully considered and chosen;

7.3.3.4.2 Undergraduate, Honours and BTech students can be inclined to choose projects which interest them, but which may involve sensitive or ethically challenging issues or complexities for which some students are poorly equipped to deal, for example, termination of pregnancy, drug abuse in pregnancy, etc.;

7.3.3.4.3 Undergraduate, Honours and BTech students are strongly encouraged to conduct only minimal risk research (see *Section 6.4.2: Minimal risk research* for definition of minimal risk research);

7.3.3.4.4 **NOTE:** Small minimal risk studies also tend to fit better into the time-sensitive requirements of these academic programmes;

7.3.3.5 The following is intended to serve as a guideline to supervisors in decision-making around whether a project requires UREC review;

7.3.3.6 **Undergraduate, Honours or BTech project requires UREC review:**

7.3.3.6.1 The proposed project is **health research** i.e. a systematic investigation that will lead to generalizable knowledge in the field of health;

7.3.3.6.2 The results of the project will be **presented external to the classroom** environment e.g. presentation at a conference, publication in a journal;

7.3.3.6.3 The intended research will be **conducted in the public domain** e.g. in a school or hospital environment, recruiting scholars or patients as participants.

7.3.3.7 **Undergraduate, Honours or BTech project may not require UREC review:**

7.3.3.7.1 The intended project is an **educational exercise** only;

7.3.3.7.2 The results of the project will be kept entirely internal i.e. there is **no intention to present or publish** in any forum external to the student's own classroom environment;

7.3.3.7.3 For further guidance refer to *Appendix VII*: *Guidance on educational exercises and health research*)

7.3.3.7.4 **NOTE:** Many undergraduate research projects provide interesting and valuable results that may be worthy of publication. Proof of ethical clearance will be required for publication and this cannot be given retrospectively.

7.3.3.8 UREC application and review process: minimal risk undergraduate, Honours and BTech research

7.3.3.8.1 **To submit a UREC application for new research:** As far as possible before a submission deadline, submit an electronic copy of the UREC application

package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

7.3.3.8.2 Guidelines for submissions are available from the Health Research Ethics Office website at www.sun.ac.za/healthresearchethics, see *Forms & Instructions;*

7.3.3.8.3 UREC applications for new *minimal risk Undergraduate, Honours and BTech* research can be submitted on a rolling basis, but must be received by the published bi-monthly UREC submission deadlines;

7.3.3.8.4 UREC front office administration reviews the application for completeness and may request additional information from the applicant;

7.3.3.8.5 The UREC coordinator allocates the application to one reviewer;

7.3.3.8.6 A UREC member reviews the minimal risk research application and submits their proposed review outcome to the UREC Chairperson or their designated deputy for approval;

7.3.3.8.7 The research application and review outcome are approved, at the discretion of the UREC Chairperson;

7.3.3.8.8 Applicants are notified in writing of the UREC review decision and may commence with their research if their application has been approved, on condition that any additional modifications or feedback required by HREC following the convened full meeting at which the review decision is ratified will be adhered to and implemented by the applicant effective immediately;

7.3.3.8.9 The UREC review decision is ratified at the next available convened HREC meeting;

7.3.3.8.10 HREC reserves the right to suspend UREC approval and to request changes or clarifications from student applicants. If there are minor problems, HREC may request additional information or changes without suspending UREC approval. If the problems are deemed more substantial, the UREC approval will be suspended and the applicant will be notified that the project will need to be reviewed and discussed at the next convened HREC meeting. The UREC coordinator will notify the applicant (and if applicable, the supervisor) of this suspension within 1 day of receiving the notice of suspension from HREC;

7.3.3.8.11 The HREC will regard the supervisor as the investigator who assumes ultimate responsibility for the student project. The project will be registered under the name of the student and all correspondence will be addressed directly to the student and cc'd to the supervisor.

7.3.3.9 Full committee review (convened HREC meeting): review of more than minimal risk undergraduate, Honours and BTech research

4.7.3.4.1 Please refer to *Section 6.5: Full Committee Review (Convened HREC meeting)* for review requirements and processes relating to full committee review of *more than minimal risk* research (including Undergraduate, Honours and BTech *more than minimal risk* research);

4.7.3.4.2 The HREC will regard the supervisor as the investigator who assumes ultimate responsibility for the student project. The project will be registered under the name of the student and all correspondence will be addressed directly to the student;

4.7.3.4.3 Undergraduate, Honours and BTech students are strongly encouraged to conduct only *minimal risk* research. These also tend to fit better into the time-sensitive requirements of these academic programmes;

7.3.3.10 Documents required for UREC application: new Undergraduate, Honours and BTech research

UREC requires the following documents as part of the application package for review of undergraduate, honours and BTech research applications for new research:

7.3.3.10.1 Completed electronic UREC Application Form submitted via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za

7.3.3.10.2 A cover letter, signed by the supervisor, stating clearly that this is undergraduate research and motivating for a "minimal risk" review process;

7.3.3.10.3 The **written protocol** they have developed as part of their course requirements, which should include a budget and timeline;

7.3.3.10.4 A **protocol synopsis:** between 750 – 1000 words providing a clear, concise summary of the research;

7.3.3.10.5 The **student applicant's Curriculum Vitae (CV)**The **supervisor's Curriculum Vita (CV);**

7.3.3.10.6 Signed **investigators declaration and conflict of interest forms** from both the student applicant and the supervisor, as well as from any other members of the research team (e.g. group members, co-supervisor); **and**

7.3.3.10.7 **Informed consent and assent forms** OR motivated request for a waiver of informed consent:

7.3.3.10.7.1 Submit drafted informed consent and assent forms in either English or Afrikaans. Once the HREC-required changes, if any, have been made, submit translations in English, Afrikaans and Xhosa, along with a translation certificate or letter of authenticity;

7.3.3.10.7.2 If translated consent forms are not necessary for the particular study, specifically justify this in the protocol under "Ethical considerations";

7.3.3.10.8 **HREC payment instruction form and Proof of payment for HREC review fee:**

7.3.3.10.8.1 HREC has a graded administrative fee structure in place, which is revised annually. The HREC fee structure is available on the HREC website: www.sun.ac.za/healthresearchethics;

7.3.3.10.8.2 Sponsored/funded student research: Submit both a Payment instruction form for health research AND Proof of payment through internal requisition or external bank deposit;

7.3.3.10.8.3 Non-sponsored student research conducted for degree purposes at Stellenbosch University is exempt from HREC fees. Submit only a Payment instruction form for health research;

7.3.3.10.8.4 See *Section 12: HREC Review fees* for detailed HREC review fee requirements and payment process.

8. REVIEW CRITERIA

8.1 Policy

The essential policy of HREC is to protect the dignity, rights, safety, and well-being of all human participants in health-related research. HREC will do this through independent, prospective and ongoing ethics review of all health research projects undertaken by members of staff, registered students and affiliates of the University.

8.2 Purpose

The purpose of this policy is to outline the considerations and factors that may influence the scientific validity and ethical acceptability of the research.

8.3 Review criteria

Please see *Appendix I: HREC review guide* for the detailed HREC review framework. HREC uses the following criteria for review:

8.3.1 **Social and scientific value:** The proposed research must demonstrate relevance to:

8.3.1.1 The community involved and/or the greater South African and/or African community; **and**

8.3.1.2 The advancement of knowledge/the scientific field in the proposed area of study and/or related areas of study.

8.3.2 **Scientific validity:** The proposed research must be:

8.3.2.1 scientifically valid; **and**

8.3.2.2 Research must be well designed and conducted (e.g. clear aims, rigorous design, adequate sample, adherence to GCP, sound data analysis). Even a valuable research question can be poorly researched, resulting in unreliable data. Poorly designed research that is not scientifically sound is unethical because it wastes resources and exposes participants to risks and inconvenience for no purpose if the research yields inaccurate conclusions/ misleading answers;

8.3.2.3 To meet ethical requirements, research ought not expose patients and volunteers to inconvenience or risk of harm without possible benefit to society or where the research will not generate the intended knowledge;

8.3.2.4 The proposed investigators/researchers/study coordinators must be:

8.3.2.4.1 *Suitably qualified to undertake the research*. Studies that have a substantial clinical component, where the principal Investigator is not a clinician, s/he should appoint an HPCSA-registered clinician as a co-Investigator to the study; **and**

8.3.2.4.2 *Registered with the Health Professions Council of South Africa (HPCSA)* or other South African statutory body, as appropriate. If not registered with HPCSA or other statutory body, the committee shall, based on the applicant's CV and other documentary submissions, satisfy itself that the applicant is competent to undertake the roles described in the protocol, subject to legal requirements; **or**

8.3.2.4.3 For non-South African citizens, proof of registration with an equivalent body in their home country *and* in South Africa will be necessary. Where this is not

available, then a motivation and/or other supporting documents from a locally registered person or appropriate authority should accompany the application as evidence of competence;

8.3.2.5 The proposed research has the following resources:

8.3.2.5.1 Adequate number of qualified staff;

8.3.2.5.2 Adequate facilities;

8.3.2.5.3 Access to a population that will allow recruitment of the necessary number of participants;

8.3.2.5.4 Availability of medical or psychosocial resources that participants might need as a consequence of the research.

8.3.3 **Reasonable risk-benefit ratio:**

8.3.3.1 The potential risks to individual subjects in the proposed research must be outweighed by the benefits to the individual or society; Risks to participants are reasonable in relation to:

5.3.3.3.1 The *anticipated benefits* to participants and/or the broader community; **and**

5.3.3.3.2 The *importance of the knowledge* that may reasonably be expected to result.

8.3.3.2 ALL the following requirements must satisfied:

8.3.3.2.1 The potential risks to individual participants are identified and minimized;

8.3.3.2.2 The proposed research involves procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk;

8.3.3.2.3 Risk minimization measures are undertaken and stated in the protocol;

8.3.3.2.4 When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants; and

8.3.3.2.5 Whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

8.3.3.3 The potential benefits of the research to participants and/or the wider community are identified and maximized. **NOTE:** Compensation for time and inconvenience, and reimbursement for expenses such as travel are <u>not</u> considered research benefits;

8.3.3.4 In evaluating risks and benefits, HREC shall consider only those risks and benefits that may result from the research itself (as distinguished from risks and benefits of therapies participants would receive as standard clinical practice, even if not participating in the research). HREC shall not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among the research risks and benefits that fall within the purview of its responsibility;

8.3.3.5 As per SA-GCP 2.2:

8.3.3.5.1 the HREC risk-benefit analysis takes full cognizance of benefits and harms beyond the life of the study itself, particularly in relation to chronic life-threatening conditions;

8.3.3.5.2 If placebos are to be used, whether their use is justified;

8.3.3.5.3 Making specific recommendations regarding the continuation of treatments beyond the life of the study, or mechanisms to ensure that participants are fairly protected;

8.3.3.5.4 Whether the product will be made available to participants after the study ends, and if so whether there is any cost to participant to continue treatment.

8.3.4 **Fair selection of participants**

8.3.4.1 The selection of research participants for the proposed research must be fair and just;

8.3.4.2 In making this assessment HREC shall take into account the purpose of the research and the setting in which the research will be conducted and shall be particularly cognisant of the special challenges of research involving vulnerable populations, such as children, prisoners, pregnant women, intellectually impaired persons, or economically or educationally disadvantaged persons;

8.3.4.3 Participants must be selected:

8.3.4.3.1 *According to the scientific goals of the study* (not for non-scientific reasons e.g. convenient, vulnerable, less able to protect their rights); and

8.3.4.3.2 *To minimize risks* (some participants may be eligible for scientific reasons, but at substantially higher risk of harm, e.g. impoverished and vulnerable to undue inducements);

8.3.4.3.3 To *fairly distribute benefits and burdens.* Research can provide direct and indirect **benefits.** Participants should be selected so that these benefits are fairly distributed;

8.3.4.4 Participants and/or communities **should not be excluded without sound justification.** Unfair exclusion from research may deny these participants and/or communities relevant knowledge/ health interventions;

8.3.4.5 Individuals and groups who bear the burdens of the research should share its benefits (new knowledge or products). Those who stand to benefit from research must contribute to its risks and discomforts. No group of persons should be asked to bear more than their fair share of the burdens of research; no group (e.g. impoverished) should be asked to bear research risks in order that others (e.g. the wealthy) enjoy benefits (new knowledge or products);

8.3.4.6 The research should avoid vulnerable participants when less vulnerable persons could be involved;

8.3.4.7 When some or all of the participants are likely to be vulnerable, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, the applicant has:

8.3.4.7.1 Justified why vulnerable individuals/communities are included;

8.3.4.7.2 Included, and clearly articulated, additional safeguards in the proposed research to minimize risks for, and protect the rights and welfare of, these participants (see *Appendix II: Vulnerable communities and research requiring additional attention*);

8.3.4.8 The use of socially constructed categories, such as race, ethnicity and gender:

8.3.4.8.1 HREC recognizes that human categories such as race, ethnicity and gender are social constructs;

8.3.4.8.2 The use of socially constructed categories, such as race, ethnicity and gender in research must be adequately justified;

8.3.4.8.3 The onus is on the research applicant to adequately justify to the HREC the value and meaning of the use of such categories, inclusive of how it will be documented and reported on for the purposes of the study;

8.3.4.8.4 The researcher(s) must have the necessary expertise/ background to carefully navigate the contours of these complex constructs, and evidence of such expertise and/or support must be provided to HREC;

8.3.4.8.5 Participants must retain the right to self-identification and preference not to answer;

8.3.4.8.6 Research proposing the use of socially constructed categories will warrant review by two reviewers and if deemed necessary be discussed at a full HREC meeting. The discussion will be documented in HREC meeting minutes;

8.3.4.8.7 When reviewing research protocols where human categories are included in the fabric of the study (e.g. in the aim, methodology, research instrument(s), ICF and or recruitment strategies) HREC reviewers must carefully consider the rationale, justification and evidence of the careful unpacking of intricacies as provided by the researcher(s) for the inclusion of such variables(s) for data collection, analysis or reporting;

8.3.4.8.8 HREC follows a structured and disciplined process as outlined by the SA Constitution, international and national guidelines, for example the NDOH guidelines (2015) that explicitly states that:

8.3.4.8.8.1 It must be necessary to collect this data: "Information about a person's race or ethnic origin must be necessary (s 29(a)) or for affirmative action purposes (s 29(b))"; and that

8.3.4.8.8.2 Nobody may be excluded based on race, gender, etc.: "Persons should not be excluded unreasonably or unfairly on the basis of any of the prohibited grounds for discrimination: race, age, sex, sexual orientation, disability, education, religious belief, pregnancy, marital status, ethnic or social origin, conscience, belief or language (s 8 of the Constitution); or

8.3.4.8.8.3 Nobody may be unfairly targeted based on race, gender, etc.: "Similarly, persons should not be unfairly targeted for research merely on the basis of one or other of these grounds."

8.3.5 **Informed consent process**

The informed consent process for the proposed research allows for:

8.3.5.1 An informed and voluntary decision from each prospective participant, or the participant's legally authorized representative, in accordance with, and as required by *Section 11: Informed Consent* of this document; and

8.3.5.2 Appropriately documented written informed consent, in accordance with, and as required by *Section 11.6: Documentation of Informed Consent* of this document;

8.3.5.3 Informed consent and assent templates, including templates for child research, genetic research, case reports, and online research, can be found on the HREC website www.sun.ac.za/healthresearchethics under *Forms and Instructions*.

8.3.6 **Respect for participants.**

When reviewing the protocol, HREC ensures that:

8.3.6.1 The proposed research demonstrates respect for the dignity of participants throughout the course of the research;

8.3.6.2 Participants may withdraw from the study at any time without prejudice;

8.3.6.3 There are adequate provisions to protect the privacy of participants and to maintain the confidentiality and security of participant data;

8.3.6.4 **Maintaining privacy and confidentiality** respects participants' rights to choose to whom, and what personal information, is disclosed. Participants must consent to the ways in which confidentiality will be maintained (e.g., using codes instead of identifiers, restricted access to data), as well as to how the results will be published, and to any limits to confidentiality where these apply;

8.3.6.5 There are adequate measures in place to monitor participant welfare throughout; and

8.3.6.6 The research plan makes adequate provisions for monitoring data to ensure the safety of participants. HREC will consider the following provisions:

8.3.6.6.1 What safety information will be collected, including serious adverse events;

8.3.6.6.2 How the safety information will be collected (e.g. at study visits, by telephone calls with participants, etc.);

8.3.6.6.3 The frequency of data collection, including when safety data collection starts;

8.3.6.6.4 The frequency or periodicity of review of cumulative safety data;

8.3.6.6.5 Whether or not a data monitoring committee is present and the frequency of reporting;

8.3.6.6.6 Other provisions for oversight, as deemed appropriate, in the event of high-risk research;

8.3.6.7 Participants are informed of research results

8.3.7 **Respect for communities**

8.3.7.1 The proposed research demonstrates respect for communities by appropriate community interaction and feedback of results;

8.3.7.2 There are adequate provisions to respect the autonomy of communities and to maintain the confidentiality and security of community data;

8.3.7.3 There is appropriate community consultation, for example, discussions with Community Advisory Boards (CABs) and/or other community representatives during the planning phase of the research, before the commencement of the research, i.e. the community should be part of the research process; and

8.3.7.4 Communities are informed of research results.

9. HREC APPLICATION REQUIREMENTS AND REVIEW PROCESS: CONTINUING REVIEW

9.1 Routine continued review (Annual progress reports)

9.1.1 Purpose

International and local guidelines and regulations (Dept of Health, ICH GCP, SA GCP, SAPHRA and 45 CFR 46,) require that ethics committees conduct substantive and meaningful continuing review of all approved research at least yearly and more frequently if the level of risk warrants this. The HREC will determine whether the protocol needs verification from sources other than the researchers that no material changes have occurred since the previous HREC review and that the research is still in compliance with the original review criteria.

9.1.2 Purpose

The purpose of this policy is to provide guidance on the continuing review process for active research protocols.

