HEALTH RESEARCH ETHICS COMMITTEES
Human Research
(HREC)

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
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STANDARD OPERATING PROCEDURES AND GUIDELINES

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V4.2

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1. TERMS OF REFERENCE

1.1 The Faculty of Medicine and Health Sciences is served by two, equivalent, Health Research Ethics Committees: HREC1 and HREC2 (hereafter referred to as HREC) (international equivalent titles: Institutional Review Board (IRB), Independent Ethics Committee). These committees are mandated to fulfill their function by the Senate of the University of Stellenbosch through the Senate Research Ethics Committee, to which HREC will report at least annually in writing.

1.2 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.

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

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:

- in vitro diagnostic products, such as general purpose laboratory equipment, reagents and test kits, including monoclonal antibody technology
- certain electronic radiation emitting products with medical applications, e.g. diagnostic ultrasound products, Xray machines and medical lasers.

In other words, 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:

- intended for use in the diagnosis of a disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, OR
- 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".

Note: Adapted largely from: U.S. Food and Drug Administration, 2013. Medical devices: Is the product a medical device? Available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/

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

1.5 HREC functions in compliance with, but not limited to, the following documents and guidelines:

- The SA National Health Act. No. 61 of 2003.
- The SA Department of Health (2004) *Ethics in health research: Principles, structures and processes* and (2006) *South African good clinical practice guidelines.*
- Declaration of Helsinki (Current version)
- The Belmont Report,

- 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,
- ICH-GCP-E6 Sections 1-4 and,
- The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite).

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.

1.6 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.

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

2. APPOINTMENT AND MEMBERSHIP

2.1 Policy

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 (2004) *Ethics in health research: Principles, structures and processes* and (2006) *South African Good Clinical Practice Guidelines*, and as specified in the US Federal Wide Assurance.

2.2 Purpose

The purpose of this policy is to outline the procedure for appointing the HREC Chairpersons and Committee members, to describe their responsibilities and duties, and to define the operational procedures of the HREC.

2.3 Appointment

2.3.1 Appointment to the Committee will be by nomination and co-option. The total number of members on each committee must be no less than 14.

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

2.3.3 On appointment, HREC members sign a confidentiality and non-disclosure agreement.

2.3.4 HREC members will serve for a term of 3 years, renewable.

2.3.5 The Chairperson and Vice Chairperson(s) are elected by HREC members, for a renewable term of three years.

2.3.6 Members not attending 2 consecutive meetings without a valid written reason, and without submitting their reviews, risk termination of their membership.

2.3.7 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 1 & 2.

2.4 Membership

2.4.1 The committee shall:

2.4.1.1 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.

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

2.4.1.3 Be representative of the communities it serves and, increasingly, reflect the demographic profile of the population of South Africa.

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

2.4.1.5 Have at least 14 members;

2.4.1.6 Have a chairperson and 2 vice-chairpersons;

2.4.1.7 Consider a quorum present if 60% of members are in attendance. This must include one non-affiliated member and one non-scientific member (this may be the same person). 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. Meetings will only be conducted when a quorum is present.

2.4.1.8 Include at least two lay persons who have no affiliation to the institution, are not currently involved in medical, scientific or legal work and are preferably from the community in which the research is to take place.

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

2.4.1.10 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.

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

2.4.1.12 Include at least one member who is legally trained.

2.4.1.13 Ensure that the membership is equipped to address all relevant considerations arising from the categories of research likely to be submitted to it.

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

2.4.1.15 Expect all members to provide the HREC administrative office with an abbreviated CV at the beginning of their term.

2.4.1.16 Require members to have continuous personal development in research ethics.

2.4.1.17 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.

2.4.2 The membership and composition of the HREC will be reflected on the committee roster.

2.4.3 The membership and composition of the HREC will be continuously monitored to ensure appropriate representation. 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.

2.5 Conflict of interest

2.5.1 Members of the HREC are expected to make decisions and conduct their oversight responsibilities in an independent manner, free from bias and undue influence. HREC members (and members of their immediate families) 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”

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

2.5.2.1 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

2.5.2.2 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.

2.5.2.3 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,

2.5.2.4 Financial Interest: The HREC member has a financial interest 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.

2.5.3 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.

2.5.3.1 HREC members should make disclosures to the chairperson. The chairperson and committee shall determine whether a conflict exists. The determination of whether or not a conflict exists shall be reflected in the minutes.

2.5.3.2 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.

2.5.4 Recusal

2.5.4.1 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. 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.

2.5.4.2 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.

2.4.5.3 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.

2.6 Confidentiality

2.6.1 "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.

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

2.7 Continuous professional development in research ethics

2.7.1 All members undergo an orientation training session pre appointment to HREC.

2.7.2 All members are required to complete the online TRREE ethics-training course, within 3 months of joining the HREC, and for continued development.

2.7.3 To stay abreast with recent development in the broad area of research ethics and science, HREC members are supported through the HREC office for continued GCP training and selected continued training in research ethics.

2.8 Consultants and Ad Hoc Reviewers

2.8.1 HREC may use consultants or ad hoc reviewers where additional or specialized expertise is needed to review specific protocols. Reasons for seeking additional or special competence may include but are not limited to the need for:

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

2.8.2 Consultants and ad hoc reviewers:

- 2.8.2.1 Must have access to all documents submitted to the HREC relevant to the specific study under review.
- 2.8.2.2 May take part in deliberations and may make recommendations concerning the study.
- 2.8.2.3 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.
- 2.8.2.4 Must affirm that they have no conflict of interest with respect to the specific studies that they are invited to review.
- 2.8.2.5 Must maintain strict confidentiality with respect to the specific protocol and the meeting's proceedings.
- 2.8.2.6 May provide information about a specific study by written reports and/or by attending the meeting.

3. APPLICATION AND ADMINISTRATIVE REQUIREMENTS

3.1 Policy

This policy covers all research activities involves the investigator responsibilities for submitting documents to the HREC and delineate the specific protocol, informed consent, checklists, CVs, declarations, educational certificates and other related documents that must be submitted to the HREC.

3.2 Purpose

To establish guidelines for submitting the required documents to the HREC for research activities involving human participants.

3.3 Procedure

Application forms and guidelines for submission are available from Research Development and Support (RDS), Room 5007, Teaching Building, the Faculty of Medicine and Health Sciences. Visit our website at www.sun.ac.za/rds/

3.3.1 Applications can be submitted on a rolling basis, but must be received 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.

NOTE: *Submission of a research application by the agenda due date does not guarantee that application will be incorporated into a specific agenda. If the number of research applications submitted by a particular agenda due date is too large for one committee meeting to accommodate, the research application will appear at the next available meeting.*

3.3.2 The dates of meetings are available from the RDS administrative office and website at www.sun.ac.za/rds.

3.3.3 To submit research for ethical review, electronic and hard copies of the HREC application package, should be submitted to the HREC office.

- One electronic copy to ethics@sun.ac.za; **and**
- One hard copy (Human and student research) to Elvira Rohland, Research Development and Support, Room 5007, Teaching Building; **or**
- Two hard copies (Clinical trials) to Elvira Rohland, Research Development and Support, Room 5007, Teaching Building

The contents of the hard copy application must exactly match the contents of the electronic application submitted to ethics@sun.ac.za.

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

NOTE: Bolded documents are REQUIRED for all research applications. *Documents in italics are applicable only to drug/medical device trials*

3.3.4.1 Current Health Research Ethics Committee (HREC) application form
3.3.4.2 Checklist ("General" or "Clinical Trials")
3.3.4.3 Proof of payment for HREC review fee (Payment Instruction form for clinical trials; Payment instruction form for human/health research AND Proof of payment through internal requisition or external bank deposit for other research)

3.3.4.4 Research protocol

3.3.4.5 Protocol synopsis or summary This should be between 750-1500 words and include a clear and concise summary of research objectives and methods.

3.3.4.6 Participant Information leaflet and Consent Form (ICF) OR motivated request for a waiver of informed consent. Submit in either English or Afrikaans. Once the requested changes, if any, have been made, submit translations in English, Afrikaans and Xhosa, along with a translation certificate or letter of authenticity OR if translated consent forms are not necessary for the particular study, specifically justify this in the protocol under "Ethical considerations."