9.1.3 **Application and review process: Annual progress reports** (routine continued review)

9.1.3.1 **Ethics approval is valid for one year only;**

9.1.3.2 A progress report is an application for renewal of ethics approval and must be submitted annually, unless the HREC deems the project to be of particularly high risk and requests more frequent progress reports;

9.1.3.3 Progress reports must be submitted to HREC annually until such time as the investigator submits a final study report (this includes the premature completion of the study) and/or a notice of termination of the study;

9.1.3.4 A study is considered active while analysis of any data collected or resulting from the study is ongoing;

9.1.3.5 No research may continue without this process and re-approval;

9.1.3.6 Progress reports must be submitted around 2 months before the ethics approval expiry date, so that the submission can be reviewed, and the project re-approved **prior** to the expiry date;

9.1.3.6.1 HREC recognizes the logistical advantages of keeping the expiration date of the HREC approval period constant from year to year throughout the life of a research project;

9.1.3.6.2 Therefore, when the HREC performs continuing review and reapproves (with or without conditions) the research within 30 days *before* the current HREC approval period expires, the HREC may retain the anniversary of the expiration date of the initial HREC approval as the expiration date of each subsequent one-year approval period;

9.1.3.7 All clinical trials falling under the jurisdiction of the SAPHRA must submit a progress report to SAPHRA six monthly. Copies of these SAPHRA progress reports should accompany the

annual progress report submitted to the HREC. Please do not submit your 6 monthly SAPHRA progress report outside of this annual reporting to our HREC, unless necessary for safety reasons;

9.1.3.8 The HREC office accepts new minimal risk research applications at any time, on a rolling basis

9.1.3.9 Submit an electronic copy of the HREC annual progress report application package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

9.1.3.10 HREC front office administration reviews the application for completeness and may request additional information from the applicant;

9.1.3.11 If a project was eligible for expedited review when initially approved, the continuing review may occur via an expedited process:

- 9.1.3.11.1 The HREC Coordinator allocates the application to one HREC reviewer;
- 9.1.3.11.2 An HREC member reviews the minimal risk research application and submits their proposed review outcome to the HREC office;
- 9.1.3.11.3 The research application and review outcome are approved, at the discretion of the HREC Chairperson, and ratified at the next available convened HREC meeting;
- 9.1.3.11.4 Once a decision is made, an HREC official notification will be sent to the investigator;
- 9.1.3.11.5 After review, the HREC member can recommend that the research, or components thereof, represent more than minimal risk and refer the review to the next available convened HREC meeting;

9.1.3.12 If the original project was not eligible for expedited review, e.g. clinical trial, then the continuing review must occur at a convened and quorate meeting.

- 9.1.3.12.1 The progress report will be distributed to all HREC members prior to each meeting for discussion and renewal of approval;
- 9.1.3.12.2 The convened HREC will agree to approve or disapprove the study as stipulated in *Section 6.5: Full committee review (convened HREC meeting*) of this document;
- 9.1.3.12.3 The minutes of the HREC meeting will document separate deliberations for each protocol undergoing continued review by the convened HREC meeting;
- 9.1.3.12.4 An official HREC letter will be forwarded to the applicant with any queries and or findings regarding the submitted documents included in the progress report. Communication between the applicant/researcher and HREC will then follow procedure described in *Section 10: Communication of Review Decisions;*

9.1.3.13 If the researcher does not provide continuing review information to the HREC or the HREC has not approved a protocol by the expiration date, approval will lapse and the investigator will have to provide a reason for such delay, specify all research activities which occurred during this lapsed period and seek approval by the convened HREC for the use of the data collected during the lapsed period. If deemed necessary, the HREC may consider the following:

9.1.3.13.1 Data collected during periods where HREC approval has lapsed is not eligible for use in the research;

9.1.3.13.2 Suspension of research (temporary halt in HREC approval of some or all research activities OR termination of research (permanent halt in HREC approval of ALL research activities);

9.1.3.13.3 Cessation of intervention and interaction on current participants;

9.1.3.13.4 Cessation of new enrollment of participants;

9.1.3.13.5 The suspension or termination of a trial as determined by the convened HREC will result in a letter sent from HREC office to the principal investigator with notice of the HREC decision. The letter will also include the instructions:

9.1.3.13.5.1 Actions to protect the rights and welfare of the currently enrolled participants;

9.1.3.13.5.2 Procedure to follow for the withdrawal of enrolled participants with regard to medical care arrangements, transfer to different site, etc;

9.1.3.13.5.3 Informing participants or the termination or suspension of the research study and the reason for such a decision;

9.1.3.14 Suspension and termination of HREC approval must be reported to the Sponsor and FDA (if applicable) within 30 days of notification receipt from HREC;

9.1.3.15 HREC does not need verification from sources other than the researchers that no materiel changes have occurred since previous HREC review;

9.1.3.16 The progress report should contain sufficient information to allow the reviewer to conduct a substantive and meaningful review of the progress of the project, including any challenges or problems encountered;

9.1.3.17 All investigators whose projects are funded by US government federal funds (NIH, CDC etc) must comply fully with OHRP requirements for continuing review. These can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm;

9.1.4 **Documents required for HREC application: Annual progress reports** (routine continued review)

HREC requires the following documents as part of the application package for review of annual progress reports:

9.1.4.1 Completed electronic HREC Application Form for progress report submitted via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

9.1.4.2 Cover letter

9.1.4.3 **Proof of payment of the HREC review fee for progress reports** must accompany this submission (Payment Instruction form for clinical trials; Proof of payment through internal requisition or external bank deposit for other research);

9.1.4.4 An updated complete protocol, incorporating all approved amendments should be submitted approximately every three years unless there have been no, or minimal changes to the project;

9.1.4.5 Copies of published abstracts, may be submitted as attachments, if appropriate and self-explanatory;

9.1.4.6 The Serious Adverse Event (SAE) Summary and Protocol Noncompliance Summary are applicable primarily to clinical research studies with an experimental design. If not applicable, then these pages need not be included and can be deleted;

9.1.4.7 For multi-site studies the **information in the progress report must pertain specifically to local (SU) sites**. For each of the reporting requirements listed below, the PI must report specifically for the local site(s), while putting these local reports into perspective by reporting them relative to the larger study:

9.1.4.7.1 the number of participants recruited;

9.1.4.7.2 a summary of any unanticipated problems and available information regarding adverse events (in many cases, such a summary could be a simple 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 brochure);

9.1.4.7.3 a summary of any withdrawal of participants from the research since the last Research ethics committee (REC) review;

9.1.4.7.4 a summary of any complaints about the research since the last REC review; a summary of any recent literature that may be relevant to the research and any amendments or modifications to the research since the last REC review; any relevant multi-center trial reports;

9.1.4.7.5 any other relevant information, especially information about risks associated with the research;

9.1.4.7.6 A copy of the current informed consent document and any newly proposed consent document.

9.2 Protocol amendments

9.2.1 Policy

In line with local and international guidelines, amendments to an approved protocol may become necessary as a study proceeds. The HREC must review and approve all proposed protocol amendments *before* the amendment is implemented in the study.

9.2.2 Purpose

The purpose of this policy is to outline the procedures involved in applying for an amendment to an approved protocol.

9.2.3 Definitions

Amendments are planned changes to an approved study protocol, made in advance. Amendments may be classified as minor or major (substantive).

9.2.3.1 Minor amendments:

Minor amendments do not change the risk benefit profile of the study in any way. Examples of typical minor amendments:

9.2.3.1.1 Additional Investigators or study sites;
9.2.3.1.2 Small changes in the Informed Consent;
9.2.3.1.3 Change in background information or update of literature review;
9.2.3.1.4 Extension of period of study;
9.2.3.1.5 Other changes that do not affect study design and will not affect study outcomes or results;
9.2.3.1.6 Administrative changes;
9.2.3.1.7 Stricter inclusion or exclusion criteria.

9.2.3.2 Major or substantive amendments

Major or substantive amendments require a change(s) to the study methodology or procedure that may result in an alteration of the risk benefit profile of the study. Examples include:

9.2.3.2.1 Change in study aims, objectives or design;
9.2.3.2.2 Resulting changes to consent documents;
9.2.3.2.3 Additional study procedures;
9.2.3.2.4 Easing of inclusion or exclusion criteria;

9.2.3.3 Changes in approved research that are initiated without HREC approval to eliminate apparent immediate hazards to the participant must be reported to the HREC within 30 days to determine whether the change was consistent with ensuring the participants continued welfare. In the same way, it is the researcher responsibility to must report the premature completion to HREC;

9.2.3.4 HREC will determine whether any significant new findings that arise from the review process and that may relate to participants willingness to continue participation are provided to participants.

9.2.4 HREC application and review process: Amendment application

9.2.4.1 **To submit an HREC application for review of an amendment:** submit an electronic copy of the HREC progress report application package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

9.2.4.2 HREC amendment applications can be submitted on a rolling basis, but must be received by the published HREC submission deadline in order to be considered for the agenda of that meeting;

9.2.4.3 HREC front office administration reviews the application for completeness and may request additional information from the applicant;

9.2.4.4 The final decision as to whether an amendment is minor or major and whether it requires expedited or full committee review rests with the HREC Chairperson, or a person delegated this authority by the HREC.

9.2.4.5 The HREC Coordinator allocates the application to one HREC reviewer;

9.2.4.6 An HREC member reviews the amendment application and submits their proposed review outcome to the HREC office;

9.2.4.7 The amendment application and review outcome are approved, at the discretion of the HREC Chairperson, and ratified at the next available convened HREC meeting;

9.2.4.8 Once a decision is made, an HREC official notification will be sent to the investigator;

9.2.4.9 After review, the HREC member can recommend that the amendment, or components thereof, represent a major amendment and refer the review to the next available convened HREC meeting;

9.2.4.10 The amendment should not be implemented prior to HREC approval. An exception to this would be where it is necessary to eliminate an immediate hazard to trial participants or when the change involves only administrative or logistical elements e.g. change of telephone number.

9.2.5 Documents required for HREC application: Amendment

9.2.5.1 Completed electronic HREC Amendment Application Form submitted via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

9.2.5.2 Cover letter;

9.2.5.3 Revised documents (e.g. protocol, informed consent, etc.) with proposed revisions indicated in TRACK CHANGES throughout the document;

9.2.5.4 **Proof of payment of the HREC review fee for amendments** must accompany this submission (Payment Instruction form for clinical trials; Proof of payment through internal requisition or external bank deposit for other research).

9.3 Protocol deviations

9.3.1 Policy

In line with local and international guidelines, any changes to an approved protocol (no matter how minor) must receive prior HREC approval before implementation – unless such change is intended to eliminate an immediate hazard or harm to the research participant.

9.3.2 Purpose

The purpose of this policy is to outline the reporting of protocol deviations to the HREC.

9.3.3 Definitions

9.3.3.1 A deviation is a "once off" instance when, for some reason, the protocol is not followed e.g. the protocol states that only people over the age of 18 will be enrolled. However, a participant, aged 17 years and 6 months meets all admission criteria and is deliberately enrolled in this study. Protocol deviations can also occur when mistakes are made e.g. the wrong follow update is given and thus follow up occurs outside of a specified time frame;

9.3.3.2 Major protocol deviation

A major protocol deviation may affect a participant's willingness to continue participating in the research by:

- Affecting the safety, condition and/or status of the research participant;
- Affecting the scientific integrity and/or validity of the study data;
- Posing a significant risk of harm to the research participant;
- Altering the balance of risks and benefits of the research;
- Constituting a willful breach of ethical and/or regulatory policies; and/or
- Involving a serious and/or continuing non-compliance with institutional, ethical and/or regulatory policies.

9.3.3.3 Minor protocol deviation

A minor protocol deviation does not meet the above criteria, however, nevertheless constitutes a deviation from the approved protocol. Such examples include, but are not limited to:

- Patient visits outside a protocol window period
- Study procedure missed or conducted out of sequence
- Missing pages of a completed informed consent form

9.3.4 Procedure for submission of protocol deviations

9.3.4.1 **To submit an HREC application for review of a protocol deviation:** submit an electronic copy of the HREC protocol deviation application package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

9.3.4.2 If the protocol deviation is planned, prior HREC approval must be obtained before implementing such a deviation, unless such change is intended to eliminate an immediate hazard or harm to the research participant;

9.3.4.3 In the case of unplanned protocol deviations, as soon as the deviation is identified in a study, it must be reviewed, documented and categorized as major or minor by the investigator;

9.3.4.4 It is the investigator's responsibility to categorize a protocol deviation as major or minor;

9.3.4.5 Major protocol deviations must be reported to the HREC within a maximum of 15 days after becoming aware thereof;

9.3.4.6 Minor protocol deviations can be listed with the next progress report;

9.3.5 Documents required for HREC application: Protocol deviation

9.3.5.1 Completed electronic HREC Protocol deviation Application Form submitted via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za;

9.3.5.2 Cover letter;

9.3.5.3 Electronic copies of relevant supporting documents.

9.4 Unanticipated problems involving risks to research participants/others, (including adverse events)

9.4.1 Policy

In line with local and international guidelines, the HREC has written procedures to ensure timely reporting of unanticipated problems (including serious adverse events) which might place a human research participant at a greater risk of physical, psychological, economic and/or social harm.

9.4.2 Purpose

The purpose of this policy is to outline the timelines and procedures for reporting and reacting to unanticipated problems.

9.4.3 Definitions

9.4.3.1 Unanticipated problems: An unanticipated problem is an adverse incident, experience, outcome or event, that in the investigator's opinion:

9.4.3.1.1 is **unforeseen or unexpected** in that the nature, specificity or severity, and/or frequency of occurrence is not consistent with the information currently provided to the HREC or participants. For human research, such information may include the informed consent document, clinical investigator's brochure, product labelling, package inserts, the risk information provided in the initial protocol application, or any other existing documentation regarding the research conducted to date under the protocol;

9.4.3.1.2 is **related (or possibly related) to participation in the research**; and

9.4.3.1.3 suggests the research **places the participants or others at a greater risk of physical, psychological, economic or social harm** than was previously recognized and/or known;

9.4.3.1.4 Examples of unanticipated problems include, but are not limited to:

9.4.3.1.4.1 Physical abuse of a spouse or partner for participation in a research study;

9.4.3.1.4.2 Loss of a computer containing confidential information regarding trial participants;

9.4.3.1.4.3 Publication of a Data Monitoring Report which indicates an unexpected increase in the potential risks of the study;

9.4.3.2 Adverse event (AE): An adverse event is defined as:

9.4.3.2.1 any untoward medical or psychological occurrence in a human research participant, including any abnormal laboratory finding, symptom or disease;

9.4.3.2.2 Any event that can affect research participants or data integrity negatively, or that has the potential to impact negatively on members of the research team, or on the project as a whole;

9.4.3.2.3 Adverse events can thus include a wide range of events such as breach of confidentiality, injury sustained during a procedure e.g. exercise program, assault or robbery of staff members, needle stick injuries etc.;

9.4.3.2.4 Adverse events may obviously, in certain studies also include adverse drug events;

9.4.3.3 Serious adverse event (SAE): Any adverse drug experience, occurring at any dose that results in any of the following outcomes:

9.4.3.3.1 Death;

9.4.3.3.2 A life-threatening incident;

9.4.3.3.3 Inpatient hospitalisation or prolongation of existing hospitalization;

9.4.3.3.4 Significant or persistent disability/incapacity;

9.4.3.3.5 Congenital abnormality/birth defect;

9.4.3.3.6 Important medical events that may not result in death, be life threatening, or require hospitalization, may be considered a SAE when based on appropriate medical judgment; they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition e.g. allergic bronchospasm, blood dyscrasias;

9.4.4 Procedure for reporting and reacting to unanticipated problems including adverse events

9.4.4.1 Unless otherwise specified, the investigator should report the following to HREC **within 7 calendar days** after first becoming aware thereof:

9.4.4.1.1 **Unanticipated problem** (including fatal, life threatening and/or other adverse event) which, in the investigator's opinion:

9.4.4.1.1.1 **Is related (or possibly related) to participation in the research;**

9.4.4.1.1.2 **May increase the risk of harm to research participants and/or others**;

9.4.4.1.2 Any other AE or SAE which, in the investigator's opinion, could have serious negative consequences for research participants, research team members, the project as a whole, or the university;

9.4.4.1.3 New information that may alter the balance of risks and benefits in a study, for example an individual case report or a major safety finding from another source (including but not limited to an unfavourable DSMB report or publication of results from another study) that may warrant consideration of substantive changes in the overall conduct of the research;

9.4.4.1.4 Unexpected adverse events occurring at other South African and/or international sites which, in the investigator's opinion are related (or possibly related) to the research, and may increase the risk of harm to research participants and/or others;

9.4.4.1.5 Expected adverse events which, in the investigator's opinion, are deemed to have occurred and/or be occurring at a significantly higher frequency and/or severity than expected;

9.4.4.1.6 **To submit an HREC application for review of an unanticipated problem:** submit an electronic copy of the HREC Unanticipated problem application package via the HREC online application portal, *Infonetica©* at: https://applyethics.sun.ac.za. Include a more detailed narrative if the event occurred at the investigator's site.

9.4.4.2 **Report to HREC in the annual progress report**

9.4.4.2.1 Adverse events that do not meet the criteria laid out in Section 9.4.4.1 above can be reported to HREC summarized as part of the annual progress report and should only include additional supporting documentation if deemed necessary by the sponsor. Additional supporting documentation not requested by HREC but deemed necessary by the sponsor will not be reviewed by HREC;

9.4.4.3 A summary of all submitted reports will be compiled each month and distributed to the Chairperson, as well as to all HREC committee members, for review and discussion at the monthly meeting;

9.4.4.4 Events that are unexpected or repeated may be investigated further and if deemed necessary by the Chairperson, will be reported to the Research Integrity Office and/or the HREC EXCO. Appropriate remedial action will be taken, if deemed necessary. Such action may include, but is not limited to:

9.4.4.4.1 Protocol revision/amendment, including possible modification of eligibility criteria in order to mitigate the newly identified risks;

9.4.4.4.2 Suspension of enrolment of new research participants;

9.4.4.4.3 Suspension of additional procedures in currently enrolled research participants;

9.4.4.4.4 Modification of informed consent documents to include additional information about newly identified risks to new research participants;

9.4.4.4.5 Provision of additional information about newly identified risks to currently enrolled research participants and a requirement for such participants to sign an informed consent addendum and/or update;

9.4.4.4.6 Suspension and/or termination of the research; and/or

9.4.4.4.7 Reporting to the appropriate regulatory agencies if deemed necessary and required by the study protocol;

10 COMMUNICATION OF REVIEW DECISIONS

10.1 Policy

To ensure that investigators are appropriately informed about HREC review decisions

10.2 Purpose

The purpose of this policy is to outline the procedure for the communication of HREC decisions to investigators.

10.3 HREC decisions

For each review conducted by HREC, one of the following decisions must be made:

10.3.1 **Approved:** The proposed research is approved in its current form, with no changes required. The date of approval is considered the date that all conditions were determined to be met;

10.3.2 **Approved with stipulations:** The proposed research is approved with minor alterations required. The onus is left on the research applicant to meet these stipulations prior to the start of any research related activities;

10.3.3 **Modifications required:** The proposed research has no major ethical concerns, but a number of clarifications or methodological changes are required. The research applicant must resubmit the revised research application. The review can be finalised by an expedited review process i.e. without having to serve before the full committee again;

10.3.4 **Deferred:** The proposed research has major methodological and/or ethical concerns and requires considerable revision. The research applicant must resubmit the revised research application. The revised research application will be reconsidered at a convened (full) committee meeting;

10.3.5 **Rejected:** The proposed research may not be resubmitted;

10.4 Procedure for the communication of HREC decisions

10.4.1 Decisions taken at an HREC meeting, or via a minimal risk review process, are communicated in writing to the applicant;

10.4.2 Investigators can address any queries to the HREC office, which will attempt to resolve problems and liaise with the Chairperson when necessary;

10.4.3 The average **turnaround times** for notifying research applicants of the review outcome are:

10.4.3.1 **Full committee review**: **5-6 weeks** after the HREC submission deadline;

10.4.3.2 **Minimal risk review**: **3-5 weeks** after the HREC submission deadline;

10.4.4 These expected turnaround times apply to research applications that are scientifically and ethically sound. It may take considerably longer to finalise review decisions for research applications that are scientifically and/or ethically problematic or flawed. Review time is also subject to HREC capacity, and the timing of the application;

10.4.5 Research applicants should follow up with the HREC office if they have not received an HREC letter within the time frames specified above;

10.4.6 Follow up with the HREC office before this time is preemptive and unlikely to have an effect on the review time;

10.4.7 HREC letters are issued electronically via *Infonetica©.* Please check your SU email address, including the junk folder;

10.4.8 It is not unusual for the committee to request some changes to the project, information and consent form, or clarification of certain issues. Only once these requirements are satisfactorily fulfilled will a formal letter of approval be issued;

10.4.9 The research applicant may start the project only once an **HREC approval letter** has been received. If modifications are required, then all requested changes must be made before a final letter of approval is issued;

10.4.10 It is the responsibility of the research applicant to comply with all requests and return the requested documentation with a covering letter responding to the points raised, to the HREC as soon as possible but not later than 6 months from the date of issue. **The application will be cancelled if no feedback is received from the research applicant within 6 months;**

10.4.11 All requested protocol and informed consent form changes must be clearly marked. The **tracked changes** facility on the word processor should be used;

10.4.12 The primary HREC reviewer (or another HREC member, if requested to do so by the primary reviewer or Chairperson) will carefully check all amended documentation, including patient information and consent forms.

10.4.12.1 If correct, the said documentation will be forwarded to the Chairperson for final approval;

10.4.12.2 If not correct, a second letter will be sent to the investigator clarifying what aspects of the project still need to be addressed or changed. If the committee requested major alterations to the protocol i.e. DEFERRED the protocol, it must be resubmitted to a convened HREC meeting i.e. a full sitting of the committee;

10.4.13 For those research applications reviewed via minimal risk review, approval will be considered for ratification by the HREC, at the next available meeting. Reviewer reports are made available to all committee members in the electronic agenda distributed prior to the meeting;

10.4.14 HREC has the authority to suspend the approval of any project approved via a minimal risk review process and request further changes or additional information. All research activities must cease until this process is concluded;

10.4.15 **The initial period of approval is one year from the date of final approval.** A progress report and request for re-approval should be submitted at least 8 weeks before expiry of approval;

10.4.16 Please note the final HREC approval date will be recorded as the research start date and approval will expire in 1 year from this date.

11 INFORMED CONSENT

11.1 Policy

11.1.1 Except as provided elsewhere in this document, no investigator may involve a human being as a participant in research covered by this policy unless the investigator has obtained the legally effective informed consent of the participant or the participant's legally authorized representative, where appropriate;

11.1.2 An investigator shall seek such consent only under circumstances that provide the prospective participant, or their representative, with sufficient opportunity to consider whether or not to participate and that minimise the possibility of undue influence or coercion;

11.1.3 The information that is given to the participant or the representative shall be presented in language and/or format that optimally promotes understanding of the proposed research by the participant or the participant's legally authorized representative, where appropriate;

11.1.4 No informed consent may include any exculpatory language through which the participant or their representative is made to waive or appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence;

11.1.5 Written informed consent should always be obtained unless an alternative process is adequately justified and approved in advance by HREC;

11.1.6 The process of recruitment and documentation of informed consent must be described clearly and in detail in the study protocol;

11.1.7 For multi-site/multinational clinical trials, the participant information and consent form must be adapted to the requirements of the local community and potential participants.

11.2 Purpose

The purpose of this policy is to describe the minimum elements that are required in an informed consent document, as well as the way in which informed consent is sought and documented in research process.

11.3 Elements of informed consent

11.3.1 **Basic elements of informed consent**

Except as provided below, the following information shall be provided to each participant when seeking informed consent:

11.3.1.1 A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

11.3.1.2 A description of any reasonably foreseeable risks or discomforts to the participant;

11.3.1.3 A description of any benefits to the participant or to others which may reasonably be expected from the research;

11.3.1.4 A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant;

11.3.1.5 A statement describing the extent to which confidentiality of records identifying the participant will be maintained;

11.3.1.6 For research involving more than minimal risk, a statement that the researcher and/or sponsor will adhere to the South African Good Clinical Practice Guidelines (*SAGCP (2016) Section 8: Insurance against trial related injury*); an explanation that there is a risk that the study medicine(s) or procedure(s) may cause harm and if so, the sponsor will reimburse the medical expenses; details as to what medical treatments will be provided if injury occurs, what these treatments consist of, and where further information may be obtained (see *Appendix IV: Compensation for Injury: Template for Informed Consent*);

11.3.1.7 A statement that the participant will be remunerated for their time and inconvenience and reimbursed for any expenses related to the research;

11.3.1.8 An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of research-related injury to the participant;

11.3.1.9 A statement that participation is voluntary and that refusal to participate will involve no penalty or loss of benefits or reduction in the level of care to which the participant is otherwise entitled;

11.3.1.10 A statement that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled; and

11.3.1.11 A statement that when the participant withdraws from the study, the data collected on the participant to the point of withdrawal remains part of the study database and cannot be removed.

11.3.2 **Additional elements of informed consent**

When appropriate, one or more of the following elements of information shall also be provided to each participant:

11.3.2.1 A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or foetus, if the participant is or may become pregnant) which are currently unforeseeable;

11.3.2.2 Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent;

11.3.2.3 Any additional costs to the participant that may result from participation in the research;

11.3.2.4 The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant;

11.3.2.4.1 Should the participant choose to withdraw from the study the participant has the option to provide continued follow up information and data collection subsequent to their withdrawal from the interventional portion of the study;

11.3.2.4.2 To ensure the participant understands and consents to the option above the investigator must distinguish between study related intervention and continued follow up of non -invasive clinical information;

11.3.2.4.3 Should the participant choose not to continue with the non-invasive clinical outcome follow up, the investigator may not access the participants confidential or medical records requiring the participants consent

11.3.2.5 A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant; **and**

11.3.2.6 The approximate number of participants involved in the study;

11.3.2.7 The participant authorizes that regulatory authorities such as the FDA, EMA, SAPHRA and HREC and the sponsor (if applicable) to be granted direct access to their original medical records for verification of clinical trial data collected.

11.4 Variation of consent procedures (including waiver of informed consent)

11.4.1 HREC may approve a consent procedure which does not include, or which alters some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided HREC finds and documents that:

11.4.1.1 The research involves no more than minimal risk to the participants;

11.4.1.2 The waiver or alteration will not adversely affect the rights and welfare of the participant(s);

11.4.1.3 The research could not practicably be carried out without the waiver or alteration; **and**

11.4.1.4 Whenever appropriate, the participants will be provided with additional pertinent information after participation;

11.4.1.5 HREC may in selected cases consider a waiver of parental consent,

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

11.4.3 The informed consent requirements in this SOP are not intended to pre-empt any applicable governmental or local laws which require additional information to be disclosed in order for informed consent to be legally effective;

11.4.4 Nothing in this policy is intended to limit the authority of a registered health professional to provide emergency medical care, to the extent the registered health professional is permitted, under applicable governmental or local law;

11.4.5 The participant must, having been fully informed, be asked to give his/her free and voluntary consent to inclusion in the study;

11.4.6 Where a relationship of dependence exists between participant and researcher (e.g. service provider/service recipient), consent should be obtained by an independent person.

11.5 Informed consent for Research Databases, Registries and Repositories or Biobanks

11.5.1 Policy

Databases, registries and repositories collect, store and manage data and/or biological materials from participants or donors for research purposes. Linked or identifiable data or specimens may be used by many researchers and for multiple studies over time. Although biological materials and data may be separate from their sources (whether living or deceased), they symbolize or represent the individuals who donate them and can contain codes that link data to their donor's identity. This policy describes the informed consent procedures and documentation required for the collection of biological materials and data for health research databases, biobanks or repositories as a future research resource.

11.5.2 Purpose

The purpose of this policy is to describe how informed consent should be conducted and documented for the collection of biological materials and data for health research databases, registries or biobanks (repositories) as a future research resource by any researcher/person wishing to register a health research database, registry or biobank/repository with the Stellenbosch University Health Research Ethics Committee (HREC).

11.5.3 Definitions

11.5.3.1 **Restrictive or specific consent:** the participant donates of biological materials and data with permission for single use only. Specific consent restricts sharing of leftover biological materials and data as well as usage of biological materials and data outside the scope of the current consent. **New consent** is required for sharing and further use of biological materials and data;

11.5.3.2 **Tiered or multi-layered consent:** the participant provides specific consent for the use of his/her biological materials and data for the primary study and chooses whether to permit storage and sharing of biological materials and data for future specified and/or un-specified use in the same field of research**;**

11.5.3.3 **Broad consen**t: the participant donates biological materials and data with permission to use them for a broad range of un-specified future studies in the same field as the current research, subject only to further prior ethics review and approval of each future study;

11.5.3.4 **Blanket or open consent:** the participant donates human biological materials and data and permits the usage of material and data for any type of research in the future. Blanket or open consent for collection and storage of biological materials and data in a health research database, repository or biobank and usage of the biological materials and data in any type of unspecified future research is not considered acceptable by the HREC.

11.5.4 General Informed Consent Requirements for Databases, Registries and Repositories

11.5.4.1 The HREC has the authority to review and approve any informed consent documentation for collection of biological materials and data for creation of health research databases, biobanks or repositories as a future research resource;

11.5.4.2 Written informed consent is required before removal of biological material and data from a living participant or donor for storage in a health research database, registry or biobank/repository as a current or future research resource;

11.5.4.3 Written informed consent allows individuals to exercise their fundamental right to decide whether and how their body, body parts and associated data will be used in research;

11.5.4.4 The collection, storage, use and reuse of data and biological material from individuals capable of giving informed consent must be voluntary in accordance with the World Medical Association Declaration on "Ethical Considerations regarding Health Databases and Biobanks"[1] and the South African Department of Health Ethics in Health Research guidelines[2];

11.5.4.5 In the case of a deceased person, consent to removal and use of biological materials and data may be found in the Will of the person, in a written statement or in a witnessed oral statement or it may be provided by "the spouse, partner, major child, parent, guardian, major brother or major sister of that person in the specific order mentioned"[2];

11.5.4.6 The rights to autonomy, privacy and confidentiality also entitle individuals to exercise control over the use of their personal data and biological materials;

11.5.4.7 Investigators must demonstrate sensitivity to the values, beliefs and attitudes of the persons from whom the biological materials and data are derived and ensure that their dignity, autonomy, privacy and confidentiality are protected at all times;

11.5.4.8 The informed consent documentation for donors or participants should explain clearly:

- 11.5.4.8.1 The purpose and nature of a health database and biobank, including the specifics for which consent is being sought, how the health database or biobank works and the types of research it supports;
- 11.5.4.8.2 The conditions and requirements under which data or material will be shared with other investigators (the rules of access to the health research database, biobank or repository);
- 11.5.4.8.3 How privacy and confidentiality interests will be protected;
- 11.5.4.8.4 The nature and extent of specific risks of harm related to use and storage of materials or data, especially if identifiers are retained;
- 11.5.4.8.5 The procedure for disclosure of results in case of incidental findings;
- 11.5.4.8.6 In the case of genetic or genomic research, information should be provided about the implications of genetic testing (e.g. paternity determinations, insurance risks, reproduction decisions) and associated confidentiality risks;
- 11.5.4.8.7 Potential benefits (if any);
- 11.5.4.8.8 Where applicable, that biological materials and data may be used for future research not yet identified;
- 11.5.4.8.9 Where applicable, that biological materials and data may be shared with or transferred to other institutions;
  The freedom to withdraw consent at any time and to request withdrawal of data and that unused identifiable material be destroyed. If this is not possible, the information should clearly indicate this;
- 11.5.4.8.10 Information about the length of storage time;
- 11.5.4.8.11 When the current consent to use materials or data will expire;

11.5.4.8.12 Information about possible secondary use of stored materials and data;

11.5.4.8.13 Information about possible creation of an immortalized cell line based on the specimen and implications of this;

11.5.4.8.14 The potential decision to anonymize data, and in case of irreversible anonymization, the fact that the individual will not be able to know what is done with their data and biological material;

11.5.4.8.15 Where applicable, commercial use and benefit sharing, intellectual property issues and the transfer of data or material to other institutions or third parties;

11.5.4.9 There are four different types of informed consent in health research: 1) blanket or open consent; 2) broad consent; 3) restrictive or specific consent; and 4) tiered or multi-layered consent;

11.5.4.10 In accordance with the DOH guidelines, the HREC accepts/endorses only three of these four informed consent types, namely broad consent; restrictive or specific consent; and tiered or multi-layered consent;

11.5.4.11 Blanket or open consent for collection and storage of biological materials and data in a health research database, repository or biobank and usage of the biological materials and data in any type of unspecified future research is not considered acceptable by the HREC.

11.5.5 Requirements for Specific or Restrictive informed consent

11.5.5.1 See detailed requirements for specific informed consent in *Section 11: Informed consent*;

11.5.5.2 Restrictive or specific consent by participants for the use of their biological materials and data is for single use in a specified research project only. Specific consent restricts sharing of biological materials and data outside the scope of the specified research question and is therefore generally not appropriate for use in research databases, registries and biobanks that collect and store biological materials and data as a future research resource;

11.5.6 Requirements for Tiered (multi-layered) informed consent

11.5.6.1 Investigators may obtain tiered or multi-layered consent from participants or donors of biological materials and data for storage of their biological materials and data in a health research database, repository or biobank as a future research resource;

11.5.6.2 Tiered consent allows usage of biological materials and data for a primary specified study and donors of the biological materials and data can also choose whether to permit storage and sharing of biological materials and data in a health research database, registry or biobank for future specified or un-specified use in the same field of research;

11.5.6.3 Examples of language used in the range of options generally presented to participants in tiered or multi-layered consent include[3] but are not limited to: "*I want my sample to be used in this research only"* or *"I do not want my sample to be shared with other investigators but you can use it in your future research in this disease"* or *"My sample can be shared with other investigators for future research in the same field i.e. cardiovascular research"*;

11.5.7 Requirements for Broad Consent

11.5.7.1 Investigators may obtain broad consent from participants or donors of biological materials and data for collection and storage of their biological materials and data in a health research database, biobank or repository as a future research resource;

11.5.7.2 Broad Consent allows investigators to use the biological materials and data from donors for the current research and store the biological materials and data for possibly future research purposes even though the precise nature of future research may be unclear at present;

11.5.7.3 The nature of the further usage should be described as fully as possible and should stipulate that further prior HREC review of any new study is necessary;

11.5.7.4 HREC endorses **broad consent** for collection and storage of biological materials and data for health research databases, biobanks or repositories. However, broad consent is generally acceptable if the nature of future research is within the same field as the current research, e.g. HIV or cancer;

11.5.7.5 An example of language used in broad consent follows[3]: *"In order to do the research we have discussed; we must collect and store blood and health information from people like you. We will do some of the tests right away. Other tests may be done in the future. Once we have done the research that we are planning for this project, we would like to store your blood and information. The study you are being asked to participate in involves "Diseases ABC" and your sample and health information will only be used in ""Diseases ABC" by other investigators or scientists in the future. If the other investigators decide to use your blood and health information to study other diseases in the future, they will have to get new consent from you as a patient. All future studies that will use your samples and health information will need to first ask for HREC approval."*

11.5.8 Requirements for the secondary use of data or biological materials in the absence of informed consent for future use

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

11.5.8.1 Use of existing or archived materials and data collected for clinical or diagnostic purposes, including waste and surplus samples, requires HREC expedited review;

11.5.8.2 The nature of the previously obtained consent should be determined to ascertain whether subsequent usage was envisaged and whether subsequent usage in the newly proposed research falls within the scope of the previously obtained consent;

11.5.8.3 If the newly proposed research falls within the scope of the previously obtained consent, new consent is not required but proof of original consent to store and use the samples for future research will have to accompany the submission to the HREC;

11.5.8.4 If the scope of the newly proposed research falls outside of the scope of the original consent for future use of samples, then new consent may be required;

11.5.8.5 If samples are anonymous and the results of research would not place any individual, family or community at social, psychological, legal or economic risk of harm, then new consent is not required;

11.5.8.6 Failing being able to demonstrate consent as in the above three steps, and with justification as to why new consent cannot be obtained, the HREC may consider a strongly motivated waiver of consent request which demonstrates not just the conditions of anonymized and aggregated data at the point of data collection and aggregated findings, but also justification as to why this research is believed to not pose the risks outlined in 3.7.7. iii) (p. 44) in the DoH guidelines, and highlighting the social value of the research as outlined in the sub-section below on the request for a waiver of consent;

11.5.8.7 If the link to identifiers exists but it is not provided to the research team and the results of research will not place any individual, family or community at social, psychological, legal or economic risk of harm, the new consent may not be required;

11.5.8.8 The person who holds the code or link should sign an explicit written agreement not to release the identifiers to the research team. This agreement should accompany the submission to the HREC;

11.5.8.9 If the samples can be linked to identifiers, the HREC will decide on a case-by-case basis whether expedited or full review is necessary.