3.3.4.7 Short Curriculum Vitae (CV) of all investigators and supervisors (max 2 pages), including MPS number, HPCSA number and category of registration. The CV must demonstrate experience relevant to the proposed research.

3.3.4.8 Investigator Declaration for all investigators Complete and sign an "investigator declaration" and declare any conflict of interest for the principal investigator, co-investigators, and sub-investigators.

3.3.4.9 If the study is for degree purposes, a supervisor declaration should be signed by the study supervisor.

3.3.4.10 Budget & Financial contract Submit a budget (if not included in the protocol) and financial contract (if applicable i.e. external funding)

3.3.4.11 Cover letter

3.3.4.12 Flow chart

3.3.4.13 A description of the study site, including the available infrastructure and the roles and responsibilities of study staff

3.3.4.14 MCC approval or proof of application (if applicable)

3.3.4.15 NHREC approval or proof of application

3.3.4.16 Proof of insurance for participants (if applicable)

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

3.3.4.18 Material for distribution to patients, including diary cards, QOL questionnaires etc.

3.3.4.19 Recruitment material and advertisements (if applicable)

3.3.4.20 Proof of GCP training

3.3.4.21 SA approved package insert(s) of registered comparators

3.3.4.22 Investigator's brochure

3.4 Review Fees

3.4.1 HREC has a graded administrative fee structure in place, which is revised annually. Student projects and projects funded solely from a Stellenbosch University Departmental budget are exempt from fees.

3.4.2 The current administrative fee structure is available in ***Appendix VIII: HREC Review Fees*** and on our website: www.sun.ac.za/rds/

3.4.3 HREC reserves the right to not review a research application if administrative fees are outstanding.

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

3.4.5 Requirements:

3.4.5.1 Clinical Trials:

3.4.5.1.1 Submit a completed and signed *Payment instruction form: clinical trial* along with your application for a new project, progress report, amendment etc.

3.4.5.1.2 You/your sponsor will receive an invoice.

3.4.5.1.3 Payments made directly into SU bank account must contain the invoice number as a reference.

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

3.4.5.1.5 You will not receive your HREC outcome letter until this invoice has been settled.

3.4.5.2 Health Research:

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

3.4.5.2.2 Submit proof of payment or internal requisition number with the PI name as a reference.

3.4.5.2.3 Research applications with outstanding HREC review fees will not enter the review process.

4. REVIEW PROCESSES

4.1 Policy

The HREC reviews research applications according to predefined review processes:

- Exempt
- Case reports and case series
- Minimal risk
- Convened (Full) meeting
- Student research

4.2 Purpose

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

4.3 Exempt from Review

4.3.1 Certain kinds of research activities may be exempt from HREC review. These may include, but are not limited to:

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

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

4.3.1.3 Research on commercial cell lines;

4.3.1.4 Undergraduate educational activities (no intention to publicly present or publish - See *Student research: Undergraduate research projects* for detailed requirements)

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

4.3.2 In general, exempt research does not require submission to HREC for review. In cases where a journal editor or funder asks for notification of ethics exemption, HREC will process the request and provide the research applicant with an exemption letter.

4.3.3 The HREC office accepts new exempt research applications at any time, on a rolling basis. The application for an HREC exemption letter should include:

4.3.3.1 Health Research Ethics Committee (HREC) *Application form: Ethics Exemption* (see ***Appendix III: HREC Application Form: Ethics exemption***);

4.3.3.2 Protocol synopsis (max 2 pages); and

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

4.4 Case reports and case series

4.4.1 In general, case reports and case series do not require submission to HREC for review. In cases where a journal editor or funder asks for notification of ethics approval, HREC will process the request, review the application and provide the research applicant with an HREC letter.

4.4.2 In general, informed consent should be obtained from the patient before publishing a case report or case series. Case reports can sometimes reveal very personal

information of patients and may even possibly lead to their recognition by readers of the report, particularly if photographs are used.

4.4.3 The HREC office accepts new case report and case series applications at any time, on a rolling basis. The application for HREC review should include:

4.4.3.1 Current Health Research Ethics Committee (HREC) application form (see ***Appendix IV***);

4.4.3.2 Cover letter outlining the rationale for the case report and steps taken to protect patient privacy and confidentiality;

4.4.3.3 Signed consent from the patient(s) or their legally appointed representative, or an explanation stating why consent was not obtained. HREC will consider clear and adequately motivated justification for the lack of formal informed consent. A template informed consent document for case reports (adapted from he consent form required by BMJ Case Reports, is available at www.sun.ac.za/rds/;

4.4.3.4 The case report or draft article.

4.4.4 For more information on the publication of case reports and case series, see BMJ Case Reports http://casereports.bmj.com

4.5 Minimal risk review (expedited review)

4.5.1 Definition: 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:

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.*

4.5.2 A "**minimal risk**" review process may be used, at the discretion of the HREC chairperson, or any other person delegated this responsibility by the chairperson, under the following circumstances:

4.5.2.1 All proposed research that meets the criteria for minimal risk research, for the purposes of a degree or diploma (under or postgraduate).

4.5.2.2 When an investigator specifically and adequately motivates for and justifies a "minimal risk" review process.

4.5.2.3 Any minimal risk project identified as suitable by the chairperson or any other person delegated by the chairperson for this purpose.

4.5.3 See ***Appendix V*** for projects considered suitable for minimal risk review according to US-HHS requirements. HREC adheres to the requirements stipulated in this document, except for those related to clinical drug/device trials.

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

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

4.5.4.2 Multi-institutional and/or multi-site collaborative research projects

4.5.4.3 International grant funded research

4.5.5 HREC Review Process

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

4.5.5.1 Front office administration reviews the application for completeness and may request additional information from the applicant. (The contents of the hard copy application must exactly match the contents of the electronic application submitted to ethics@sun.ac.za).

4.5.5.2 The HREC office captures each minimal risk research application and allocates the application to one HREC reviewer.

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

4.5.5.4 The research application and review outcome are approved, at the discretion of the HREC Chairperson, and ratified at the next available HREC convened (full) meeting.

4.6 Convened (full) meeting

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

***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.*

4.6.2 HREC 1 and 2 each convene on a monthly basis, except January and December, to review and consider:

- Continuing Review Reports: *Progress Reports* for active research and *Final Reports* for closing/finalised research;
- New research applications requiring a convened (full) meeting i.e. research that poses more than minimal risk to participants;
- New research applicastions approved via minimal risk review, for ratification of approval;
- Major protocol amendments;
- Adverse events reported in previously approved studies;
- General and policy matters; and/or
- Allegations of misconduct in research or other complaints.

4.6.3 Pre-meeting process

4.6.3.1 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. 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.

4.6.3.2 Front office administration reviews the application for completeness and may request additional information from the applicant. (The contents of the hard copy application must exactly match the contents of the electronic application submitted to ethics@sun.ac.za).

4.6.3.3 HREC administration captures each research and allocates each research application to two members of the committee, at three weeks prior to the meeting for evaluation and review.

4.6.3.4 The chairperson 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.

4.6.3.5 Committee members submit their completed reviews one week prior to the meeting.

4.6.3.6 The HREC coordinator collates all the available reviews into the meeting agenda and distributes the agenda, via InfoEd, 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.

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

4.6.4 HREC review process

The meeting proceeds as follows:

4.6.4.1 The chairperson opens the meeting.

4.6.4.2 A quorum, as described earlier must be present for all decision making.

4.6.4.3 The secretary records those present and also notes apologies.

4.6.4.4 The minutes of the previous HREC meeting are corrected and accepted.

4.6.4.5 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:

- 4.6.4.5.1 Matters arising from the previous meeting;
- 4.6.4.5.2 General items;
- 4.6.4.5.3 Project progress reports/re-approvals;
- 4.6.4.5.4 New applications;
- 4.6.4.5.5 Resubmission of "referred back" projects;
- 4.6.4.5.6 Ratification of projects approved by minimal risk review;
- 4.6.4.5.7 Discussion and review of projects forwarded to the full committee after minimal risk review;
- 4.6.4.5.8 Major amendments for discussion. (A major amendment is one that may alter the risk-benefit assessment of the study or result in significant change in study procedures);
- 4.6.4.5.9 Ratification of amendments approved via the minimal risk review process. NB Minor amendments such as minor changes to ICFs; administrative protocol changes; do not need to be ratified by the committee;
- 4.6.4.5.10 Serious adverse events (SAEs);
- 4.6.4.5.11 Other documents/submissions for noting/approval.

4.6.4.6 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.

4.6.4.7 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.

4.6.4.8 Investigators will not attend the meeting routinely unless requested to do so by the chairperson, or unless they request to present information to the committee that will assist with decision making.

4.6.4.9 The chairperson facilitates discussion and summarises the perceived viewpoint of the committee.

4.6.4.10 The HREC will vote on a proposal as summarized by the chair. One of the following decisions must be made:

4.6.4.10.1 Approved: The proposed research is approved in its current form, with no changes required.

4.6.4.10.2 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.

4.6.4.10.3 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.

4.6.4.10.4 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.

4.6.4.10.5 Rejected

4.6.4.11 Voting will be recorded as number for, against and abstaining.

4.6.4.12 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 and ensure that a quorum is always present.

4.7 Student research

4.7.1 PhD research

4.7.1.1 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 with the project.

4.7.1.2 NB: 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 (See ***Appendix VI: PhD Review Process***)

4.7.2 Postgraduate research for degree and diploma purposes

4.7.2.1 All postgraduate health research for degree and diploma purposes must be submitted to HREC for review prior to the start of study related activities. Given the time limitations for many postgraduate students, it is recommended that postgraduate students either:

4.7.2.1.1 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**

4.7.1.1.2 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.

4.7.2.2 HREC review process:

4.7.2.2.1 The HREC office accepts new postgraduate research applications at any time, on a rolling basis.

4.7.2.2.2 The postgraduate research applicant should submit:

- All necessary documentation for a new application; **and**
- A cover letter motivating for a "minimal risk" review process.

NOTE: *If the study is being done for the purposes of a degree or diploma, the covering letter should be written and signed by the student's Supervisor. A signed supervisor declaration and CV is required for all post graduate research applications.*

4.7.2.2.3 Front office administration reviews the application for completeness and may request additional information from the applicant. (The contents of the hard copy application must exactly match the contents of the electronic application submitted to ethics@sun.ac.za).

4.7.2.2.4 HREC administration captures each postgraduate research application into InfoEd.

4.7.2.2.5 HREC coordinators allocate each postgraduate research application, via InfoEd, to the HREC chairperson, or an HREC member appointed by the chairperson

4.7.2.2.6 The chairperson, or an HREC member appointed by the chairperson, will review the research application and provide the chairperson with a written report. At the discretion of the chairperson, one of the following decisions must be made:

4.7.2.2.6.1 Approved: The proposed research is approved in its current form, with no changes required.

4.7.2.2.6.2 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.

4.7.2.2.6.3 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. All requested changes must be made before a final letter of approval will be issued. The member delegated to the original review will check that the response/ changes are acceptable.

4.7.2.2.6.4 Deferral to convened (full) committee: The proposed research has major methodological and/or ethical concerns and is referred for review and discussion at a convened (full) committee meeting.

4.7.2.2.7 The research application and review outcome are approved, at the discretion of the HREC Chairperson, and ratified at the next available HREC convened (full) meeting.

4.7.3 Undergraduate research projects

4.7.3.1 Many undergraduate students are required to complete small research projects or educational exercises during the course of their studies. Only some of these research projects will require ethical review.

4.7.3.2 It is the supervisor's responsibility to decide whether or not the project requires formal ethical clearance. Supervisors of undergraduate research projects should please note the following:

4.7.3.2.1 The scope and ethical sensitivity of the research project should be carefully considered and chosen. Undergraduate students can be inclined to choose projects which interest them, but which may involve:

- Sensitive or ethically challenging issues; and/or
- Complexities for which undergraduates are poorly equipped to deal, for example, termination of pregnancy, drug abuse in pregnancy etc.

4.7.3.2.2 It is the supervisor's responsibility to decide, within the applicable laws and regulations relating to research ethics, whether or not the project requires formal ethical review. The following is intended to serve as a guide in this decision-making. Supervisors are advised to seek further guidance and confirmation from the HREC Chairperson or a delegated member.

HREC guide: Does this undergraduate research project require formal ethical review?

HREC review required	May not require HREC review
The intended research project is **health research** i.e. a systematic investigation that will lead to generalizable knowledge	The intended research project is an **educational exercise** only
The results of the project will be **presented external to the classroom** environment e.g. at a conference, or possible publication in a journal	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
The intended research will be **conducted in the public domain** e.g. in a school or hospital environment, recruiting scholars or patients as participants	

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.*

4.7.3.3 HREC review process:

4.7.3.3.1 The HREC office accepts new undergraduate research applications at any time, on a rolling basis.

4.7.3.3.2 Undergraduate research applicants should submit:

- The written protocol they have developed as part of their course requirements;
- A completed HREC application form;
- A completed HREC General Checklist;
- A cover letter, signed by the supervisor, stating clearly that this is undergraduate research and motivating for a "minimal risk" review process;
- The supervisor's CV; **and**
- Signed supervisor declaration and conflict of interest.

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

4.7.3.3.4 The chairperson will appoint a suitable member to review the project and if necessary discuss the project with the supervisor and request corrections or changes.

4.7.3.3.5 The same minimal risk review procedures as described above will be followed.

5. REVIEW CRITERIA

5.1 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.

5.2 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.

5.3 Review criteria

HREC uses the following criteria for review:

5.3.1 Social and scientific value

The proposed research is relevant to:

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

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

5.3.2 Scientific validity

5.3.2.1 The proposed research is scientifically valid; **and**

5.3.2.1.1 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;

5.3.2.1.2 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.

5.3.2.2 The proposed investigators/researchers/study coordinators are:

5.3.2.2.1 *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**

5.3.2.2.2 *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**

5.3.2.2.3 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.

5.3.3 Reasonable risk-benefit ratio

5.3.3.1 The potential risks to individual subjects in the proposed research are outweighed by the benefits to the individual or society. ALL the following requirements are satisfied:

5.3.3.1.1 The potential risks to individual participants are identified and minimized

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

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

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

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

5.3.3.2 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.*

5.3.3.3 The potential risks to individual subjects should 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*, if any, to participants and/or the wider community; **and**

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

5.3.3.4 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.

5.3.4 Fair selection of participants

5.3.4.1 The selection of research participants for the proposed research must be fair and just. In making this assessment HREC shall take into account the

purposes 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.

5.3.4.2 Participants must be selected:

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

5.3.4.2.2 *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).

5.3.4.3 The research has avoided involving the vulnerable when less vulnerable persons could be involved; or

5.3.4.3.1 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:

- Justified why vulnerable individuals/communities are included;
- 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)**.

5.3.4.4 *To fairly distribute benefits and burdens*

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

5.3.4.4.2 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;

5.3.4.4.3 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).

5.3.5 Informed consent process

The informed consent process for the proposed research allows for:

5.3.5.1 An informed and voluntary decision from each prospective participant, or the participant's legally authorized representative, in accordance with, and as required by *Standard Operating Procedure #8: Informed Consent* of this document; and

5.3.5.2 Appropriately documented written informed consent, in accordance with, and as required by *Standard Operating Procedure #8.5: Documentation of Informed Consent* of this document.

5.3.6 Respect for participants

5.3.6.1 The proposed research demonstrates respect for the dignity of participants throughout the course of the research.

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

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

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

5.3.6.2.3 Participants are informed of research results

5.3.6.3 **Maintaining 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.

5.3.7 Respect for communities

5.3.7.1 The proposed research demonstrates respect for communities by appropriate community interaction and feedback of results.

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

5.3.7.3 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

5.3.7.4 Communities are informed of research results.

6. CONTINUING REVIEW

6.1 Routine Continued Review (Progress Reports)

6.1.1 Policy

International and local guidelines and regulations (Dept of Health, ICH GCP, SA GCP, MCC 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.

6.1.2 Purpose

The purpose of this policy is to provide guidance on the continuing review process.

6.1.3 Procedure

6.1.3.1 **Ethics approval is valid for one year only** and annual reapproval must be submitted to the HREC a minimum of **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. No research may continue without this process and re-approval.