11.5.9 Requirements for a waiver of informed consent

11.5.9.1 The HREC will consider applications for a waiver of consent on a case-by-case basis;

11.5.9.2 The HREC may approve **a waiver of consent** for secondary use of materials or data where no more than minimal risk of harm is likely; and the participant's or donor's rights and welfare interests are unlikely to be adversely affected; and the research cannot be conducted if the waiver were not approved;

11.5.9.3 In normal circumstances, a waiver of informed consent is granted when data are anonymised and aggregated. However, in order to ensure quality control, identifiers might be required until the end of the data collection period where after identifiers should be removed permanently;

11.5.9.4 HREC will consider whether granting a waiver of informed consent for use of data and samples is ethically appropriate given the unique circumstances and potential social value argued for by the applicant;

11.5.9.5 If HREC were to grant a waiver of informed consent, it would be based on consideration of whether the requirement for informed consent (respect for autonomy) could in this case be trumped by the potential social value (anticipated benefit to society) of the research and any potential benefits to patient management/care that are anticipated;

11.5.9.6 The researcher is encouraged to submit convincing evidence of these anticipated benefits and social value in the submission to the HREC.

11.6 Documentation of informed consent

Except as provided in above, informed consent must be documented by the use of a written consent form approved by HREC and signed by the participant or the participant's legally authorized representative. In addition, only an approved investigator or another suitable person designated by the investigator may conduct the consent interview and this process which must be documented in the source notes of the research participant.

11.6.1 The written consent document must include the elements of informed consent as outlined above. This form may be read to the participant or the participant's legally authorized representative, but in any event, the investigator or a suitable person designated by the investigator shall give either the participant or the representative adequate opportunity to read it before it is signed. If the participant is unable to read or write there shall be an independent witness to the oral presentation who must be present and verify in writing that the informed consent process was valid and in accordance with the requirements of this SOP document;

11.6.2 After the written consent document and any other written information to be provided to the participants, is read and explained to the participant or the participant's legal representative, and after the participant's legal representative has orally consented to the participant's participation in the trial and, If capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document;

11.6.3 By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legal representative, and that consent was freely given by the participant or the participant's legal representative;

11.6.4 In the case of a long and/or complicated informed consent form, HREC may request a 2-page summary of the informed consent in lay language, to be used in addition to the actual informed consent form. This summary should include the following:

11.6.4.1 A statement that the elements of disclosure required by regulations have been presented orally to the participant or the participant's legally authorized representative;

11.6.4.2 The basic and required additional elements of disclosure;

11.6.5 Applicants may apply for a waiver of the formal documentation of informed consent. HREC may waive the requirement for the investigator to obtain a signed consent form for some or all participants if it finds either:

11.6.5.1 That the only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality;

11.6.5.2 That the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context. In cases in which the written documentation requirement is waived, HREC may require the investigator to provide participants with a written statement regarding the research;

11.6.6 The HREC provides template participant informed consent forms that are available in English, Afrikaans and Xhosa and should be used as a guide when drawing up your study-specific informed consent form(s). See our HREC website www.sun.ac.za/healthresearchethics for templates, including templates for child research, genetic research, case reports, and online research;

11.6.7 Once the participant has agreed to participate, 2 copies of the signed form must be made. The original signed informed consent form must be kept at the investigator site, one copy must be given to the participant, and one copy must be kept in the participant's medical records;

11.6.8 The entire informed consent process must be appropriately documented in the participant's source documents.

11.7 Translation of the informed consent document(s)

In seeking informed consent, the information that is given to the participant shall be presented in a language, and format that optimally promotes understanding of the proposed research by the participant or the participant's legally authorized representative, where appropriate.

11.7.1 The principle of justice requires that potential research participants of all local language groups should be afforded the opportunity to participate in research;

11.7.2 In the Western Cape informed consent should generally be available in 3 languages: English, Afrikaans and Xhosa;

11.7.3 HREC does not require translation into all 3 languages for every research application. Rather than imposing a prescriptive requirement that may not fit all research, HREC considers it more critical to focus on the **detail provided in the recruitment strategy.** What is critical is the intended recruitment strategy, more specifically:

11.7.3.1 *Who* are researchers planning to recruit?

11.7.3.2 *Where* will participants be recruited from? And

11.7.3.3 *How* best to approach participants in order to optimize voluntariness and understanding of the research?

11.7.4 The requirement for translation into additional language(s) is therefore not absolute. The informed consent process, and language in which it is conducted, should essentially be adapted to the requirements of potential participants;

11.7.5 Before approval of the proposed consent documentation, HREC will review the recruitment strategy provided in the protocol for adequate motivation and justification, based on the particular target participant population, of what would be the best language(s), and/or process(es), for informed consent in a particular context;

11.7.6 Informed consent documents may be submitted for HREC approval, in either English or Afrikaans. Once the original document is approved it is the responsibility of the investigator to arrange for translations of the forms into other languages, where appropriate. A proficient translator must be assigned to this task. Xhosa translations should preferably be done 'back-to- back' i.e. English to Xhosa and back to English, by different translators. If the research is to be conducted elsewhere in South Africa, other translation requirements may be applicable;

11.7.7 Once completed, the **translations must be submitted to the HREC office** accompanied by either a certificate of translation/back-translation or letter from the PI declaring that the translation is an accurate reflection of the approved English version;

11.7.8 The committee will acknowledge receipt of translations. However **only the original English or Afrikaans version will be officially approved**. The committee reserves the right to check translations and delay approval of the study, if the translations are deemed to be of poor quality;

11.7.9 Investigators and sponsors are encouraged to ensure that the informed consent process and the information that is given to the participant are presented in a language, and format, that optimally promotes understanding. This is of particular importance where the unavailability of informed consent in a particular language may act as an unjustifiable barrier to recruitment.

12 HREC REVIEW FEES

12.1 Policy

12.1.1 HREC has a graded administrative fee structure in place, which is revised annually. The HREC fee structure is available on the HREC website: www.sun.ac.za/healthresearchethics;

12.1.1 The following research is **exempt** from HREC review fees:

12.1.1.1 Non-sponsored student research for degree purposes at Stellenbosch University;

12.1.1.2 Research funded solely from Stellenbosch University departmental budgets;

12.1.1.3 Harry Crossley funded research; and

12.1.1.4 Self-funded research.

12.1.2 The HREC will consider a well-motivated written request for reduction of fees. A decision will be made and communicated to the researcher in writing. Decisions taken should be viewed as final;

12.1.3 HREC reserves the right to not review a research application, and will withhold an HREC letter, if HREC fees are outstanding;

12.2 HREC review fee: requirements and payment process:

12.2.1 Industry-sponsored clinical trials:

12.2.1.1 Submit a completed and signed *Payment instruction form: clinical trial* along with your application for a new project, or continuing review submission (e.g. progress report, amendment application, etc.);

12.2.1.2 The *Payment instruction form: clinical trial* is available on our HREC website: www.sun.ac.za/healthresearchethics;

12.2.1.3 You/your sponsor will receive an HREC invoice;

12.2.1.4 Payments should be made directly into SU bank account;

12.2.1.5 Payment reference: **HREC invoice number;**

12.2.1.6 Please submit proof of payment to Ms Elvira Rohland elr@sun.ac.za

12.2.2 **International and national grant funded research:**

12.2.2.1 **Stellenbosch University applicants**: Submit the following along with your HREC submission:

12.2.2.1.1 A completed and signed *Payment instruction form: health research*; **and**

12.2.2.1.2 Proof of payment or internal requisition number with the **PI name and Project Id as a reference**;

12.2.2.1.3 Interdepartmental requisitions are payable to: **Cost Centre 0885;**

12.2.2.1.4 Payment reference:

12.2.2.1.4.1 New project application: **PI's surname, Initial and Project Id**; **or**

12.2.2.1.4.2 Continuing review submission (e.g. progress report, amendment): **HREC number** (e.g. N16/03/024, S10/01/001)

12.2.2.2 **External applicants**

12.2.2.2.1 Submit a completed and signed *Payment instruction form: health/human research* along with your HREC application for a new project, progress report, amendment etc.;

12.2.2.2.2 You will receive an HREC invoice;

12.2.2.2.3 Payment reference: **“invoice number”**;

12.2.2.2.4 Research applications with outstanding HREC review fees will not receive their HREC letter.

13 PARTICIPANT INSURANCE

13.1 Policy

The South African Department of Health (2016) Clinical trial guidelines: Good practice for clinical trials with human participants (3rd edition – 2016, also known as the SA GCP 2016) stipulates that the sponsor of a trial must ensure that the participants of a clinical trial are covered by comprehensive insurance in the event of physical (bodily) harm or injury, including death. Guideline 8: Insurance against trial-related injury of the SA GCP 2016 states that the sponsor of a study should pay the costs for the medical treatment of any bodily injury **without the participant having to prove that the sponsor was at fault**.

13.2 Purpose

To ensure that research participants are adequately insured in the event of a research related injury.

13.3 Requirements for adequate participant insurance against research related injury

13.3.1 In accordance with SAGCP guidelines, the sponsor's insurance company will compensate a participant for **medical expenses** which may have resulted directly from their participation in a particular clinical trial (either from using the medicine in question or participating in the required procedures);

13.3.2 **Industry-sponsored clinical trials:** the sponsor's insurance company is responsible for insurance cover;

13.3.3 **Health research by Stellenbosch University staff and students:** Stellenbosch University's insurance company is responsible for insurance cover (Please see *Section 13.4* below for details of the procedure for acquiring participant insurance through Stellenbosch University);

13.3.4 These costs must be reasonable and **do not include costs for, for example, a loss of income, compensation for pain or emotional suffering**. This was recently confirmed in the decision by the Western Cape High Court in the matter of *Venter v Roche;*

13.3.5 The sponsor will, however, not have to pay these costs if the injury or harm was caused by:

13.3.5.1 the use of unauthorised medicine or substances during the study;

13.3.5.2 an injury that results from the participant not following the protocol requirements or the instructions that the study doctor had provided;

13.3.5.3 an injury that arises from any action or lack of action to deal adequately with a side effect or reaction to the study medication on the part of the participant; [*This point must be very carefully checked in each case – it is unacceptable to impose a burden on participants who may not recognize symptoms or have the ready means to take action.];*

13.3.5.4 an injury that results from any other negligence on the part of the participant*;*

13.3.6 It is important to explain to the participant that:

13.3.6.1 By agreeing to participate in this study, **he/she agrees that there is a risk that the study medicine or procedures may cause her harm**. If it does, the sponsor will reimburse him/her for his/her **medical expenses**;

13.3.6.2 The participant may, however, still claim for emotional pain and suffering but if he/she so chooses. In this event, he/she will have to prove that the sponsor was negligent and did not take all reasonable and foreseeable steps to prevent the injury or emotional trauma. This will be a separate legal matter;

13.3.7 Insurance taken out for this clinical trial does not replace a clinician's malpractice insurance;

13.3.8 Guideline 8 of the SA GCP 2016 states that the participant will normally be asked to accept that any payment made under the Guidelines will be in full settlement of the claim;

13.3.9 See *Appendix IV: Compensation for injury: Template for Informed Consent* for a template that can be used by principal investigators in their informed consent form. See also *Appendix V: Compensation for injury: Important information to be conveyed to participants*

13.4 Procedure for acquiring participant insurance through Stellenbosch University

13.4.1 All **new research applicants** should contact the financial planning and asset management office to **register their new research project with the Stellenbosch University insurance brokers**;

13.4.2 Please contact the Stellenbosch University insurance brokers directly:

Mr Wium van Kerwel, Assistant Accountant
Financial Planning and Asset Management
tel: 021 - 808 2809
fax: 021 - 808 3664
e-mail: wvankerwel@sun.ac.za

13.4.3 The HREC communicates a formal declaration of all active or recently approved health research to Stellenbosch University's insurance brokers on an annual basis, prior to the commencement of the insurance year.

14 COMPENSATION OF RESEARCH PARTICIPANTS

14.1 Policy

The South African National Health Research Ethics Council Guidelines for payment of research participants in South Africa recommends that participants should be compensated appropriately for their time and inconvenience and reimbursed for their expenses. See: NHREC (2012) Payment of trial participants in South Africa: Ethical considerations for Research Ethics Committees. Available at: http://www.nhrec.org.za/wp-content/uploads/2012/payment_considerations.pdf

14.2 Purpose

To ensure that research participants are adequately compensated for their time and inconvenience and reimbursed for their research-related expenses, with an amount and method of payment that does not present an undue influence.

14.3 Requirements for adequate participant compensation

HREC reviews the amount and method of payment to research participants in accordance with the provisions of the *National Health Research Ethics Council (NHREC)*. Key principles are summarized here:

14.3.1 Neither the amount nor method of compensation for research participants must present the potential for undue influence;

14.3.2 Compensation to participants must be prorated and not wholly contingent on completion of the study by the participant;

14.3.3 Compensation to child participants must be child-appropriate. Compensation should also be offered to the child's parent/caregiver for time and expenses incurred for accompanying the child on research visits.

14.3.4 Research participants should be compensated appropriately for their time;

14.3.4.1 Time payments should be made at rates commensurate with unskilled labour rates. This acknowledges that research participation (while valuable) does not necessarily require special skills and training, but does entail expending effort;

14.3.4.2 The above recommendation recognises that payment is being made for what the 'work' of research participation is worth, and not what the participants' actual time is worth;

14.3.4.3 Even if participants are not formally employed, it could be considered that participation in research may compete with efforts to find other similar economic opportunities and that participants forgo other opportunities while they are engaged in research, therefore participants should be compensated for their time;

14.3.4.4 **Investigators will be asked to estimate the amount of time participants will spend engaged in research activities for each research visit.**

14.3.5 Research participants may be compensated for inconvenience.

14.3.5.1 In some studies participants will be required to undergo certain procedures that may cause inconvenience or discomfort. Consideration should be given to compensating participants for this inconvenience, over and above time payments;

14.3.5.2 Payment amounts for inconvenient procedures should reasonably reflect the extent of such inconvenience. For example: the inconvenience attached to answering a simple and unobtrusive questionnaire may be lower than a blood draw;

14.3.5.3 Slightly higher payments for inconvenience may complement time payments that usually turn out to be very modest;

14.3.5.4 **Investigators will be asked to judge whether participants will undergo certain inconvenient or uncomfortable procedures at select research visits.**

14.3.6 Research participants should be reimbursed for their expenses

14.3.6.1 Direct costs incurred by participants for research participation should be reimbursed;

14.3.6.2 **Investigators will be asked to estimate costs that participants will incur because of their research participation;**

14.3.6.3 The costs of participation should be established in consultation with community representatives who may be familiar with expenses for, for example, travel, parking, meals or child-care. Investigators are well-placed to consult representatives regarding these expenses;

14.3.6.4 The cost for participants of being away from their individual place of work should not be considered.

15 RESEARCH INVOLVING VULNERABLE RESEARCH PARTICIPANTS

15.1 Policy

HREC must include review of the following elements for research involving vulnerable subjects:

15.1.1 Strategic issues include inclusion and exclusion criteria for selecting and recruiting participants, informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data;

15.1.2 HREC must carefully consider group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects. The investigators must not over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population;

15.1.3 HREC must be knowledgeable about applicable laws that bear on the decision- making abilities of potentially vulnerable populations, such as issues relating to competency to consent for research, minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research;

15.1.4 Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring each subject's capacity, understanding, and informed consent and assent. When weighing the decision of whether to approve or disapprove research involving vulnerable subjects, HREC must look to see that such procedures are part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph;

15.1.5 HREC may require additional safeguards to protect potentially vulnerable populations. For instance, HREC may require that the investigator submit each signed informed consent form to the HREC, that someone from the HREC oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

15.2 Purpose

To provide guidance for HREC regarding protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, capacity-impaired persons, or economically or educationally disadvantaged persons. HREC must also ensure that it has adequate representation to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

15.3 Research involving children

15.3.1 Children are a "vulnerable population," because they are considered easily susceptible to coercion and undue influence and incapable of completely understanding the risks and benefits in making

the decision to participate in research. The respect for persons elaborated in the Belmont Report requires that the decision to participate in research be wholly informed and voluntary. HREC recognizes the importance of conducting scientifically sound research and ethically designed studies in this population. Excluding them from participating in the research is not an answer. Instead special precautions should be incorporated into the design of the study to protect the rights and welfare of child participants;

15.3.2 The extent of protection of the child's rights and welfare considered by HREC depends on the risk of harm and the likelihood, the degree of the benefit to the child from involvement in the study, and the age range of the children who are being asked to participate. This policy discusses these special considerations and protections.