6.1.3.2 Progress reports:

6.1.3.2.1 All clinical trials falling under the jurisdiction of the MCC must submit a progress report to the MCC six monthly. **Copies of these MCC progress reports should accompany the ANNUAL progress report submitted to the HREC. Please DO NOT submit your 6 monthly MCC progress report outside of this annual reporting to our HREC, unless necessary for safety reasons.**

6.1.3.2.2 In the case of all other research, yearly progress reports are required, unless the HREC deems the project to be of particularly high risk and requests more frequent progress reports.

6.1.3.3 The HREC progress report form should be used for the purposes of this submission.

6.1.3.4 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.

6.1.3.5 For multi-centre studies the **information in the progress report must pertain specifically to local (SU) sites**. A site-specific progress report must be submitted annually, for ethics approval, using the HREC progress report form.

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

6.1.3.7 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.

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

6.1.3.9 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.

6.1.3.10 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

6.1.3.11 Information that must be included in the progress report:

For multi-site studies: 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;

- the number of participants recruited;
- 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)
- a summary of any withdrawal of participants from the research since the last Research ethics committee (REC) review;
- 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;
- any other relevant information, especially information about risks associated with the research;
- A copy of the current informed consent document and any newly proposed consent document.

6.1.3.12 The above information will be distributed to all HREC members prior to each meeting for discussion and renewal of approval.

6.1.3.13 The minutes of the HREC meeting will document separate deliberations for each protocol undergoing continued review by the convened HREC meeting.

6.1.3.14 OHRP requirements stipulate that continuing review and subsequent re-approval of federally funded or supported research must occur within one year of the approval date that correlates with a meeting i.e. the START DATE would be the Approval or Conditional Approval date, if the protocol

was reviewed by the full HREC, or the ratification date if the protocol was reviewed via an expedited review.

6.1.3.15 The HREC has the authority to place restrictions on, suspend, or terminate any study in which the investigator fails to comply with the review process OR where such actions are deemed appropriate and justified by a fully convened HREC meeting.

6.1.3.16 If a project was eligible for expedited review when initially approved, the continuing review may occur via an expedited process. However if the project was not eligible for expedited review e.g. Phase III clinical trial, then the continuing review must occur at a convened and quorate meeting.

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

6.1.3.18 Progress reports are required annually until such time as the investigator submits a final study report or a notice of termination of the study.

6.2 Protocol amendments

6.2.1 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 protocol amendments to protocols involving human research participants before implementation.

6.2.2 Purpose

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

6.2.3 Definitions

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

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

- 6.2.3.1.1 Additional Investigators or study sites
- 6.2.3.1.2 Small changes in the Informed Consent
- 6.2.3.1.3 Change in background information or update of literature review
- 6.2.3.1.4 Extension of period of study
- 6.2.3.1.5 Other changes that do not affect study design and will not affect study outcomes or results
- 6.2.3.1.6 Administrative changes
- 6.2.3.1.7 Stricter inclusion or exclusion criteria.

6.2.3.2 **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:

6.2.3.2.1 Change in study aims, objectives or design
6.2.3.2.2 Resulting changes to consent documents
6.2.3.2.3 Additional study procedures
6.2.3.2.4 Easing of inclusion or exclusion criteria

6.2.4 Procedure

6.2.4.1 To obtain HREC approval for amendments, the investigator must submit these changes to the HREC 1 OR 2 as a requested "study amendment" using the application form for amendments and not 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.

6.2.4.2 **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).

6.2.4.3 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. The same criteria for expedited review of new applications apply to amendments.

6.3 Protocol deviations

6.3.1 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.

6.3.2 Purpose

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

6.3.3 Definitions

6.3.3.1 A protocol 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 up date is given and thus follow up occurs outside of a specified time frame.

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

6.3.3.2.1 **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 wilful breach of ethical and/or regulatory policies; and/or
- Involving a serious and/or continuing non-compliance with institutional, ethical and/or regulatory policies.

6.3.3.2.2 **A minor 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

6.3.4 Procedure

6.3.4.1 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.

6.3.4.2 In the case of unplanned protocol deviations:

6.3.4.2.1 As soon as the deviation is identified in a study, it must be reviewed, documented and categorized as major or minor by the investigator.

6.3.4.2.2 Major protocol deviations must be reported to the HREC 1 OR 2 within a maximum of 15 day after becoming aware thereof.

6.3.4.2.3 Minor protocol deviations can be listed with the next progress report.

6.4 Unanticipated problems involving risks to research participants and others, including adverse events

6.4.1 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.

6.4.2 Purpose

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

6.4.3 Definitions

6.4.3.1 Unanticipated problems

6.4.3.1.1 An unanticipated problem is an incident, experience or outcome that:

6.4.3.1.1.1 is unforeseen in terms of nature, severity,and/or frequency of occurrence; **or**, if anticipated, it is not fully addressed or specified in the information provided to the HREC or to participants. For human research, such information may include the informed consent document, clinical investigator's brochure, product labelling, package inserts, initial protocol application, or any other existing documentation regarding the research conducted to date under the protocol;

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

6.4.3.1.1.3 suggests that 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.

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

6.4.3.1.2.1 Physical abuse of a spouse or partner for participation in a research study.

6.4.3.1.2.2 Loss of a computer containing confidential information regarding trial participants.

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

6.4.3.2 Adverse events

6.4.3.2.1 An adverse event is defined as any untoward medical or psychological occurrence in a human research participant, including any abnormal laboratory finding, symptom or disease, and which does not necessarily have a causal relationship with the research or any risk associated with the research. 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, and that is deemed significant by the investigator should be reported to the HREC 1 or 2, whichever approved the original study. 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. Adverse event may obviously, in certain studies also include adverse drug events.

6.4.3.2.2 An adverse drug reaction is an adverse event which, in the investigator's opinion, has a causal relationship with the research.

6.4.3.2.3 An unexpected adverse event is one in which one or more of the following apply:

6.4.3.2.3.1 The specificity or severity is not consistent with the current investigator's brochure

6.4.3.2.3.2 The event is not consistent with the risk information in the current protocol application

6.4.3.2.3.3 The event is occurring more frequently than anticipated.

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

6.4.3.2.4.1 Death

6.4.3.2.4.2 A life threatening incident

6.4.3.2.4.3 Inpatient hospitalisation or prolongation of existing hospitalisation,

6.4.3.2.4.4 Significant or persistent disability/incapacity,

6.4.3.2.4.5 Congenital abnormality/birth defect.

6.4.3.2.4.6 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.

6.4.3.2.4.7 Any other serious study related event, which in the opinion of the investigator is significant with respect to study participants, staff or data integrity, should also be reported to HREC 1 or 2.

6.4.4 Procedure

6.4.4.1 The investigator should report the following problems to HREC 1 or 2:

6.4.4.1.1 Within 7 calendar days after first becoming aware thereof:
Unanticipated problems that increase the risk of harm to research participants and/or others;

- Fatal and life-threatening, unexpected adverse event and/or adverse drug reaction which, in investigator's opinion, are related (or possibly related) to the research;
- Any other event and/or adverse drug reaction 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; and/or
- New information that may alter the balance of risks and benefits in a study, for example an individual case report and/or a major safety finding from another source (including but not limited to an unfavourable DSMB report and/or publication of results from another study) that may warrant consideration of substantive changes in the overall conduct of the research.
- A standard reporting form for **drug** related SAEs must be completed and submitted, if applicable, and should be attached to a more detailed narrative if the event occurred at the investigator's site. Other adverse events can be briefly summarised in a letter.

6.4.4.1.2 **Within 21 calendar days** after first becoming aware thereof:

- Serious, unexpected, non-fatal adverse drug reactions;
- Expected drug reactions whether serious or not 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;
- A standard reporting form for **drug** related SAEs must be completed and submitted, if applicable, and should be attached to a more detailed narrative if the event occurred at the investigator's site. Other adverse events can be briefly summarised in a letter.

6.4.4.2 Serious 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, at other sites should be reported to the HREC 1 or 2 in a line listing format, if deemed necessary, by the investigator.

6.4.4.3 A summary of all submitted reports will be compiled each month and distributed to all HREC 1 or 2 committee members, for review and discussion at the monthly meeting.