15.3.3 Definition of a child

15.3.3.1 A "child" is defined as someone younger than 18 years in the Bill of Rights of the Constitution of South Africa;

15.3.3.2 Research involving children must conform to ethical guidelines and the law. Research with children should comply with the South African DoH (2015) Ethics Guidelines (Section 3.2.2) and be undertaken only when the research cannot be carried out equally well with adults, and the research question will not be answered using adult participants. The purpose of the research must be to obtain knowledge relevant to the health needs of children;

15.3.3.3 S DHHS funded research with children must comply with US 45 CFR 46.404-407 in addition to relevant South African legislation and regulations;

15.3.4 Requirements for the submission of new child research

15.3.4.1 If a proposed research project involves children, the research applicant must indicate in the relevant sections of the HREC Application form:

15.3.4.1.1 The age range of potential child participants;

15.3.4.1.2 That this is essential research for children;

15.3.4.1.3 The research, including observtaional research, is not contrary to the best interest of the minor;

15.3.4.1.4 Whether the research is therapeutic or non-therapeutic, with a brief justification

15.3.4.1.4.1 **Therapeutic research**: Interventions hold out the prospect of direct health-related benefit for the child participant;

15.3.4.1.4.2 **Non-therapeutic research:** Interventions do not hold out the prospect of direct health-related benefit for the child participant but results may be produced that significantly contribute to generalisable knowledge about the participant's condition; Which risk category the research falls into, with a brief justification

15.3.4.1.4.3 The research poses **no more than minimal risk** to the child (that is, the risk commensurate with daily life or routine medical or psychological examinations – referred to as 'negligible risk' in some guidelines);

15.3.4.1.4.4 The research poses **more than minimal risk but holds out the prospect of direct benefit** for the child participant;

15.3.4.1.4.5 The research poses **a minor increase over minimal risk, with no prospect of direct benefit** to the child participant, but will likely yield generalisable knowledge about the condition under study;

15.3.4.1.4.6 The research does not meet the conditions for the risk categories above, but the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

15.3.4.1.5 Adequate provision should be made for obtaining assent from all children involved in a clinical study and consent from their parents or legal guardians;

15.3.4.1.6 Research involving children must respect their evolving capacity to give consent and therefore the study must provide an opportunity to re-consent if the minor turns 18 years old during the course of the study;

15.3.4.1.7 Where parents and legal guardians are not available, HREC shall be guided by applicable laws and guidelines, the merits of the study and expert opinion on legal and technical points concerning the proposed study. Parental substitutes should be used in descending order as listed:

15.3.4.1.7.1 The minor chooses whether to participate and thus expresses his/her will AFTER;

15.3.4.1.7.2 The parent gives assistance with understanding (so the minor makes an informed choice);

15.3.4.1.7.3 If no parent, then guardian, either court-appointed OR as indicated by the parent in a Will (section 27 Children's Act);

15.3.4.1.7.4 If no guardian, then foster parent (per order of Children's Court);

15.3.4.1.7.5 If no foster parent, then caregiver (section 1 Children's Act: defined as "any person other than a parent or guardian, who factually cares for a child and includes – (a) a foster parent; (b) a person who cares for the child with the implied or express consent of a parent or guardian of the child; (c) a person who cares for the child whilst the child is in temporary safe care; (d) the person at the head of a child and youth care centre where a child has been placed; (e) the person at the head of a shelter; (f) a child and youth care 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");

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

15.3.4.1.8 HREC provides a template informed assent form (see our HREC website www.sun.ac.za/healthresearchethics) in English, Afrikaans and Xhosa and should be used as a guide when drawing up informed assent forms for children;

15.3.4.2 *The HREC may exercise the Minister's delegated power in terms of the National Health Act in approving research with children that includes non-therapeutic components. The HREC*

will ensure that their deliberations on these components are properly minuted and recorded;

15.3.4.3 The HREC must indicate for each project:

15.3.4.3.1 Whether the research is therapeutic or non-therapeutic, with a brief justification;

15.3.4.3.2 The degree of risk of harm evaluated against the likelihood of benefit to the child participant as outlined in one of the risk categories above;

15.3.4.4 HREC will assess the documentation of assent and parental consent as well as the assent and parental consent process.

15.3.5 Paediatric Blood Volume

Research involving blood draws from children must conform to the following guideline for the maximum allowable blood draw volumes:

15.3.5.1 It is important to take the child's clinical condition into account when determining what volume can be used for research purposes;

15.3.5.2 Blood volume should not exceed 5% of the total blood volume during a one-off sampling of total blood volume (including routine blood specimens for clinical care);

15.3.5.3 Blood volume should not exceed 5% of the total blood volume within 3-months (including routine blood specimens for clinical care). *(US OHRP: 3 ml/kg or up to 50 ml total within 8 weeks);*

15.3.5.4 If the blood volume necessary exceeds the above guideline, the research team need to submit additional motivation, which will be considered by the HREC and may need expert opinion prior to final approval;

15.3.5.5 HREC will assess the proposed research **and** clinical blood volumes for children during the research process;

15.3.5.6 Where there is an adequately motivated request by the principal investigator for a larger blood volume to be taken from a child participant, HREC members reference the below guideline table: HREC Maximum allowable total (clinical and research) blood draw volumes

HREC Maximum allowable total (clinical and research) paediatric blood draw volumes

This guideline is to be used by HREC members when there is an adequately motivated request by the principal investigator for a larger blood volume to be taken from a child participant. This guideline also takes into consideration the haemoglobin and is therefore a better guideline in the scenario dealing with impoverished communities and malnutrition.

Body weight (Kg)	Body weight (lbs)	**Total blood volume (mL)**	(=2.5% of Total blood volume) Maximum allowable volume in one blood draw (mL)	**Maximum allowable total volume (CLINICAL + RESEARCH) in a 30-day period (mL)**	Minimum Hgb required at time of blood draw	**Minimum Hgb required at time of blood draw if child has respiratory/ CV compromise**
1	2.2	**100**	2.5	**5**	7.0	**9.0 -10.0**
2	4.4	**200**	5	**10**	7.0	**9.0-10.0**
3	6.3	**240**	6	**12**	7.0	**9.0-10.0**
4	8.8	**320**	8	**16**	7.0	**9.0-10.0**
5	11	**400**	10	**20**	7.0	**9.0-10.0**
6	13.2	**480**	12	**24**	7.0	**9.0-10.0**
7	15.4	**560**	14	**28**	7.0	**9.0-10.0**
8	17.6	**640**	16	**32**	7.0	**9.0-10.0**
9	19.8	**720**	18	**36**	7.0	**9.0-10.0**
10	22	**800**	20	**40**	7.0	**9.0-10.0**
11-15	24-33	**880-1200**	22-30	**44-60**	7.0	**9.0-10.0**
16-20	35-44	**1280-1600**	32-40	**64-80**	7.0	**9.0-10.0**
21-25	46-55	**1680-2000**	42-50	**64-100**	7.0	**9.0-10.0**
26-30	57-66	**2080-2400**	52-60	**104-120**	7.0	**9.0-10.0**
31-35	68-77	**2480-2800**	62-70	**124-140**	7.0	**9.0-10.0**
36-40	79-88	**2880-3200**	72-80	**144-160**	7.0	**9.0-10.0**
41-45	90-99	**3280-3600**	82-90	**164-180**	7.0	**9.0-10.0**
46-50	101-110	**3680-4000**	92-100	**184-200**	7.0	**9.0-10.0**
51-55	112-121	**4080-4400**	102-110	**204-220**	7.0	**9.0-10.0**
56-60	123-132	**4480-4800**	112-120	**224-240**	7.0	**9.0-10.0**
61-65	134-143	**4880-5200**	122-130	**244-260**	7.0	**9.0-10.0**
68-70	145-154	**5280-5600**	132-140	**264-280**	7.0	**9.0-10.0**
71-75	156-185	**5680-6000**	142-150	**284-300**	7.0	**9.0-10.0**
76-80	167-176	**6080-6400**	152-160	**304-360**	7.0	**9.0-10.0**
81-85	178-187	**6480-6800**	162-170	**324-340**	7.0	**9.0-10.0**
86-90	189-198	**6880-7200**	172-180	**344-360**	7.0	**9.0-10.0**
91-95	200-209	**7280-7600**	182-190	**364-380**	7.0	**9.0-10.0**
96-100	211-220	**7680-8000**	192-200	**384-400**	7.0	**9.0-10.0**

Based on blood volume of:

1-2 kg	100mL/kg	**Pre-term infant**
> 2 kg	80mL/kg	**Term infant - adult**

This information is similar to that used by the Committee on Clinical Investigations, Children's Hospital in Los Angeles, CA; Baylor College of Medicine, Dallas, TX; and Cincinnati Children's Hospital Institutional Review Board, OH. These charts were adapted by Rhona Jack, Ph.D. Children's Hospital and Regional Medical Center Laboratory, Seattle, WA in August 2001. *Reference: Rhona Jack; www.ucdmc.ucdavis.edu/.../**Blood** Draws Maximum Allowable.doc - downloaded on 02 December 2010*

15.4 Community research

HREC must ensure that, particularly with regard to research involving communities, those communities' traditions and values are respected. This applies particularly with regards to obtaining consent to participate in research. However, permission given by a community's leader does not absolve the researcher from also obtaining the fully informed consent of each individual participant.

15.5 Prison-based studies

15.5.1 When reviewing non-expedited studies involving prisoners, HREC must ensure that:

15.5.1.1 at least one member of HREC shall be a prisoners' representative (e.g., prisoner, ex prisoner, prisoner or ex-prisoner service provider or member of an NGO representing prisoners) with appropriate background or experience and a voting member of HREC, unless the study has also been reviewed by another accredited REC on which a prisoner representative was present;

15.5.1.2 at least one member present shall be a non-scientist;

15.5.1.3 the majority of HREC members, other than the member described above, shall have no association with the prison(s) involved, apart from their membership of HREC;

15.5.1.4 the Investigator has complied with the conditions specified in the South African Department of Health (2015) Ethical Guidelines (Section 3.2.8);

15.5.2 Studies on prisoners should only be conducted on prisoners if the researcher satisfies HREC that the research cannot be carried out equally well on non-prisoners and the research question cannot be answered with non-prisoners. The purpose of the research must be to obtain knowledge relevant to the health needs of prisoners;

15.5.3 US HHS-funded studies with prisoners must comply with 45 CFR 46.301 to 45 CFR 46.306 in addition to relevant South African legislation and regulations.

15.6 Research with adult participants with diminished functional abilities related to capacity to consent

15.6.1 ICH GCP and SAGCP guidelines define those individuals who are incapable of giving consent as vulnerable, and outline procedures for the consent process, including when consent is provided by a legally acceptable representative of the participant;

15.6.2 When reviewing non-expedited studies involving such adults:

15.6.2.1 The HREC must ensure that the research should only be approved when it cannot reasonably be conducted without their participation. Their participation in research should never be justified based simply on their availability or the convenience of the researcher;

15.6.2.2 The HREC must determine that the risks to the participants are reasonable in relation to the importance of the knowledge that may reasonably be expected to result;

15.6.2.3 The HREC application should include details as to whether the participant recruitment plan includes individuals who have a condition of a type or severity likely to lead to impairment to functional abilities to the extent that it might affect capacity to consent. These include, but are not limited to:

15.6.2.3.1 Acute medical conditions;

15.6.2.3.2 Psychiatric disorders;
15.6.2.3.3 Neurological disorders;
15.6.2.3.4 Developmental disorders; and
15.6.2.3.5 Behavioral disorders.

15.6.2.4 Researchers and HREC members should be aware that some conditions might cause functional abilities to fluctuate over time, or to decrease gradually over the course of the study;

15.6.2.5 When the participant recruitment plan includes individuals likely to experience fluctuating functional abilities or functional abilities that will decrease over time, HREC members might consider whether provisions should be included for the event that participants' capacity to consent changes over the course of the study, including whether:

15.6.2.5.1 Procedures have been described for reevaluating participants' capacity to consent over the course of the study;
15.6.2.5.2 Such participants are asked to designate an individual to serve as a legally acceptable representative, if necessary;
15.6.2.5.3 Individuals identified as potential legally acceptable representatives are involved in the consent process;
15.6.2.5.4 Such participants are asked to document their wishes regarding participation in the study.

16 GENETIC RESEARCH

(Refer to Chapter 3. Section 3.3.8 of the Dept of Health "Ethics in Health Research: Principles, Structures and Processes" for detailed ethical guidelines.)

16.1 HREC requirements for a research protocol that includes genetic analysis

16.1.1 Steps to protect privacy and confidentiality of potentially identifiable genetic information must be specifically outlined in the protocol and must not be released to others, including family members without written consent;

16.1.2 The protocol must state if information and samples will be identifiable, coded or de-identified. Consequences of storing either de-identified information or coded information must be carefully considered within the context of each protocol and justified;

16.1.3 The protocol must state if samples will be stored, for how long and where and must describe the procedure that will be followed if a participant withdraws consent;

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

16.1.4.1 There is a formal collaboration that has been approved by a HREC and a Material Transfer Agreement has been signed by the appropriate authorities;

16.1.4.2 The genetic material and information is transferred in a form that ensures participants cannot be identified. (Prima facie principle)

16.2 Informed consent for genetic research

16.2.1 The Participant Information and consent document for genetic research must be separate from the main consent form;

16.2.2 Participants must be informed of the following:

16.2.2.1 That they are free to refuse consent without giving reasons and still take part in the main research;

16.2.2.2 An explanation of the genetic research study in simple layman's terms, including justification for the study must be given;

16.2.2.3 Arrangements to protect their privacy and confidentiality and whether or not specimens will be identifiable, coded but linked to identifiers or completely anonymous. The advantages and disadvantages of the chosen option should also be spelt out;

16.2.2.4 That they are free to withdraw consent for the research without explanation or prejudice and if their specimen has remained linked and is identifiable, it will be destroyed;

16.2.2.5 Be told whether or not feedback or results will be available and if not, an explanation must be given;

16.2.2.6 Be asked whether or not they wish to be told of research results that could be of relevance to them as individuals;

16.2.2.7 Give details about involvement of other family members, if applicable and must give consent for researchers to approach other family members;

16.2.2.8 Be assured that material and information will not be released for other uses without their consent;

16.2.2.9 Consent for storage should be requested. Information as to where and for how long should be provided;

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

16.3 Request for Waiver of Individual Consent for genetic analysis

16.3.1 HREC adheres to the prima facie principle is that if a researcher wishes to conduct research on stored genetic material, consent is required from the person from whom the material was derived or to whom the information relates;

16.3.2 Before granting a waiver of consent the HREC must determine:

16.3.2.1 The nature of any existing consent i.e. reviews of the original consent documents;

16.3.2.2 The justification presented for the waiver including how difficult it would be to obtain consent;

16.3.2.3 Arrangements with respect to protecting privacy and confidentiality, including de-identifying the information;

16.3.2.4 Extent to which the proposed research poses a risk to the privacy and well-being of the participant;

16.3.2.5 Whether the research proposal is an extension or closely related to the original research;

16.3.2.6 The possibility of commercial exploitation of derivatives of the sample and relevant statutory provisions.

17. HEALTH RESEARCH DATABASES, REGISTRIES AND REPOSITORIES (BIOBANKS)

17.1 Policy

Databases, registries (data banks) and repositories (specimen banks) involve the collection and storage of health information and/or biological material over time. Databases, registries and repositories may be created for clinical purposes, diagnostic purposes, and/or research purposes. This policy refers to all databases, registries and repositories created or used for research purposes. Health research databases, registries and repositories or biobanks are established to foster research that will benefit society and to make data and materials widely available to researchers for the advancement of knowledge and understanding of health issues.

17.2 Purpose

The purpose of this policy is to outline ethical requirements and guidelines for the establishment of research databases, registries and repositories. Given that health research databases, registries and biobanks (repositories) are all collections of biological materials and/or health information on individuals and population, and both give rise to similar concerns about dignity, autonomy, privacy, confidentiality and discrimination.

17.3 Definitions

17.3.1 A **Research Database** is an organised collection of health information (i.e. data) arranged for ease and speed of data retrieval in a structured manner for research purposes;

17.3.2 **A Research Registry** is an organised collection of information or databases, used for research purposes, whose organisers receive information from multiple sources; maintain the information over time; and control access to and use of the information by multiple users or for multiple purposes, which may change over time; Registries can contain codes that link data to their donor's identity;

17.3.3 **A Biobank** or **Research Repository** is a collection, storage and distribution system of biological materials for research purposes. Usually demographic and medical information about the donors is included in the biobank as are codes that link the data and specimens to the donor's identity. The terms biobank and repository can be used interchangeably: for the purposes of this document, the term 'biobank' will be used;

17.3.4 **Biological material** refers to a sample or specimen obtained from an individual human being, living or deceased, which might include genetic information, about that individual. Biological material includes but is not limited to blood, urine, faeces, bone marrow, cell aspirates, diagnostic specimens, pathology specimens, DNA, RNA, blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, tissue and growth factors from the same;

17.3.5 **Anonymous data** or specimens are data or biological material collected by researchers without any identifying information and without a link to a specific participant or donor;

17.3.6 **Identifiable data** or specimens are data or biological material collected by a researcher with identifying details e.g. name, folder number or address;

17.3.7 **Coded or De-identified** data or specimens are data or biological material for whose identifiers have been replaced with a unique number or code and a key exists to decipher the code, allowing the code to be traced back to a specific participant or donor.

17.4 Source of specimens and data

Biological materials and data may be collected in a variety of ways:

17.4.1 Biological material and data collected specifically for research purposes

17.4.1.1 Collection of materials and data specifically for research use requires prospective voluntary informed consent;

17.4.1.2 When the scope of a current research proposal is different from what the participants originally consented, new consent should be obtained;

17.4.2 Biological material and data collected originally for diagnostic or therapeutic procedures

17.4.2.1 The use of existing or archived specimens/data collected for clinical or diagnostic purposes for research will be considered in exceptional cases according to the particular facts relating to each situation;

17.4.2.2 The requirement of consent for the use of these samples/data may be waived if:

17.4.2.2.1 Donor is no longer available to give consent; deceased or uncontactable;

17.4.2.2.2 Samples will be used anonymously, and the result will not put any individual or community at risk;

17.4.2.2.3 If the link to identifiers exists but is not provided to the research team;

17.5 Privacy and confidentiality

17.5.1 In order to respect the dignity, autonomy, privacy and confidentiality of individuals, researchers have specific obligations, both ethical and legal, acting as stewards protecting information provided by participants in research projects;

17.5.2 The rights to autonomy, privacy and confidentiality also entitle individuals to exercise control over the use of their personal data and biological material. Participants therefore have the right to withdraw their samples or information at any time, provided data is identifiable;

17.5.3 Confidentiality is essential for maintaining trust and integrity in Health Databases and Repositories or Biobanks;

17.5.4 The South African Protection of Personal Information Act (2013) also gives effect to the constitutional right of citizens to privacy, by safeguarding the processing of personal information by any responsible party;

17.5.5 Measures to ensure participants' privacy and confidentiality:

17.5.5.1 **De-identification** of specimens/information - Identifiers have been replaced with a number, symbol or letter and a key exists to decipher the code allowing linkage of the code to a specific individual;

17.5.5.2 **Anonymization** of specimens/information – material or information without any linkage to donors;

17.5.6 Collection of material for genetic research should receive special consideration in terms of privacy and confidentiality as genetic information is not specific to one individual but reveals much about that person's relatives and others with a shared ancestry;

17.5.7 Special or additional protections for participants' interests may be necessary, e.g. in instances where identifiable samples or data are collected; where findings (including incidental findings) in genetic studies may pose social, psychological, legal or economic risks for a participant, his family or his community;

17.6 Governance Structure

17.6.1 Health research databases and repositories or biobanks must be appropriately managed and safeguarded in order to protect individuals and population;

17.6.2 Governance of a health research database and biobank from establishment to dissolution must be in accordance with the principles of accountability and transparency and must take into consideration applicable legal frameworks and ethical principles;

17.6.3 Health research databases and biobanks must be registered with the Department of Health as required by the Regulations of the National Health Act;

17.6.4 Health research databases and biobanks must be accredited through the South African National Accreditation System (SANAS);

17.6.5 Health research databases and biobanks must obtain Good Clinical Laboratory Practice (GCLP) Accreditation;

17.6.6 Staff in international health research database and biobank must be certified with the International Aviation and Transport Authority (IATA);

17.6.7 There must be transparency about the nature and source of the health research database's or biobank's financing/funding HBMs and information must not be sold for private gain;

17.6.8 Annual reports must be reviewed and approved by an independent research ethics committee registered with the National Health Ethics Research Council (NHERC);

17.6.9 Governance arrangements should be incorporated in a Standard Operating Procedures Document which must include the following elements:

17.6.9.1 The purpose of the Health Research Database or Biobank;
17.6.9.2 The nature of health data and biological material that will be contained in the Health Research Database or Biobank;
17.6.9.3 Arrangements for the length of time for which the data or material will be stored;
17.6.9.4 Arrangements for regulations of the disposal and destruction of data or material;
17.6.9.5 Arrangement for how the data and material will be documented and traceable in accordance with the consent of the concerned persons;
17.6.9.6 Arrangement for how the data and material will be dealt with in the event of change of ownership or closure;
17.6.9.7 Arrangement for obtaining appropriate consent or other legal basis for data or material collection;
17.6.9.8 Arrangements for protecting dignity, autonomy, privacy and preventing discrimination;
17.6.9.9 Criteria and procedures concerning the access to and the sharing of the health data or biological material including the systematic use of Material Transfer Agreement (MTA) when necessary;
17.6.9.10 The person or persons who are responsible for the governance;
17.6.9.11 The security measures to prevent unauthorized access or inappropriate sharing;

17.6.9.12 The procedures for re-contacting participants where relevant;
17.6.9.13 The procedures for receiving and addressing enquiries and complaints.

17.7 Additional requirements for establishment of health research databases, registries and repositories/biobanks

17.7.1 Biological materials and data may not be shared with any party unless approved by HREC in advance;

17.7.2 Where biological materials and data are to be exported, a valid current export permit is required;

17.7.3 Where biological materials or data are shared with Investigators in other institutions within the country, the recipient institution should agree to comply with the requirements of the Stellenbosch University HREC;

17.7.4 Where biological materials or data are exported to countries outside South Africa, they have to comply with other privacy laws in the recipient country;

17.7.5 Furthermore, use of the data or materials should comply also with any additional requirements of the recipient institution;

17.7.6 Inter-institutional sharing agreements should be confirmed in writing and a signed Material Transfer Agreement (MTA) must be in place before materials and data are transferred to other sites within the country or exported outside the country. A copy of the MTA must be submitted to HREC for record purposes;

17.7.7 If blood or tissue specimens are to be stored for future analysis and such analysis is planned to take place outside the University Stellenbosch (SU), the specimens must be stored in a repository located within the Western Cape (or as otherwise specified and approved by HREC) and released only with HREC approval and approval from a local Research Ethics Committee at the proposed site of the analysis (unless otherwise specified and approved by HREC);

17.7.8 Only HREC approved analyses may be done;

17.7.9 HREC must be provided with details of provisions made to protect the privacy of the donors and the maintenance of the confidentiality of the data;

17.7.10 Specimens may not be shared with any party unless approved by HREC in advance;

17.7.11 Where tissue samples are to be exported, a valid current export permit is required;

17.7.12 A separate consent form or section of the informed consent form, for storage of additional or residual samples is required;

17.7.13 A separate consent form for genetic testing is required (see *Section 12.2: Informed consent for genetic research*);

17.7.14 A signed Material Transfer Agreement (MTA) must be in place before samples are transferred to other sites. A copy must be submitted to HREC for record purposes.

18. MATERIAL TRANSFER AGREEMENTS (MTAS)

18.1 Policy

A material transfer agreement (MTA) or data transfer agreement (DTA) lays out the terms under which research resources can be shared between scientific institutions and is required to move research materials and/or data between institutions and/or countries.This policy refers to the processes and requirements for the review of MTA terms by the HREC.

18.2 Purpose

The purpose of this policy is to define and describe the HREC application requirements and review process for Material Transfer Agreements (MTAs).

18.3 HREC and SU institutional processes and requirements for MTAs

18.3.1 A material transfer agreement (MTA) or data transfer agreement (DTA) is required to move research materials and/or data between institutions and/or countries;

18.3.2 If material or data transfer is anticipated in a project, the research applicant completes the **HREC MTA Term Sheet** (Available at http://www.sun.ac.za/english/faculty/healthsciences/rdsd/Pages/Ethics/Forms-Instructions.aspx) and submits this completed term sheet along with their HREC application;

18.3.3 The specific terms of the MTA term sheet are reviewed by the HREC to ensure that they match the commitments in the protocol and the promises made to participants in the informed consent document;

18.3.4 Once the project, including the MTA/DTA term sheet, is approved by HREC the research applicant sends the MTA term sheet to the University's contracts office;

18.3.5 The contracts office uses the MTA term sheet to prepare an MTA which is appropriate for transferring materials as part of and in accordance with the protocol;

18.3.6 The HREC should not sign the MTA nor should they be responsible for the final review and approval of the full MTA contract;

18.3.7 The approval of MTA'S lies with SU's Research Contracts Office at the Division for Research Development. In the case of FMHS the final signatory is the Vice Dean: Research.

19. AUDIO OR VISUAL MEDIA IN RESEARCH

19.1 Policy

The essential policy of HREC is to protect the dignity, rights, safety, and well-being of all human participants in health-related research. HREC will do this through independent review of all proposed use of audio or visual media in health research projects.

19.2 Purpose

The purpose of this policy is to outline the considerations and factors that may influence the validity and ethical acceptability of the proposed use of audio or visual media in research.

19.3 Review criteria for a protocol that includes audio or visual media

HREC uses the following criteria for review of the use of all audio-visual media in research:

19.3.1 Audio clips, video clips, and/or photographic images as research tool/aid should be used only if the researcher believes, and can adequately motivate, that the media will contribute something positive, significant, meaningful, and/or substantive to the research question; OR that they may, through highlighting visually, promote the rights of a particular group;

19.3.2 Researchers should develop a standardised protocol for the use of audio or visual media during fieldwork;

19.3.3 The principal investigator should devote time and resources to awareness-raising in her research team of how to ethically manage audio or visual media;

19.3.4 There must be specific and fully Informed consent (IC) to the use of audio or visual media, preferably *before* the media is used. While it would be preferable to get informed consent before, in cases where this may alter the "real" nature of the recording, minimally consent after the record is taken and before the record is used;

19.3.5 The informed consent document should contain a separate section, which explains: the need for and contribution the media will make to the study aim; a description of how the media may be used e.g. report writing, presentations, conferences, meetings, journal; and a description of how the media files will be kept stored to protect confidentiality;

19.3.6 The researcher must offer the participant a copy of the media. Include a statement in the informed consent form, “I have been asked whether I want the photograph/video/audio sent to me and where to send it.”;

19.3.7 In the case of child research, the researcher must obtain informed assent from the child and informed consent from the child’s parent/legal guardian/caregiver, or someone with a genuine emotional attachment to the child;

19.3.8 Before seeking consent, researchers have a responsibility to provide information about the research, including its wider implications and the consequences of participant involvement, in a format that is accessible and understandable to potential participants;

19.3.9 Informed consent should be for **each use** of the media;

19.3.10 The consent may be withdrawn at any time. The researcher should guarantee the participant's ability to withdraw the media;

19.3.11 The photographer, video or audio-recorder must at all times respect the rights and dignity of the research participant in the handling of the media;

19.3.12 The researcher must endeavor to protect participant privacy and confidentiality. All media must be stored in a safe and regulated environment with controlled access. The applicant should describe measures in detail in the protocol;

19.3.13 Complete anonymity is not always possible and the minimum area of the body, or minimal identifiable features necessary should be captured (photograph, video). Only in those cases where the face is essential to the image should this area be captured;

19.3.14 Avoid signs, or other readily identifiable objects, in the immediate environment, in media that might deny individuals anonymity and inadvertently allow others to locate them in the community;

19.3.15 Allow confirmation from the participant of accurate/appropriate re-presentation before the media is published.

20. DECLARING A POTENTIAL CONFLICT OF INTEREST FOR INVESTIGATORS

20.1 Policy

A conflict of interest may involve any number or combination of conditions in which a researchers' judgement concerning a primary interest (e.g. participant welfare, scientific integrity) could be biased by a secondary interest (e.g. personal or financial gain). Any potential conflict of interest should be disclosed to the HREC for their review and consideration.

20.2 Purpose

The purpose of this policy is to describe and define conflict of interest and delineate the procedure for the reporting of potential conflict of interest.

20.3 Definition and important considerations

20.3.1 A conflict of interest (COI) occurs when professional judgement regarding an interest e.g. research, or patient care, is unduly influenced by another interest e.g. financial gain or gain in personal status;

20.3.2 Admitting to a conflict of interest is not an indication of moral failure but an honest appraisal of the potential influence of secondary interests on one's judgement and actions;

20.3.3 Conflicts of interests are an inherent and unavoidable part of the academic research environment and can be effectively managed by disclosure and transparency;

20.3.4 Investigator conflicts of interests are of particular importance when an unacknowledged or undisclosed interest, financial or otherwise, may negatively affect the wellbeing of research participants. It is this aspect of COI's that is of concern and relevance to the HREC;

20.3.5 Investigators must consider the **potential effects** that a financial relationship of any kind may have on the research or on interactions with research participants;

20.4 Procedure for the reporting of potential conflict of interest

20.4.1 All investigators are obligated to sign the Conflict of Interest Declaration that is part of the Investigator declaration;

20.4.2 In particular investigators should disclose the following **potential** conflict of interests to the HREC:

- 20.4.2.1 Equity or stock holding in a sponsor company;
- 20.4.2.2 Proprietary interests in product- patent holding, intellectual property rights, trademark, and licensing agreements;
- 20.4.2.3 Grants paid speaking arrangements, retainers for ongoing consultations, sitting on "Pharmaceutical Advisory Boards" etc.;
- 20.4.2.4 Travel/conference sponsorship;
- 20.4.2.5 Recruitment fees or other personal payments that are linked to study outcome, in any way;
- 20.4.2.6 Co-authorship of articles, where the co-author's input has been minimal;

20.4.2.7 Funding for additional staff and facilities, especially if not directly linked to the research project;

20.4.2.8 Equipment for use in a study that will then belong to the department;

20.4.2.9 Donation of equipment unrelated to study;

20.4.2.10 Contributions to a departmental budget not directly related to project expenses;

20.4.3 Please not that all of the above MAY WELL BE POTENTIAL BUT NOT ACTUAL COI'S and after due discussion by the HREC, may be deemed to be acceptable or appropriate, in a particular set of circumstances;

20.4.4 In the event where an investigator attempts to unduly influence and HREC member it is the responsibility of that HREC member to immediately report the event to the Chairperson for further management. According to the nature and the severity of the event, the matter will be referred to the Research Integrity Office or the Executive Committee as deemed appropriate.

21. RECORD KEEPING

21.1 Policy

Legal and ethical requirements regarding human research participant protection require that records be retained in an orderly and easily accessible manner for future reference and for audit purposes by the relevant federal agencies or departments. SAGCP requires retention of records for a minimum of 15 years post-clinical trial. The HREC retains all research study records for 15 years in accordance with GCP requirements.

21.2 Purpose

The purpose of this policy is to describe and delineate the HREC procedures for record keeping.

21.3 Research projects

21.3.1 A HREC reference number is allocated to all new applications. This number is recorded on all correspondence and additional attachments/amendments;

21.3.2 A research ethics data base is used to capture project information such as name of investigators, title of project etc.;

21.3.3 Hard copies of all research study related documents and correspondence are filed according to their reference numbers;

21.3.4 Records kept by HREC include the following:

- 21.3.4.1 Protocols or research plans;
- 21.3.4.2 Investigator brochure (if any);
- 21.3.4.3 Scientific evaluations, when provided by an entity other than the HREC;
- 21.3.4.4 Recruitment materials;
- 21.3.4.5 Consent documents;
- 21.3.4.6 Progress reports submitted by researchers;
- 21.3.4.7 Reports of injuries to participants;
- 21.3.4.8 Records of continuing review activities;
- 21.3.4.9 Data and safety monitoring reports;
- 21.3.4.10 Modifications to previously approved research;
- 21.3.4.11 Unanticipated problems involving risks to participants;
- 21.3.4.12 Documentation of non–compliance;
- 21.3.4.13 Significant new findings;
- 21.3.4.14 All correspondence between the HREC and the researchers;

21.3.5 Additionally, HREC will also keep copies of records for expedited/exempt review procedures including the following:

- 21.3.5.1 The justification for using the expedited/exempt review procedure;
- 21.3.5.2 Actions taken by the reviewer.

21.4 HREC meeting minutes

21.4.1 The minutes of each HREC meeting will be available for review by HREC members one week prior to the next meeting for an approval vote at the subsequent HREC meeting;

21.4.2 Written minutes of HREC meetings will document the following:

- 21.4.2.1 Separate deliberations, actions or votes for each protocol review;
- 21.4.2.2 The basis for deferring or rejecting research;
- 21.4.2.3 The basis for requiring deletions or substantive changes to research;
- 21.4.2.4 The basis for approving research;
- 21.4.2.5 The determination of the level of risk category;
- 21.4.2.6 A written summary of the discussion of controversial issues and their resolution;
- 21.4.2.7 The detailed revisions required to secure approval;
- 21.4.2.8 The approval of exempt reviews by the Chair or designee;
- 21.4.2.9 The approval of required protocol modifications must be documented in the minutes of the first HREC meeting that takes place after the date of the approval;

21.4.3 The meeting minutes must also document committee members' attendance with respect to the following:

- 21.4.3.1 Attendance at the meeting;
- 21.4.3.2 Member's absence from discussion, deliberation, and vote on specific protocols because of financial or non-financial conflict of interest;
- 21.4.3.3 The presence of a quorum at the meeting including the presence of one non-scientific member;

21.4.4 HREC meeting minutes must also document the voting results for each HREC committee action as follows:

- 21.4.4.1 Number of votes including:
  - 21.4.4.1.1 Total votes in favour (For);
  - 21.4.4.1.2 Total votes opposed (Against);
  - 21.4.4.1.3 Abstained;
  - 21.4.4.1.4 Recused (due to conflict of interest);
- 21.4.4.2 The name of HREC members who recused themselves due to conflict of interest;

21.4.5 Protocol specific findings that justify determinations on any of the following must be documented in the meeting minutes:

- 21.4.5.1 Research involving pregnant women, fetuses or neonates;
- 21.4.5.2 Research involving prisoners;
- 21.4.5.3 Research involving people with diminished capacity, cognitive impairment or mental illness;
- 21.4.5.4 Research involving children;

21.5 Record of HREC membership

An up-to-date list of HREC members identified by name; earned degrees; representative capacity; indication of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution will be retained at the HREC office and be publicly available.

22. HREC RESEARCH SITE MONITORING

22.1 Policy

According to the Department of Health's (DOH) Ethics Guidelines for Research (DHO Guidelines, 2nd Edition of 2015, section 4.5.1.10), the Guidelines for Good Clinical Practice in the Conduct of Clinical Trials with Human Participants in South Africa (SA GCP, 2nd Edition, 2006, section 8.9), ICH GCP Guidelines (ICH E6 revised Guidelines of 2015, section 3.3.3) and the Declaration of Helsinki (Guideline 23 of 2013), a Health Research Ethics Committee (HREC) has the responsibility to ensure that the conduct of all research approved by the ethics committee is monitored on an ongoing basis. The frequency and type of monitoring should reflect the degree and extent of risk of harm to research participants in the research project. Monitoring routinely involves the regular review of study progress reports, but sometimes more in-depth monitoring of a project in the form of a **site inspection** may be necessary. The objectives of a site inspection are to protect rights and welfare of research participants; assist researchers in strengthening their research studies; ensure quality of data; and ensure compliance with currently approved protocol/amendment (s), applicable regulatory requirements and GCP standards (where applicable). The HREC has the authority to conduct inspections on any active research activities involving research participants. The cost of inspections will be factored in HREC fees.

22.2 Purpose

The purpose of this SOP is to describe how the Health Research Ethics Committee (HREC) in the Division of Research Development and Support in the Faculty of Medicine and Health Sciences at the Stellenbosch University shall conduct site inspections of research studies that are approved by the HREC.

22.3 Definitions

22.3.1 **Case Report Form (CRF):** A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each research participant;

22.3.2 **Essential Documents:** Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements**;**

22.3.3 **Impartial witness:** A person, who is independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process if the research participant or the research participant's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the research participant**;**

22.3.4 **Inspection:** The act by a regulatory authority (ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the clinical trial/study and that may be located at the site of the study, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority (ies)**;**

22.3.5 **Source Documents:** Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, research participant's diaries or evaluation

checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, research participant's files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial/study.

22.4 Scope

Senate Research Ethics Committee (SREC); Executive Committee (EXCO) of HRECs and UREC; HREC members and Secretariat; Investigators; and Research teams

22.5 Responsibility

22.5.1 The HREC Chairperson or a person appointed by the HREC assumes responsibility for the conduct of an inspection, directs the process and acts as a facilitator for the inspection;

22.5.2 Parties generally involved in the process include the investigator/researcher, the research team, the HREC Secretariat, the HREC Chairperson and the inspector/inspection team.

22.6 Allowable exceptions

This SOP is meant to be followed without deviation.