6.4.4.4 Events that are unexpected or repeated will be investigated further and appropriate remedial action taken, if deemed to be necessary by the HREC 1 or 2. Such action may include, but is not limited to:

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

6.4.4.4.2 Suspension of enrolment of new research participants;

6.4.4.4.3 Suspension of additional procedures in currently enrolled research participants;

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

6.4.4.4.5 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;

6.4.4.4.6 Suspension and/or termination of the research

7. COMMUNICATION OF REVIEW DECISIONS

7.1 Policy

To ensure that investigators are appropriately informed about HREC review decisions

7.2 Purpose

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

7.3 Procedure

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

7.3.2 Investigators can address any queries to the HREC office, which will attempt to resolve problems and liaise with the chairperson when necessary.

7.3.3 The average turnaround times for notifying research applicants of the review outcome are detailed below. **The research applicant should only follow up with the HREC office if they have not received an HREC letter within the time frames specified below, preferably not before**. Follow up with the HREC office before this time is preemptive and unlikely to have an effect on the review time.

HREC guide: Expected turnaround times for notification of review outcome

NOTE: *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.*

7.3.4 HREC letters are issued electronically via InfoEd. NOTE: Please check your SU email address, including the junk folder.

7.3.5 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.

7.3.6 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.

7.3.7 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.

7.3.8 All requested protocol and ICF changes must be clearly marked. The **tracked changes** facility on the word processor should be used.

7.3.9 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.

7.3.9.1 If correct, the said documentation will be forwarded to the chairperson for final approval.

7.3.9.2 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 full sitting of the committee.

7.3.10 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.

7.3.11 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.

7.3.12 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 12 weeks before expiry of approval.

7.3.13 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.

NOTE: *If the project is funded by a US federal agency then the date the project was reviewed at a full meeting and given conditional approval will be considered the research start date. Project re-approval must occur within 1 year of this date.*

NOTE: *HREC administration reserves the right to not issue approval letters if administrative fees are outstanding.*

8. INFORMED CONSENT

8.1 Policy

8.1.1 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.

8.1.2 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.

8.1.3 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.

8.1.4 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.

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

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

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

8.2 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.

8.3 Elements of Informed Consent

8.3.1 Basic Elements of Informed Consent

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

8.3.1.1 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;

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

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

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

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

8.3.1.6 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 Section 4.11: Compensation to participants*); 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 VII: Compensation for Injury – Template for Informed Consent*)

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

8.3.1.8 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;

8.3.1.9 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; **and**

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

8.3.2 Additional Elements of Informed Consent

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

8.3.2.1 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;
8.3.2.2 Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent;
8.3.2.3 Any additional costs to the participant that may result from participation in the research;
8.3.2.4 The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant;
8.3.2.5 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**
8.3.2.6 The approximate number of participants involved in the study.

8.4 Variation of Consent Procedures (including waiver of informed consent)

8.4.1 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:

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

8.4.1.2 The waiver or alteration will not adversely affect the rights and welfare of the participants;

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

8.4.1.4 Whenever appropriate, the participants will be provided with additional pertinent information after participation.

8.4.2 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.

8.4.3 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.

8.4.4 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.

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

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

8.5 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, the researcher must document the informed consent process in the source notes of the research participant.

8.5.1 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 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 verify in writing that the informed consent process was valid and in accordance with the requirements of this SOP document. ‘

8.5.2 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.

8.5.3 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:

8.5.3.1 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.

8.5.3.2 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.

8.5.4 The HREC provides template participant information and consent forms (PICF) that are available in English, Afrikaans and Xhosa and should be used as a guide when drawing up a PICF. The following forms are available from RDS or visit the website at www.sun.ac.za/rds/:

- Informed consent template - General
- Informed assent form template - Children
- Informed consent form template - Case reports
- Informed consent from template - Genetic studies

8.5.5 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.

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

8.6 Translation of the participant informed consent document

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.

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

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

8.6.3 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:

8.6.3.1 *Who* are researchers planning to recruit?

8.6.3.2 *Where* will participants be recruited from? and

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

8.6.4 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.

8.6.5 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.

8.6.6 PICF 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.

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

8.6.8 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.

8.6.9 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.

9. PARTICIPANT INSURANCE

9.1 Policy

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 are covered by comprehensive insurance in the event of physical (bodily) harm or injury, including death. 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**.

9.2 Purpose

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

9.3 Procedure

9.3.1 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).

9.3.2 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.*

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

- 9.3.3.1 the use of unauthorised medicine or substances during the study;
- 9.3.3.2 an injury that results from the participant not following the protocol requirements or the instructions that the study doctor had provided;
- 9.3.3.3 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.]*
- 9.3.3.4 an injury that results from any other negligence on the part of the participant.

9.3.4 It is important to explain to the participant that:

- 9.3.4.1 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**.
- 9.3.4.2 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.

9.3.5 See ***Appendix IX: 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 X: Important information to be conveyed to participants***

9.3.6 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.

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

10. PAYMENT OF RESEARCH PARTICIPANTS

10.1 HREC must review the amount and method of payment to research participants in accordance with the provisions of the *National Health Research Ethics Council (NHREC).* See *NHREC (2012) Payment of trial participants in South Africa: Ethical considerations for Research Ethics Committees (RECs)* http://www.nhrec.org.za/wp-content/uploads/2012/payment_considerations.pdf

10.2 Neither the amount nor method of payment for research participants must present the potential for undue influence.

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

10.4 The amount and method of payment to research participants should reflect the following three components:

10.4.1 Compensation for time;

10.4.2 Compensation for inconvenience; and

10.4.3 Reimbursement of expenses.

10.5 Key sections of the *NHREC (2012) Payment of trial participants in South Africa: Ethical considerations for Research Ethics Committees (RECs)* are summarized below.

10.5.1 Research participants should be ***compensated appropriately for their time***

10.5.1.1 Time payments should be made at rates commensurate with unskilled labour rates. This acknowledges that trial participation (while valuable) does not necessarily require special skills and training, but does entail expending effort. For example, hourly rates for unskilled civil engineering workers are approximately R10.00 per hour in South Africa.

10.5.1.2 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.

10.5.1.3 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.

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

10.5.2 Research participants may be ***compensated for inconvenience****.*

10.5.2.1 In some studies, including phase I and phase IIa, 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.

10.5.2.2 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.

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

10.5.2. Investigators will be asked to judge whether participants will undergo certain inconvenient or uncomfortable procedures at select trial visits.

*10.5.3 Research participants should be **reimbursed for their expenses***

10.5.3.1 Direct costs incurred by participants for research participation should be reimbursed.

10.5.3.2 Investigators will be asked to estimate costs that participants will incur because of their research participation.

10.5.3.3 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.

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

11. RESEARCH INVOLVING VULNERABLE RESEARCH PARTICIPANTS

11.1 Policy

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

11.1.1 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.

11.1.2 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.

11.1.3 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.

11.1.4 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.

11.1.5 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.

11.2 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.

11.3 Research involving Children

11.3.1 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.

11.3.2 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.

11.3.3 Definitions

11.3.3.1 A "child" is defined as someone younger than 18 years in the Bill of Rights of the Constitution of South Africa.

11.3.3.2 Research involving children must conform to ethical guidelines and the law. Research with children should comply with the South African DoH (2004) Ethics Guidelines (Section 5.1) 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.

11.3.3.3 US DHHS funded research with children must comply with US 45 CFR 46.404-407 in addition to relevant South African legislation and regulations.

11.3.4 Procedure

11.3.4.1 All research involving children is reviewed by HREC at a full committee meeting and may not be submitted for minimal risk review (SREC decision February 2014).

11.3.4.2 If a proposed research project involves children, the research applicant must indicate in the relevant sections of the HREC Application form:

11.3.4.2.1 The age range of potential child participants;
11.3.4.2.2 Whether the research is therapeutic or non-therapeutic, with a brief justification;
11.3.4.2.3 Which risk category the research falls into, with a brief justification (see below);
11.3.4.2.4 That this is essential research for children

11.3.4.3 The HREC must categorise each project as therapeutic or non-therapeutic, with a brief justification.

11.3.4.3.1 ***Therapeutic research****: Interventions hold out the prospect of direct health-related benefit for the child participant.*

11.3.4.3.2 ***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.

11.3.4.4 Research involving children should be determined by HREC as falling into one of the following risk categories:

11.3.4.4.1 "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);

11.3.4.4.2 The research poses more than minimal risk but holds out the prospect of direct benefit for the child participant.

11.3.4.4.3 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;

11.3.4.4.4 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.

11.3.4.5 Adequate provision should be made for obtaining assent from children and consent from their parents or legal guardians. HREC provides a template informed assent form (available from RDS or visit the website at www.sun.ac.za/rds/) in English, Afrikaans and Xhosa and should be used as a guide when drawing up informed assent forms for children.

11.3.4.6 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.

11.3.5 Paediatric Blood Volume

11.3.5.1 Research involving blood draws from children must conform to the following guideline for the maximum allowable blood draw volumes:

11.3.5.1.1 Blood volume should not exceed 3% of the total blood volume during a time period of 4 weeks; and

11.3.5.1.2 Blood volume should not exceed 1% of the total blood volume at any single time; and

11.3.5.1.3 Note: Total blood volume is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight.

11.3.5.2 If the blood volume necessary exceeds the above guideline, the research team must provide appropriate and adequate motivation, which will be considered by the HREC.

11.4 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.

11.5 Prison-based studies

11.5.1 When reviewing non-expedited studies involving prisoners, HREC must ensure that:

11.5.1.1 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,

11.5.1.2 at least one member present shall be a non-scientist,

11.5.1.3 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,

11.5.1.4 the Investigator has complied with the conditions specified in the South African DoH (2004) Ethical Guidelines (Section. 5.11).

11.5.2 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.

11.5.3 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.

11.6 Research with Adult Participants with Diminished Functional Abilities Related to Capacity to Consent

11.6.1 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.

11.6.2 When reviewing non-expedited studies involving such adults:

11.6.2.1 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.

11.6.2.2 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.

11.6.2.3 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:

11.6.2.3.1 Acute medical conditions,

11.6.2.3.2 Psychiatric disorders,

11.6.2.3.3 Neurological disorders,

11.6.2.3.4 Developmental disorders, and

11.6.2.3.5 Behavioural disorders.

11.6.2.4 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. 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:

11.6.2.4.1 Procedures have been described for reevaluating participants'capacity to consent over the course of the study;

11.6.2.4.2 Such participants are asked to designate an individual to serve as a legally acceptable representative, if necessary;

11.6.2.4.3 Individuals identified as potential legally acceptable representatives are involved in the consent process;

11.6.2.4.4 Such participants are asked to document their wishes regarding participation in the study.

12. GENETIC RESEARCH

(Refer to Chapter 9 of the Dept of Health "Ethics in Health Research: Principles, Structures and Processes" for detailed ethical guidelines.)

12.1 HREC requirements for a research protocol that includes genetic analysis:

12.1.1 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.

12.1.2 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.

12.1.3 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.

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

12.1.4.1 There is a formal collaboration that has been approved by a HREC and a Material Transfer Agreement has been signed by the appropriate authorities

12.1.4.2 The genetic material and information is transferred in a form that ensures participants cannot be identified. (Prima facie principle)

12.2 Informed Consent

12.2.1 The Participant Information and consent document for genetic research must be separate from the main consent form.

12.2.2 Participants must be informed of the following:-

12.2.2.1 That they are free to refuse consent without giving reasons and still take part in the main trial.

12.2.2.2 An explanation of the genetic research study in simple layman's terms, including justification for the study must be given.

12.2.2.3 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.

12.2.2.4 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

12.2.2.5 Be told whether or not feedback or results will be available and if not, an explanation must be given.

12.2.2.6 Be asked whether or not they wish to be told of research results that could be of relevance to them as individuals.

12.2.2.7 Give details about involvement of other family members, if applicable and must give consent for researchers to approach other family members.

12.2.2.8 Be assured that material and information will not be released for other uses without their consent.

12.2.2.9 Consent for storage should be requested. Information as to where and for how long should be provided.

12.2.2.10 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.

12.2.3 Request for Waiver of Individual Consent for genetic analysis

12.2.3.1 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.

12.2.3.2 Before granting a waiver of consent the HREC must determine:

- 12.2.3.2.1 The nature of any existing consent i.e. reviews of the original consent documents.
- 12.2.3.2.2 The justification presented for the waiver including how difficult it would be to obtain consent.
- 12.2.3.2.3 Arrangements with respect to protecting privacy and confidentiality, including de-identifying the information.
- 12.2.3.2.4 Extent to which the proposed research poses a risk to the privacy and well-being of the participant.
- 12.2.3.2.5 Whether the research proposal is an extension or closely related to the original research.
- 12.2.3.2.6 The possibility of commercial exploitation of derivatives of the sample and relevant statutory provisions.

13. STORED TISSUE

13.1 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).

13.2 Only HREC approved analyses may be done.

13.3 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.

13.4 Specimens may not be shared with any party unless approved by HREC in advance.

13.5 Where tissue samples are to be exported, a valid current export permit is required.

13.6 A separate consent form or section of the informed consent form, for storage of additional or residual samples is required.

13.7 A separate consent form for genetic testing is required**.**

13.8 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.

14. PHOTOGRAPHS IN RESEARCH

14.1 Photographs as a research tool/aid should be used if the researcher believes that the photographs 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.

14.2 Researchers should develop a standardised protocol for taking photos during fieldwork.

14.3 The principal investigator should devote time and resources to awareness-raising in her research team of how to ethically manage photos.

14.4 There must be specific and fully Informed consent (IC) to photography *before* the photography takes place. It would be preferable to get informed consent before but in cases where this may alter the "real" nature of the photo, minimally consent after the photo is taken and before the photo is used.

14.5 The informed consent document should contain a separate section, which explains: the need for and contribution the photograph(s) will make to the study aim; a description of how the photograph(s) may be used e.g. report writing, presentations, conferences, meetings, journal; and a description of how the photograph(s) will be kept stored to protect confidentiality.

14.6 The researcher must offer the participant a copy of the photograph. Include a statement in the informed consent form, "I have been asked whether I want the photograph sent to me and where to send it."

14.7 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, or someone with a genuine emotional attachment to the child.

14.8 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.

14.9 Informed consent should be for **each use** of the image.

14.10 The consent may be withdrawn at any time. The researcher should guarantee the participant's ability to withdraw the photograph(s).

14.11 The photographer must at all times respect the rights and dignity of the research participant in the handling of photos.

14.12 The researcher must endeavor to protect participant privacy and confidentiality. All images must be stored in a safe and regulated environment with controlled access. The applicant should describe measures in detail in the protocol.

14.13 Complete anonymity is not always possible and the minimum area of the body, or minimal identifiable features necessary should be photographed. Only in those cases where the face is essential to the image should this area be photographed.

14.14 Avoid signs, or other readily identifiable objects, in the immediate environment, in pictures that will deny individuals anonymity and inadvertently allow others to locate them in the community.

14.15 Allow confirmation from the participant of accurate/appropriate re-presentation before the photograph is published.

15. CONFLICT OF INTEREST POLICY FOR INVESTIGATORS

15.1 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. 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. Conflicts of interests are an inherent and unavoidable part of the academic research environment and can be effectively managed by disclosure and transparency.

15.2 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.

15.3 Investigators must consider the **potential effects** that a financial relationship of any kind may have on the research or on interactions with research participants.

15.4 All investigators are obligated to sign the Conflict of Interest Declaration that is part of the Investigator declaration. In particular investigators should disclose the following **potential** conflict of interests to the HREC:

15.4.1 Equity or stock holding in a sponsor company
15.4.2 Proprietary interests in product- patent holding, intellectual property rights, trademark, and licensing agreements.
15.4.3 Grants paid speaking arrangements, retainers for ongoing consultations, sitting on "Pharmaceutical Advisory Boards" etc.
15.4.4 Travel/conference sponsorship
15.4.5 Recruitment fees or other personal payments that are linked to study outcome, in any way
15.4.6 Co-authorship of articles, where the co-author's input has been minimal.
15.4.7 Funding for additional staff and facilities, especially if not directly linked to the research project.
15.4.8 Equipment for use in a study that will then belong to the department
15.4.9 Donation of equipment unrelated to study.
15.4.10 Contributions to a departmental budget not directly related to project expenses.

15.5 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.

16. RECORD KEEPING

16.1 Purpose

16.1.1 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. 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.

16.2 Research projects

16.2.1 A HREC reference number is allocated to all new applications. This number is recorded on all correspondence and additional attachments/amendments.

16.2.2 A research ethics data base is used to capture project information such as name of investigators, title of project etc.

16.2.3 Hard copies of all research study related documents and correspondence are filed according to their reference numbers.