22.7 Procedures

22.7.1 HREC will conduct both **routine (announced) inspections** and **for cause (unannounced) inspections**;

22.7.2 **Routine (announced) inspections** will be conducted on the following types of sites and studies:

22.7.2.1 Inexperienced sites;

22.7.2.2 High-recruiting sites;

22.7.2.3 Sites recruiting vulnerable patients;

22.7.2.4 Investigator-driven studies;

22.7.2.5 Research that is more "risky"; and

22.7.2.6 Sites that are reporting many SAEs resulting in deaths;

22.7.3 Sites for routine inspections will be selected randomly by the HREC Secretariat and tabled at the next HREC meeting;

22.7.4 The HREC will have to approve the selected sites before site inspections are conducted**;**

22.7.5 Notification letters of intended routine inspections will be sent to Principal Investigators (PIs) of the selected sites and the sites will be given at least 2 weeks to prepare for the inspections and ensure their active participation and to protect their right to due process;

22.7.6 **For cause or unannounced inspections** will be conducted on the following types of studies and sites:

22.7.6.1 Sites from which complaints have been received (whether by a research participant, sponsor or some other 3rd party such as press reports);

22.7.6.2 Sites, at which it is suspected that the procedures approved by the HREC are not being followed, based on evidence provided in progress reports or in sponsor monitoring notes;

22.7.7 Sites **for unannounced inspections** will be selected on an ad-hoc basis as necessary, either after discussion by the HREC, or on specific instructions from the Senate Research Ethics Committee or the EXCO and/or at the request of Deputy Dean of Research in the Faculty of Medicine and Health Sciences;

22.7.8 An independent and suitably qualified inspector may be appointed to act on behalf of the HREC, on a per project contract basis to conduct the site inspection**;**

22.7.9 **Principal Investigators of the selected sites will not be notified of the intended for cause (unannounced) inspection**;

22.7.10 **During each inspection,** the inspection team/inspector will examine the structure of the PI's research organization and their standard operating procedures (SOP) to determine whether he/she complies with the ethical standards and regulatory requirements governing research involving research participants as detailed in the specific areas of focus during site inspections below;

22.7.11 In the case of **for cause/unannounced inspections**, the inspection team/inspector will be supplied with an Inspection Brief, which may outline the complaint/concern and indicate specific focus areas for the inspection;

22.7.12 The main focus of the inspection team is to ensure that the research is being conducted in an ethical manner and that research participants' interests are fully recognised, represented and protected.

22.8 Special areas of focus during site inspections

Some or all of the following documents may be examined by the inspection team during the inspection process, depending on the nature of the inspection and the nature of the study:

22.8.1 **Review of Investigator's Site File (ISF) Documents /Essential Documents:**

- 22.8.1.1 Confirmation of Regulatory Approval by the SAHPRA;
- 22.8.1.2 Signed funding agreement and copies of receipts or financial correspondence (where applicable);
- 22.8.1.3 Signed copy of the final protocol and any amendments;
- 22.8.1.4 Specimen diary card, questionnaires, etc;
- 22.8.1.5 Dated, signed CVs of all study site personnel;
- 22.8.1.6 Specimen of signatures of site staff;
- 22.8.1.7 Responsibilities list;
- 22.8.1.8 Correspondence and communication with funders, and other authorities e.g. Provincial government authority;
- 22.8.1.9 Record relating to equipment loan during the study;
- 22.8.1.10 Equipment calibration logs;
- 22.8.1.11 Laboratory certification (including updates);
- 22.8.1.12 Laboratory normal reference ranges (including updates);
- 22.8.1.13 Any correspondence with the HREC;
- 22.8.1.14 List of HREC HREC members;
- 22.8.1.15 Letter of HREC approval and approval of any protocol amendments or other changes;
- 22.8.1.16 Annual progress report to HREC;
- 22.8.1.17 Annual ethics re-approval from HREC;
- 22.8.1.18 Notification to HREC of end of study (if applicable);

22.8.1.19 Insurance statement/certificate (if applicable);
22.8.1.20 Signed indemnity letter (if applicable);
22.8.1.21 Any advertisement used for participant recruitment;
22.8.1.22 Specimen participant information consent forms;
22.8.1.23 Signed consent forms;
22.8.1.24 Participant screening list/log;
22.8.1.25 Participant recruitment log;
22.8.1.26 Participant identification record;
22.8.1.27 Copies of serious adverse events reported to Sponsor, HREC and SAHPRA (where applicable);
22.8.1.28 Copies of protocol deviations/violations reported to Sponsor, HREC and SAHPRA (where applicable);

22.8.2 **Review of training of research staff**
22.8.2.1 Ensure research staff are trained in the protocol;
22.8.2.2 Ensure research staff are trained in GCP (where applicable);
22.8.2.3 Ensure research staff are trained in research ethics;
22.8.2.4 Ensure research staff are trained in how to obtain consent**;**

22.8.3 **Review of signed informed consent documents**
22.8.3.1 Ensure all informed consent forms are signed by research participants and PI/person obtaining consent and dated appropriately;
22.8.3.2 Ensure impartial witnesses sign consent documents of illiterate research participants**;**

22.8.4 **Review of pharmacy and drug records** (if applicable)
22.8.4.1 Dispensing dates match up with visit date;
22.8.4.2 Drug logs are complete;
22.8.4.3 Tablet counts are recorded;
22.8.4.4 All drug returns are counted;
22.8.4.5 Boxes containing drugs for return are labelled for return;
22.8.4.6 Drug storage is appropriately recorded;

22.8.5 **Case Report Form (CRF) and Source Data Verification (SDV)**
22.8.5.1 Review selected CRFs and their source documents to ensure they are as legible, accurate and complete as possible (source documents vs CRFs);
22.8.5.2 Ensure all amendments/corrections in the CRFs are made correctly;
22.8.5.3 Date of patient visits match recruitment logs;
22.8.5.4 Laboratory result, x-ray results, etc.;
22.8.5.5 Ensure all trial details are filed in appropriate place**;**
22.8.5.6 If ECRFs are being used, review the ECRFs and ensure that there is an audit trail;

22.8.6 **Interviews/discussions with selected research staff (site personnel) and selected research participants**
22.8.6.1 Selected research staff will be interviewed to assess their knowledge of the protocol/study and identify any concerns they may have about the conduct of the study;
22.8.6.2 Selected research participants will be interviewed to understand what they know about the study and identify any concerns they may have about their participation in the study;

22.8.7 **Observation of the recruitment and consent process:** Depending on the nature and timing of the inspection, the inspection team may observe the recruitment and informed consent process or other research procedures;

22.8.8 **Review of transport logs**

22.8.8.1 Review all transport logs and ensure that both research participants and delegated site persons signed and dated the transport logs;

22.8.8.2 Ensure payments to research participants are in accordance with the NHREC TIE guidelines and the approved budget;

22.8.9 **Layout of facility/site and storage of documents/record keeping and security**

22.8.9.1 The layout of the site will be inspected to ensure maintenance of privacy, security and confidentiality;

22.8.9.2 Storage of documents will be checked to ensure safe keeping, security and confidentiality

22.9 Inspection report and follow up

After conducting the inspection, the following will be done:

22.9.1 The inspection team will compile a draft inspection report, which will be submitted to the Chairperson of the HREC and to the PI;

22.9.2 The PI will be requested to respond formally in writing to the inspection report and address each point/query. The PI's report should also include a corrective action plan, if appropriate;

22.9.3 The inspection team or the HREC will then review the report, identifying irregularities in the statements and/or documents, summarising the issues that justify or refute the reasons for the initial complaint, where applicable and proposing a plan or corrective action if appropriate;

22.9.4 The inspector/team may arrange a formal meeting with the PI, inspection team, representatives from the HREC or SREC, where appropriate, to discuss any findings of the inspection including any findings of non-compliance. This meeting is formal and should be minuted in detail;

22.9.5 The Inspection Report, PI's written response and minutes of the follow up meeting are confidential and will usually be tabled at a forthcoming HREC meeting;

22.9.6 The HREC Chairperson and Deputy Dean of Research may jointly, in certain circumstances, decide not to table the full inspection report. However, this decision should not compromise the institutional independence of the HREC;

22.9.7 Major audit findings may be reported to the SREC on a regular basis;

22.9.8 The summary report of the findings may be reported to the National Health Research Ethics Council (NHREC);

22.10 HREC deliberation and decisions on the inspection report

22.10.1 The full HREC will review the inspection team's summary report, the PI's written response and the minutes of the follow up meeting report, where applicable;

22.10.2 The HREC will decide either by consensus or by vote to:

22.10.2.1 Accept the inspection findings and PI's written response as acceptable with no cause for further action. A final letter will be sent to the PI, briefly summarising the outcome and declaring the matter satisfactorily resolved;

22.10.2.2 Request the PI to provide additional information, or take some other form of corrective action, which may even, involve a suspension of approval of the research study involved until proof of corrective action has been provided;

22.10.2.3 Withdraw study approval; and/or

22.10.2.4 Refer the matter to line management, the Deputy Dean of Research and/or the Research Integrity Office (RIO) or the SREC for further investigation and action where appropriate.

22.10.3 All correspondence between the HREC, inspector/inspection team and PI will remain confidential except in cases of serious research non-compliance in which instance the report may be forwarded to external regulatory bodies or funders as deemed appropriate by the EXCO after discussion with the Chairperson of the HREC and other relevant stakeholders;

23. APPEALS AND COMPLAINTS

23.1 Definitions

23.1.1 **Appeals** arise because a Health Research Ethics Committee[4] (HREC) rejects a research proposal, adjudges a protocol deviation or violation to be sufficiently serious to merit calling a halt to 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;

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

23.1.3 Complaints should be directed, in the first instance, to the Chairperson of the relevant HREC. However, if the researcher deems the matter extremely serious and urgent, the complaint can be submitted directly, in writing, to the Chairperson of the SREC.

23.2 Appeal process

The process described below may be a two-stage process involving first the HREC against which the appeal has been lodged. If the HREC agrees or prefers, the matter can be referred to the Senate Research Ethics Committee to be finalised. However, in order to retain the decisional integrity and independence of a HREC within its own institution, PI's may not appeal directly to the SREC. The researcher retains the right to appeal or complain to the National Health Research Ethics Council, if the research falls under the jurisdiction of this council i.e. fulfils the definition of Health Research as defined in the National health Act No.61.2003.

23.2.1 **Appeal process (HREC level)**

23.2.1.1 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 and should exercise this right before launching an appeal;

23.2.1.2 An appeal **must** be directed to the Chairperson of the relevant HREC. A researcher may not appeal directly to the Senate Research Ethics Committee (SREC);

23.2.1.3 The Chairperson of the HREC must appoint a subcommittee to revisit the substance of the application together with any additional information put forward by the PI. The subcommittee must obtain at least one independent, external, expert review of the research project and the substance of the appeal. Additional reviews should be obtained if deemed appropriate. The subcommittee may have the same powers as the HREC, if constituted by the REC concerned;

23.2.1.4 The appeal is usually considered on the grounds of written submission only. However, the Chairperson of the appeal subcommittee may invite the PI to provide an additional oral submission to the subcommittee and answer questions;

23.2.1.5 After deliberation of all the information placed before it, the subcommittee must either

23.2.1.5.1 Uphold the appeal;

23.2.1.5.2 Reject the appeal; or

[4] Health Research Ethics Committee (HREC) 1 and 2, Non-medical REC; Animal Care and Use REC; Biosafety REC

23.2.1.5.3 Refer the matter to the Senate Research Ethics Committee (SREC);

23.2.1.6 In the event of upholding or rejecting the appeal, the decision of the HREC (or HREC-subcommittee) is final;

23.2.1.7 If the HREC or HREC-subcommittee refers the matter to the Senate Research Ethics Committee (SREC) it undertakes to adhere to any decision taken by the SREC, regarding the matter;

23.2.1.8 Researchers conducting 'health research' retain the right to complain or appeal to the National Health Research Ethics Council in the event that they remain dissatisfied with the outcome of the appeal[5];

23.2.2 **Appeal process (Senate Research Ethics Committee Level)**

23.2.2.1 Notice in writing of the intention to refer the matter must be given by the chair of the health research ethics committee (HREC) to the chair of the Senate Research Ethics Committee (SREC). The PI must also be notified of this decision. The chair of the SREC must notify the Vice-Rector Research of the receipt of the appeal;

23.2.2.2 The basis of the appeal and all the relevant documentation must be submitted in writing to the chair of the SREC within seven (7) days of the notice in 1) above;

23.2.2.3 The matter is usually heard on the basis of written submissions only, that is, no oral evidence is led. It is therefore important that the chair of the REC ensure that all the information that is relevant is before the Appeal Panel of the SREC. 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 SREC (see below under Appointment of Appeal Panel);

23.2.2.4 **Composition of Appeal Panel**

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

23.2.2.4.2 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;

23.2.2.4.3 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;

23.2.2.5 **Appointment of Appeal Panel**

The panel must be appointed by the Chair of the Senate Research Ethics Committee (SREC) who must draw up timelines for the submission of documentation, for the hearing of the appeal and for delivery of the panel's decision;

23.2.2.6 **Powers of Appeal Panel**

The appeal panel is empowered:

23.2.2.6.1 to request further information if needed;

[5] The National Health Research Ethics Council has been given the mandate by the National Health Act No.61. 1983 (NHA) to investigate and manage complaints related to the review and approval of 'health research' as defined in the NHA, by research ethics committees.

23.2.2.6.2 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;

23.2.2.6.3 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

23.2.2.6.4 to recommend to the HREC that the appeal be upheld; or

23.2.2.6.5 to recommend to the HREC that the appeal be dismissed;

23.2.2.7 Researchers conducting 'health research' as defined by the SA National Health Act No.61.2003, retain the right to submit an appeal or complaint to the National Health Research Ethics Council if unsatisfied with the outcome of the process

23.3 Complaints process

23.3.1 All complaints against an 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;

23.3.2 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 Research Ethics Committee (SREC);

23.3.3 The Chairperson of the SREC shall notify the Chairperson of the HREC that a complaint has been made against the HREC, inform him/her of the nature and substance of the complaint and request that he/she responds in writing to the complaint, providing sufficient detail;

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

23.3.5 The SREC shall compile a report of its findings and recommended action. The report shall be submitted to the Vice Rector: Research, the Chairperson of the REC and other parties if deemed necessary by the SREC;

23.3.6 The PI shall be notified of the outcome of the SREC investigation.

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APPENDICES

Appendix I: HREC review guide

1. INTRODUCTION, SPECIFIC AIMS, LITERATURE REVIEW
Is the literature review adequate? Are the study aims and objectives clearly specified? Is there appropriate justification for this study protocol? Is there adequate preliminary data to justify the study? Why is it important to conduct this study? Will it add important knowledge to the field? Why is this study worth doing in this particular setting? Are adequate references provided? (Where possible, the literature review should include pertinent references to local research in the proposed field of study). Is there a mechanism for those affected by the study to express their views, clarify their needs and contribute to the research?
2. SCIENTIFIC DESIGN
Is the selected scientific design appropriate to answer the study question(s)? Is the scientific design adequately described and justified? Does the study involve a placebo? If so, is there a persuasive justification for using a placebo? Could the study be done without a placebo? Are study aims and objectives achievable in the given time frame? Do the principal and co-investigators have appropriate academic and clinical credentials and experience to conduct this study? **Qualitative research:** Is the selected scientific design appropriate to answer the study question(s)? Is the scientific design adequately described and justified? Are study aims and objectives achievable in the given time frame? Does the researcher and/or their supervisor/co-investigators have experience in conducting qualitative research? Does the researcher demonstrate an understanding of the qualitative paradigm and method chosen?
3. SELECTION OF PARTICIPANTS
Is the selection of participants appropriate for the study question being asked? Is the rationale for the proposed number of participants reasonable? Is participant selection equitable? Are inclusion and exclusion criteria clearly stated and reasonable? Is the inclusion of children, pregnant women or other vulnerable groups adequately justified? Are adequate safeguards in place to protect the rights and welfare of these vulnerable groups? Can the study be done without involving vulnerable populations? Will the study target or exclude a particular ethnic or language group? Has the study population been involved in previous research and/or is the study population currently involved in research to the extent that the current study may present a significant additional burden? **Qualitative research:** Is the method of sample selection appropriate and clear? If the sample size cannot be delineated before the study begins, are a rationale and plan provided? Has the researcher clearly described how they will determine when adequate sampling (saturation) has occurred?
4. RECRUITMENT STRATEGY
Are the methods for recruiting participants clearly explained and appropriate? How and by whom will individuals be identified for recruitment? Is the location, setting and timing of recruitment acceptable? Are screening procedures prior to recruitment acceptable? Will any potential participants be in a dependent relationship with the researcher/recruiter? (e.g. student/lecturer, employee/employer, patient/doctor) Has the researcher taken steps to ensure that the participant's decision to enrol will not be inappropriately influenced by this relationship? Has the study population been involved in previous research to the extent that the proposed research may present a significant additional burden? (e.g. an existing cohort of participants already in research).
5. RESEARCH PROCEDURES

Are the rationale and details of research procedures described in sufficient detail?
Are the research procedures acceptable and in keeping with study aims and objectives?
Is there a clear distinction between research procedures and standard clinical practice and/or standard patient care?
Are the proposed tests/measurements appropriate, valid and reliable to answer the study question in the local context?
Is there a clear description of plans to inform participants of specific research results e.g. incidental findings, clinically relevant findings?
Are those performing the research procedures adequately trained? For example, in research with children, only research staff with paediatric expertise and/or experience should perform research-related procedures.

6. RISK-BENEFIT ASSESSMENT

Are risks and benefits (to individuals and/or community) adequately identified, evaluated and described? (physical, psychological, social, and economic)
Do risks and benefits stated in the protocol match those described in the Informed Consent form?
Are potential risks minimised?
Are there any specific risks to the researcher (e.g. safety concerns)?
Are potential benefits maximised?
Will counselling or support services be available, if required?
Are potential benefits realistically described and not over emphasized?
Are risks reasonable in relation to anticipated benefits?
Are risks reasonable in relation to importance of anticipated knowledge gained?
Is the risk/benefit ratio acceptable for proceeding with the research?
Is the population from which study participants are drawn likely to benefit from the research?
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)?

7. CLINICAL DRUG/DEVICE TRIAL

Has the national drug regulatory authority approval been obtained, if required?
Are the drug or device safety and efficacy data sufficient to warrant the proposed phase of testing?
Is the use of placebo adequately justified from both a scientific AND an ethical perspective?
Are there adequate provisions for safety monitoring including a DSMB?