16.2.4 Hard copy records of all communication between investigators and the HREC office are recorded and filed using this reference number.

16.3 Meetings

Written minutes of HREC meetings will be recorded in sufficient detail to:

16.3.1 Show attendance at the meetings

16.3.2 All actions taken by the HREC

16.3.3 Whether or not decision was reached by consensus or voting,

16.3.4 If by vote, then the number voting for, against and abstaining.

16.3.5 The basis for requiring changes to, or disapproval of research.

16.3.6 A written summary of the discussion of controversial issues and their resolution.

16.4 Record of membership

An up-to-date list of HREC members identified by name; earned degrees; representative capacity; indication of experience sufficient to describe each members 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.

17. GUIDELINE FOR CONDUCTING SITE AUDITS

17.1 According to the Department of Health's Ethics Guidelines for Research "an REC has the responsibility to ensure that the conduct of all research approved by an ethics committee is monitored on an ongoing basis. The frequency and type of monitoring should reflect the degree of risk to 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 audit** may be necessary. The main objective of a site audit is to ensure compliance with both the protocol and GCP guidelines, where applicable. The HREC has the authority to conduct audits on any active research activities involving human participants.

17.2 The REC chairperson or a person appointed by the REC assumes responsibility for the conduct of an audit directs the process and acts as a facilitator.

17.3 Parties generally involved in the process include the investigator, the research team, the REC, the REC chairperson, the auditor/audit team and the Deputy Dean of Research.

17.4 The REC has the authority to audit any research site. However as site audits are costly and time consuming the following sites will be prioritised:

- 17.4.1 **Routine audits,** which include but are not limited to:
  - 17.4.1.1 Inexperienced sites;
  - 17.4.1.2 High-recruiting sites;
  - 17.4.1.3 Sites recruiting vulnerable patients; and
  - 17.4.1.4 Research that is more "risky".
- 17.4.2 **For cause audits,** which include but are not limited to:
  - 17.4.2.1 Sites from which complaints have been received (whether by a participant, sponsor or some other 3rd party);
  - 17.4.2.2 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.

17.5 An independent, suitably qualified auditor will usually be appointed to act on behalf of the HREC, on a per project contract basis to conduct the site audit.

17.6 Implementation of an Audit and Notification

- 17.6.1 Sites from Group A will be selected randomly by the HREC.
- 17.6.2 Sites from group B will be selected on an ad-hoc basis as necessary, either after discussion by the HREC, or on the specific instructions of the Senate Research Ethics Committee or the Deputy Dean : Research, FHS
- 17.6.3 A notification of Sites for proposed audits will be tabled at the next HREC meeting.
- 17.6.4 The PIs will be given at least 2 weeks notice that an audit will be performed, so as to ensure their active participation and to protect their right to due process.

17.7 The audit

17.7.1 The audit team will examine the structure of the PI's research organisation and their standard operating procedures to determine whether he/she complies with the ethical standards and regulatory requirements governing research involving human participants.

17.7.2 In the case of audits in response to a complaint, the audit team will be supplied with an Audit Brief, which may outline the complaint and indicate specific focus areas for the audit.

17.7.3 In the case of random audits, the audit team reviews records maintained by the PI, including site-monitoring notes where applicable, for the duration of the study.

17.7.4 The main focus of the audit team is to ensure that the research is being conducted in an ethical manner and that participant's interests are fully recognised, represented and protected.

17.7.5 Some or all of the following documents may be examined by the audit team during the audit process, depending on the nature of the audit and the nature of the study. **(NB: Some of the documents listed here may not be applicable)**

17.7.5.1 INVESTIGATOR'S STUDY FILE:

17.7.5.1.1 Confirmation of Regulatory Approval
17.7.5.1.2 Signed funding agreement and copies of receipts or financial correspondence (where applicable)
17.7.5.1.3 Signed copy of the final protocol and any amendments
17.7.5.1.4 Specimen diary card, questionnaires, etc
17.7.5.1.5 Dated, signed CVs of all study site personnel
17.7.5.1.6 Specimen of signatures of site staff
17.7.5.1.7 Responsibilities list
17.7.5.1.8 Correspondence and communication with funders, and other authorities e.g. Provincial government authority
17.7.5.1.9 Record relating to equipment loan during the study
17.7.5.1.10 Equipment calibration logs
17.7.5.1.11 Laboratory certification (including updates)
17.7.5.1.12 Laboratory normal reference ranges (including updates)

17.7.5.2 HREC COMPLIANCE

17.7.5.2.1 Any correspondence with the HREC
17.7.5.2.2 List of Committee members
17.7.5.2.3 Letter of REC approval and approval of any protocol amendments or other changes
17.7.5.2.4 6-monthly/annual progress report to HREC
17.7.5.2.5 Annual re-approval from HREC
17.7.5.2.6 Notification of end of study
17.7.5.2.7 Insurance statement (if applicable)
17.7.5.2.8 Signed indemnity letter (if applicable)
17.7.5.2.9 Any advertisement used for participant recruitment
17.7.5.2.10 Specimen participant information consent forms
17.7.5.2.11 Signed consent forms
17.7.5.2.12 Participant screening list
17.7.5.2.13 Participant recruitment log
17.7.5.2.14 Participant identification record
17.7.5.2.15 Copies of serious adverse events

17.7.5.3 PHARMACY AND DRUG RECORDS (IF APPLICABLE)

17.7.5.3.1 Dispensing dates match up with visit date
17.7.5.3.2 Drug logs are complete
17.7.5.3.3 Tablet counts are recorded
17.7.5.3.4 All drug returns are counted

17.7.5.4.5 Boxes containing drugs for return are labelled for return
17.7.5.4.6 Drug storage is appropriately recorded

17.7.5.4 CASE RECORD FORMS

17.7.5.4.1 All CRFs are as complete as possible
17.7.5.4.2 All amendments are made correctly
17.7.5.4.3 Date of patient visits match recruitment logs
17.7.5.4.4 Laboratory result, x-ray results, etc
17.7.5.4.5 All trial details filed in appropriate place

17.7.5.5 TRANSPORT LOGS

17.7.6 Additional Points of Note:-

17.7.6.1 Interviews may be conducted with the PI and site personnel.
17.7.6.2 Depending on the nature and timing of the audit, the audit team may contact research participants, observe the informed consent process or require a third party to observe the informed consent process or research procedures.

17.8 Reporting of Audit and Follow-up

17.8.1 The audit team will compile an audit report, which is submitted to the Chairperson of the HREC and/or the Deputy Dean of Research if appropriate, and to the PI.
17.8.2 The PI will be requested to respond formally in writing to the audit report and address each point. The PI's report should also include a corrective action plan, if appropriate.
17.8.3 The audit team or the HREC then reviews 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.
17.8.4 The auditor/team may arrange a formal meeting between the PI, audit team, representatives from the HREC and the Deputy Dean of Research or Senate REC, where appropriate, to discuss any findings of the audit including any findings of non-compliance. This meeting is formal and should be minuted in detail.
17.8.5 The Audit Report, PI's written response and minutes of the follow up meeting are confidential and will usually be tabled at a forthcoming HREC meeting.
17.8.6 The HREC Chairperson and Deputy Dean: Research may jointly, in certain circumstances, decide not to table the full audit report. However this decision should not compromise the institutional independence of the HREC

17.9 REC deliberations and decisions

17.9.1 The full REC reviews the audit team's summary report, the PI's written response and the minutes of the follow up meeting report, where applicable.
17.9.2 The REC will decide either by consensus or by vote to:

17.9.2.1 Accept the audit 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.

17.9.2.2 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.

17.9.2.3 Withdraw study approval AND/OR

17.9.2.4 Refer the matter to line management, the Deputy Dean: Research or the Senate REC for further investigation and action where appropriate.

17.9.3 All correspondence between the REC, auditor 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 Deputy Dean: Research after discussion with the Chairperson of the REC and other relevant stakeholders.

17.9.4 NB When an audit is initiated in response to a 3rd party complaint about a researcher or research study, deviations from the above procedure may occur. This will depend on the nature, seriousness and context of the complaint and the involvement or not, of line and faculty management, including the Deputy Dean: Research, the Dean of the Faculty or the Senate Research Ethics committee.