8. DATA ANALYSIS AND STATISTICAL ANALYSIS

Are the plans for data and statistical analysis defined and justified?
Has the sample size and selection been adequately justified?
Qualitative research:
Is it clear and well-motivated why or how qualitative data collection methods are the most appropriate for analysis?
Is there clarity in the analytic approach?
Does the description of the analytic approach indicate how this will allow the researcher to pursue their objectives?
Has the researcher adequately described how they intend to go about coding and analysis?
Is there evidence and detail of a conceptual framework?
Is there a mechanism, such as a reference or event monitoring group, to provide ongoing oversight and impartial analysis of unanticipated incidents?

9. COMPENSATION AND COSTS FOR SUBJECTS

Are there adequate plans to avoid out-of-pocket expenses and costs to participants?
Is the amount or type of compensation or reimbursement reasonable and well justified?
If the participant does not complete the study, will compensation be pro-rated?
If children or adolescents are involved who receives compensation and is this appropriate?

10. PRIVACY AND CONFIDENTIALITY

Are there adequate measures to protect the privacy and ensure the confidentiality of the research subjects?
Does the protocol describe site-specific measure to protect privacy?
Does the protocol describe how written records, audio or videotapes, and digital recordings will be secured, for how long, and whose responsibility?
For focus groups, are participants informed that confidentiality cannot be guaranteed as group members may disclose what we discussed outside the research setting?
Are activities that could potentially result in notification e.g. abuse, neglect, potential for harming self or others, addressed in the protocol and IC form?

11. PROCESS OF OBTAINING INFORMED CONSENT AND ASSENT

Is the process adequately described? OR Has a waiver of informed consent or waiver of documentation of informed consent been requested and adequately justified?
Are all required elements of information contained in the informed consent form?
Is the language level appropriate?
Does the process minimise the potential for undue influence?
Does the process provide sufficient time, privacy and an adequate setting for participants to decide?
Will the informed consent form be translated into all required languages?
Is Assent required?
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, is it likely to 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 enroll in a study?
Is there appropriate justification for the use of proxy consent in the event that the researcher cannot obtain direct consent from the participant?
Are jargon, acronyms and abbreviations explained or defined?
Are terms such as 'randomisation' clearly defined and illustrated (e.g. like flipping a coin)?
Will an interpreter be necessary to obtain assent or consent?
Does the consent form state that participants can contact the Human Research Ethics Committee if they have a complaint or questions about their rights and welfare as research subjects?
Does the consent process meet South African legal and regulatory requirements?
In general, is the consent form consistent with the protocol?

12. OTHER

Is the investigator and research team adequately qualified to carry out/supervise the research?
Does the PI have 'human subjects protection training' /GCP?
Is the budget adequate?
Other comments related to the budget?
Are there any administrative deficiencies with the application, such as missing documents?
Has a Material/Data Transfer agreement been submitted if required?

13. AT THE END OF THE STUDY

Will post trial treatment be available?
Who will provide this treatment and for how long?
How will communities and participants be informed of significant findings?
How will findings be disseminated more broadly e.g. publishing, presenting etc?

14. STORAGE OF BIOLOGICAL SPECIMENS

Will biological specimens be stored for future use?
In the case of uniquely identified specimens, especially those containing genetic material, do the participant and family understand where and how their genetic material will be stored and protected and who will have access and why?
Where appropriate, does the consent form spell-out specific provisions for future use of participants stored biological material?
If samples will be stored for future use, does the consent form include opt-in or opt-out options?
Will samples be stored at Stellenbosch University or at an external site?

15. INSURANCE

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

16. CONFLICT 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?

RECOMMENDATION by HREC reviewer:

☐ **APPROVED**

☐ **APPROVED WITH STIPULATIONS** (research can begin subject to certain set pre-conditions – the onus rests with the research applicant to fulfil these)

☐ **MODIFICATIONS REQUIRED** (Approval will be finalised by the 1st reviewer and Chairperson once satisfied with changes/clarifications)

☐ **DEFERRED or "REFERRED BACK"** (NB: the project must serve before the committee again before it can be given "Final Approval" Status.)

PROVISIONS

Describe reason(s) for above recommendation and detail any modifications required

This content will be communicated to the research applicant in the HREC letter

Appendix II: Vulnerable communities and research requiring additional attention

1. DEFINITION: VULNERABLE COMMUNITIES - UNAIDS (2000; 2007) AND SA DoH (2015).

Vulnerable communities are defined as having some or all of the following characteristics:

- Limited economic development;
- Inadequate protection of human rights and discrimination on the basis of health status;
- Inadequate community or cultural experience with the understanding of scientific research;
- Limited availability of health care and treatment options;
- Limited ability of individuals in the community to provide informed consent;
- Culturally marginal groups
- Persons involved in illegal activities or livelihoods

2. RESEARCH REQUIRING ADDITIONAL ATTENTION: (SA GCP Guidance, DoH, 2006)

- Minors: Children and adolescents
- Women: Women and Pregnancy
- Foetuses in-utero
- Foetuses ex-utero
- Persons with mental disabilities
- Persons with substance abuse related disorders
- Persons in dependent or subservient relationships (e.g., students where the investigator is directly involved in their training; employees where the investigator has line authority over them).
- Prisoners
- Persons highly dependent on medical care
- Intensive care
- Neonatal intensive care
- Terminal care
- Persons with impaired capacity to communicate
- Unconscious persons
- Specific social collectivities
- Persons in indigenous medical systems
- Emergency care research
- Innovative therapy or intervention
- HIV/AIDS clinical and epidemiological research

Appendix III: US Federal OHRP guideline: expedited review procedure

(US Federal Government-Office for Human Research Protections (OHRP) guideline document available at http://www.hhs.gov/ohrp/humansubjects/guidance/63fr60364.htm accessed 12.04.2010)

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure[1]

Applicability

A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
B. The categories in this list apply regardless of the age of subjects, except as noted.
C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects= financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
D. The expedited review procedure may not be used for classified research involving human subjects.
E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
F. Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labelling.

NOTE: HREC does not consider any drug/device trials suitable for expedited review except in exceptional circumstances required for public benefit.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children[2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by non-invasive means.

Examples:

(a) hair and nail clippings in a non-disfiguring manner;
(b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
(c) permanent teeth if routine patient care indicates a need for extraction;
(d) excreta and external secretions (including sweat);
(e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
(f) placenta removed at delivery;
(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
(h) 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 in accordance with accepted prophylactic techniques;
(i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
(j) sputum collected after saline mist nebulization.

(4) Collection of data through non-invasive procedures (not involving general anaesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.). 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 subject or an invasion of the subject=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 the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.

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

(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 employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:
(a) where (i) the research is permanently closed to the enrolment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
(b) where no subjects have been enrolled and no additional risks have been identified; or
(c) where the remaining research activities are limited to data analysis.

(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 IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

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[1] An expedited review procedure consists of a review of research involving human subjects by the IRB Chairperson or by one or more experienced reviewers designated by the Chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

[2] Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a). Source: 63 FR 60364-60367, November 9, 1998.

Appendix IV: Compensation for injury: template for informed consent

CONSENT FOR PARTICIPATION IN A CLINICAL TRIAL

You have been asked to consider taking part in a clinical trial, sponsored by _____ _____(the sponsor).

Please take time to read the information below and make sure that you fully understand what this means:

What happens if the study causes me injury or harm or makes me ill?

The South African Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition – 2006, also known as the SA GCP 2006) stipulates that the sponsor of this trial must take out insurance in the event that this trial causes you any physical (bodily) harm or injury, including death. This means that their insurance company agrees to pay your medical expenses which may result directly from your participation in this clinical trial (either from taking this medicine or participating in the procedures explained to you). These costs must be reasonable and do not include costs for, for example, a loss of income or compensation for pain or emotional suffering. Guideline 4.11 of the SA GCP 2006 states that the sponsor of this study should pay your bills for the doctors or other medical staff who treated you due to this injury, without you having to prove that the sponsor was at fault.

The sponsor will, however, not have to pay these costs if the injury or harm was caused by

- your use of unauthorised medicine or substances during the study;
- an injury that results from you not following the protocol requirements or the instructions that the study doctor may give you;
- an injury that arises from any action, or lack of action, on your part to deal adequately with a side effect or reaction to the study medication;
- an injury that results from any other negligence on your part.

By agreeing to participate in this study, you agree that there is a risk that this new medicine or procedures may cause you harm. If it does, the sponsor will reimburse you for your medical expenses.

Above and beyond this, you may still claim for emotional pain and suffering. However, if you choose to do so, you will have to prove that the sponsor was negligent and did not take all reasonable and foreseeable steps to prevent this injury or your emotional trauma. This will be a separate legal matter.

Also please note that Guideline 4.11 of the SA GCP 2006 states that you will normally be asked to accept that any payment made under the Guidelines will be in full settlement of your claim. This means that, once you have accepted the amount that the sponsor has agreed to pay for your medical bills, you may, in general, not claim for more medical expenses at a later stage. Also remember that this insurance taken out for this clinical trial does not replace a clinician's (or a medical professional's) malpractice insurance.

Signed: _____ Date: _____

Appendix V: Compensation for injury: important information to be conveyed to participants

IMPORTANT INFORMATION TO BE CONVEYED TO PARTICIPANTS OF CLINICAL TRIALS WHEN SEEKING THEIR CONSENT

The South African Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition – 2006, also known as the SA GCP 2006) stipulate that the sponsor of a trial must ensure that the participants of a clinical trial is covered by comprehensive insurance in the event of physical (bodily) harm or injury, including death. This means that the insurance company will compensate a participant for medical expenses which may have resulted directly from their participation in a particular clinical trial (either from using the medicine in question or participating in the required procedures). These costs must be reasonable and does not include costs for, for example, a loss of income, compensation for pain or emotional suffering. This was recently confirmed in the decision by the Western Cape High Court in the matter of *Venter v Roche.* Guideline 4.11 of the SA GCP 2006 states that the sponsor of a study should pay the costs for the medical treatment of any bodily injury without the participant having to prove that the sponsor was at fault.

The sponsor will, however, not have to pay these costs if the injury or harm was caused by

- the use of unauthorised medicine or substances during the study;
- an injury that results from the participant not following the protocol requirements or the instructions that the study doctor had provided;
- an injury that arises from any action or lack of action to deal adequately with a side effect or reaction to the study medication on the part of the participant; [*This point must be very carefully checked in each case – it is unacceptable to impose a burden on participants who may not recognize symptoms or have the ready means to take action.]*
- an injury that results from any other negligence on the part of the participant.

It is important to explain to the participant that, by agreeing to participate in this study, she agrees that there is a risk that the study medicine or procedures may cause her harm. If it does, the sponsor will reimburse her for her medical expenses. The participant may, however, still claim for emotional pain and suffering but if she chooses to do so, she will have to prove that the sponsor was negligent and did not take all reasonable and foreseeable steps to prevent the injury or emotional trauma. This will be a separate legal matter. Also please note that Guideline 4.11 of the SA GCP 2006 states that the participant will normally be asked to accept that any payment made under the Guidelines will be in full settlement of the claim. Also remember that this insurance taken out for this clinical trial does not replace a clinician's malpractice insurance.

Appendix VI: HREC Disclosure of conflict of interest

I, _____
Surname and initials

hereby declare that there is a real, perceived or potential risk to my scholarly/scientific, and/or ethical and/or professional judgment in the review of one or more of the research studies serving at the Health Research Ethics Committee (HREC) meeting today.

No ☐ Yes ☐

If **Yes,** please provide

- The HREC protocol number(s) [ ]
- A brief synopsis of the nature of the conflict of interest(s)

I hereby declare that the disclosed information is correct and that no other situation of real, potential or apparent conflict of interest is known to me. I will inform the Health Research Ethics Office of any change in these circumstances, including if an issue arises during the course of the meeting or during the progression of the research study itself.

_____ _____
Member signature Date

HREC CHAIRPERSON REVIEW WHEN CONFLICT OF INTEREST IS DECLARED

In consultation with the Committee, I have reviewed the above declaration and consider the conflict of interest to be such that the member is

Recused ☐ Not recused ☐
from the meeting during the discussion of the particular project(s).

_____ _____ _____
Chairperson's Signature Chairperson's Printed Name Date

Appendix VII: Guidance on educational exercises and health research

When is formal ethics review by a Research Ethics Committee required? Student educational exercises and health research

General guidelines

Research is defined as a systematic investigation designed to develop or contribute to generalisable knowledge. There is a grey area between health research projects and educational exercises regarding when such activities require formal ethics review. According to the Stellenbosch University (SU) Policy for Responsible Research Conduct,[1] "*At SU, all research involving interaction with or observation of human subjects, or information linked to human subjects, or research involving groups of individuals, or organisations must go through a process of ethical screening and clearance*."

The following is intended as a general guideline when making such determinations. It is the supervisor's and student's responsibility to decide whether or not the exercise requires formal ethical clearance and to consult with HREC in this regard. Whether an exercise requires formal ethics review remains at the discretion of HREC, and HREC retains decision-making authority over each case. Regardless of whether an exercise is submitted for formal ethics review or not, all educational activities should be conducted with academic and scientific rigour. Supervisor/s and departments/divisions are responsible for ensuring that all educational activities undertaken at Stellenbosch University adhere to regulatory, institutional and faculty-related requirements, and are conducted in an ethical manner.

Rule of thumb: Get ethical clearance before starting the exercise. This has the advantage of being a learning experience for students, makes them aware of the ethics of conducting such exercises and, importantly, if an exercise produces interesting results, it can be disseminated – published, presented – as the exercise was conducted with ethical approval.

Scenario 1: The exercise / activity does NOT fall under the definition of health research (i.e. is legally *exempt* from review)

- As per the National Health Act (2003) and Department of Health (2015) ethics guidelines, educational exercises or research projects **that do not fall under the definition of health research** as outlined below, do not require formal ethics review by a Research Ethics Committee.
- Any exercise or project that could be **classified as health research** under the National Health Act definition **requires formal ethics review by a Research Ethics Committee**:

  "Health research" includes any research which contributes to knowledge of-
  (a) the biological, clinical, psychological or social processes in human beings;
  (b) improved methods for the provision of health services;
  (c) human pathology;
  (d) the causes of disease;
  (e) the effects of the environment on the human body;
  (f) the development or new application of pharmaceuticals, medicines and
  (g) the development of new applications of health technology.

1 http://www0.sun.ac.za/research/assets/files/Policy_Documents/POLICY%20FOR%20RESPONSIBLE%20RESEARCH%20CONDUCT%20AT%20STELLENBOSCH%20UNIVERSITY.pdf

- If an exercise / project does not fall under this definition of health research, then it probably does not require formal ethics review by a Research Ethics Committee.
- Examples of such **exercises that are exempt from formal ethics review** include:
  - Systematic reviews using information that is available in the public domain;
  - Research involving the collection of study of existing data, documents, records and/or pathological specimens that are already in the public domain;
  - Research on commercial cell lines.
- If in doubt about whether the exercise falls under the definition of health research, it is **always advisable to consult with HREC** regarding whether the exercise should be submitted for review. There may be certain kinds of research – such as health-related ethics research – that would still require formal ethics review by HREC.
- Supervisors of such student exercises are nonetheless strongly advised to ensure that the activities involve minimal risk[1], and that supervisors are providing on-site supervision during the exercise to ensure that it is being conducted ethically, and to mitigate risks.

Scenario 2: The exercise / activity falls under the definition of health research BUT the findings will not be publicly presented or published outside of the classroom environment

- As seen above, **health research is quite broadly defined** in the National Health Act, and quality assurance/improvement activities or related educational exercises that involve health facilities or systems, medical records and databases, and/or health-related diagnostic or interventional projects involving individuals or communities, may **qualify as health research** and therefore require formal ethics review.
- The Faculty of Medicine & Health Sciences at Stellenbosch University makes allowances for students to engage in *educational exercises* that **may qualify as health research** under the National Health Act (2003), as defined above.
- The *only* circumstances in which such exercises *may* be exempt from formal ethics review is when all three of the following conditions are met:
  1. The intention of the exercise is for educational purposes only **AND**
  2. There is no intention to present the findings of the research outside of the classroom environment **AND**
  3. There is no intention to publish the findings of the research.
  4. The burden placed on participants (data subjects) is low i.e. the data collection activity is low risk and ethical principles of research such as informed consent, protection of privacy and confidentiality will be adhered to.
- Supervisors of such student exercises are nonetheless strongly advised to ensure that the activities involve minimal risk[2], and that supervisors are providing on-site supervision during the exercise to ensure that it is being conducted ethically, and to mitigate risks.

Scenario 3: The exercise / activity falls under the definition of health research AND there is an intention to publicly present or publish the findings outside of the classroom environment

[1] **Minimal risk research:** the probability and magnitude of harm or discomfort anticipated in the research, is not greater, in and of itself, than that ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests. *Be aware, too, of risks related to vulnerable populations, such as children or patients with mental disabilities.

- Many undergraduate activities or exercises provide **interesting and valuable results** that may be worthy of publication. In some cases, it may in fact be unethical not to make valuable findings publicly known. Proof of ethical clearance will be required for publication or presentation and this cannot be given retrospectively.
- In these situations, where findings of exercises that fall under the definition of health research will be publicly presented or published beyond the classroom environment, **prospective ethics review** is required prior to commencement of the exercise.

What are the fundamental ethical starting points or principals that need to be considered when deciding to class an activity as either 'research' or an 'educational exercise'?

- It is only ethical to expect people to participate in research, during which they assume certain risks (including psychological or social risks such as stigmatization) if the research is going to have either direct or indirect (future) benefits for patients or society in general.
- In order to ensure an appropriate balance of risks versus benefits for participants, it is thus necessary for a Research Ethics Committee to formally review the research before it begins.
- Research participants are used as 'a means to an end'. This can be justifiable if the research provides some value either to participants, similar persons in the future, or leads to improvement in health systems from which current or future participants stand to benefit.
- When participating in an educational exercise participant are being used as a means to an end- that end involves training a new generation of health care workers and future researchers; this end is justifiable if the cost/risk/ burden to participants is kept to a minimal. If the results of educational exercises or research projects are not made public in any way, then there is no risk of exposure to potential risks such as identification and stigmatization but there also no or limited opportunity for social benefit.
- Hence it is essential that supervisors and their students think carefully before deciding that something that involves the systematic collection of data from humans is an 'educational exercise' and not research.