18. APPEALS AND COMPLAINTS

18.1 Definitions

18.1.1 **Appeals** arise because a Research Ethics Committee[1] (REC) 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 REC and wishes to appeal.

An appeal **must** be directed to the chairperson of the relevant REC. A researcher may not appeal directly to the Senate Research Ethics Committee (SREC).

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

Complaints should be directed, in the first instance, to the chair of the relevant REC. 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.

18.2 Appeal process

18.2.1 The process described below may be a two stage process involving first the REC against which the appeal has been lodged. If the REC 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 REC 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.

18.2.2 Appeal process (REC level)

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

18.2.2.2 Each committee is expected to have a mechanism whereby a PI may appeal the REC's decision. The chairperson of the REC 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

[1] Health Research Ethics Committee (REC) 1 and 2, Non-medical REC; Animal Care and Use REC; Biosafety REC

appropriate. The subcommittee may have the same powers as the REC, if so constituted by the REC concerned.

18.2.2.3 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.

18.2.2.4 After deliberation of all the information placed before it, the subcommittee must either

(a) Uphold the appeal
(b) Reject the appeal
(c) Refer the matter to the Senate REC.

18.2.2.4.1 In the event of an (a) or (b) outcome, the decision of the REC (or REC-subcommittee) is final.

18.2.2.4.2 If the REC or REC-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.

18.2.2.5 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[1].

18.2.3 Appeal process (Senate Research Ethics Committee Level)

18.2.3.1 Notice in writing of the intention to refer the matter must be given by the chair of the research ethics committee (REC) to the chair of the Senate Research Ethics Committee. 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.

18.2.3.2 The basis of the appeal and all the relevant documentation must be submitted in writing to the chair of the Senate REC within seven (7) days of the notice in 1) above.

18.2.3.3 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 Senate REC. The PI, the REC and other interested parties may make submissions to augment the existing record, in accordance with the time lines set out by the Chair of Senate REC (see below under Appointment of Appeal Panel).

[1] 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.

18.2.3.4 Composition of Appeal Panel

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

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

18.2.3.4.3 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.

18.2.3.5 Appointment of Appeal Panel

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

18.2.3.6 Powers of Appeal Panel

18.2.3.6.1 The appeal panel is empowered:

18.2.3.6.1.1 to request further information if needed;

18.2.3.6.1.2 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;

18.2.3.6.1.3 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

18.2.3.6.1.4 to recommend to the REC that the appeal be upheld; or

18.2.3.6.1.5 to recommend to the REC that the appeal be dismissed.

18.2.3.6.2 As previously stated, 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

18.3 Complaints process

18.3.1 All complaints against an REC, for matters as described above, should be submitted directly to the REC chairperson, who should make every effort to investigate the

complaint thoroughly, resolve the issue and communicate the outcome of the investigation to the complainant.

18.3.2 Only complaints that cannot be resolved effectively by the REC chairperson, or that are deemed to be irresolvable by either the researcher or REC chairperson, should be submitted to the SREC.

18.3.3 The chairperson of the SREC shall notify the chairperson of the REC that a complaint has been made against the REC, 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.

18.3.4 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.

18.3.5 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.

18.3.6 The PI shall be notified of the outcome of the SREC investigation.

19. REFERENCES / SOURCE DOCUMENTS

Codes and Guidelines

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3. Code of Federal regulations CFR Title 21 Food & Drugs revised as of April1 2003
4. CFR Title 45 Public Welfare as of April 2003
5. Dept of Health and Human Services. Financial relationship and Interests Involving Human Subjects: Guidance for Human Subject Protection. Published in Federal Register May 12th 2004.
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8. SA GCP Guidelines Dept of Health 2006.
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12. Lemens, Trudo. Singer, Peter. "Bioethics for Clinicians: Conflicts of Interest in research, education and patient care". JAMC 20 Oct 1998; 159(8)

Other

13. IRB Information Sheets- A Self Evaluation Checklist for IRB's. US Food and Drug Administration. www.fda.gov/oc/ohrt/irbs/irbchecklist.html
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16. Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research. MRC-SA 4th Edition. 2003
17. Beauchamp, Tom. Childress, James. Principles of Bioethics. 5th Edition. 2001. Oxford University Press.
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20. APPENDICES

APPENDIX I: HREC REVIEW GUIDE

CRITERIA
1. INTRODUCTION, SPECIFIC AIMS, LITERATURE REVIEW
Is the literature review adequate?
Are the study aims and objectives clearly specified?
Is there adequate preliminary data to justify the study?
Is there appropriate justification for this study protocol?
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?
2. SCIENTIFIC DESIGN
Is the scientific design adequate to answer the study question(s)?
Is the scientific design adequately described and justified?
Does the study involve a placebo? If so, is the need for placebo adequately justified? 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: Does the researcher 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 choice of participants appropriate for the study question?
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?
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?
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?
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?
4. 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 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?
5. 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 IC form?
Are potential risks minimised?
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?
6. 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?
7. 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?
8. 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 children or adolescents are involved who receives compensation and is this appropriate?
9. PRIVACY AND CONFIDENTIALITY
Are there adequate measures to protect the privacy and ensure the confidentiality of the research subjects?
Does the protocol describe stie-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?
10. 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 informed consent contained in the ICF?
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 ICF be translated into all required languages?
Is Assent required?
11. 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?
12. 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?

Other Comments:

RECOMMENDATION:

- ☐ **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"** (The project must serve before the committee again before it can be given "Final Approval" Status.)

Reason(s) for above recommendation:

APPENDIX II: VULNERABLE COMMUNITIES AND RESEARCH REQUIRING ADDITIONAL ATTENTION

1. DEFINITION: VULNERABLE COMMUNITIES - UNAIDS (2000; 2007) AND SA DoH (2004).

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

EXAMPLE ONLY!

Applicants must ensure that they use the current version of the HREC application form, available at www.sun.ac.za/rds

Applications on outdated HREC application forms will not be accepted.

	STELLENBOSCH UNIVERSITY **FACULTY OF MEDICINE AND HEALTH SCIENCES**	

HEALTH RESEARCH ETHICS COMMITTEE 1 AND 2

APPLICATION FORM: ETHICS EXEMPTION

(INFORMATION SHOULD BE TYPED)

NB: Attach a 2-page synopsis of the research to accompany this application form

SECTION 1: DETAILS OF APPLICANT/PRINCIPAL INVESTIGATOR		
First name:	**Surname:**	**SU number:**
Professional Status:		
University DIVISION:		
University DEPARTMENT:		
Complete Postal Address:		
Telephone No:	**Fax No:**	**Cell No:**
E-mail address:		

SECTION 2: TITLE OF STUDY
Title of Research Project:

SECTION 3: STUDY FOR DEGREE PURPOSES	**YES**		**NO**	
Name of Degree:	**Supervisor:**			
Supervisor division:	**E-mail:**			
Supervisor department:	**Contact No:**			

OFFICE USE ONLY

PROJECT ID NUMBER

X / /

SECTION 4: RESEARCH ACTIVITY	
1. Research involving the collection or study of existing data, documents, records and/or pathological specimens that are publicly available	
2. Research on commercial cell lines	
3. Undergraduate educational activities (no intention to publicly present or publish)	
4. Quality assurance audit (no intention to publicly present or publish)	
5. Other (please describe)	

SECTION 5: Describe the <u>format</u> in which the data/records/specimens will be obtained

SECTION 6: State the <u>source</u> of data/records/specimens and the purpose of the original collection

SECTION 7: Was <u>informed consent</u> originally obtained from participants? (Describe)

SECTION 8: Provide a brief <u>motivation</u> for your request for exemption from ethics review

SECTION 9: Declaration (Please tick the box)
☐ I have attached a 2-page synopsis of my research to accompany this application form

SECTION 10: Required signatures		
Applicant	**Supervisor** (for student research)	**Head of Division**
…….	…….	…….
Print name	Print name	Print name
…….	…….	…….
Signature	Signature	Signature
…….	…….	…….
Date	Date	Date

EXAMPLE ONLY!

Applicants must ensure that they use the current version of the HREC application form, available at www.sun.ac.za/rds

Applications on outdated HREC application forms will not be accepted.

HEALTH RESEARCH ETHICS COMMITTEE 1 AND 2

APPLICATION FORM: NEW PROTOCOL

(INFORMATION SHOULD BE TYPED)

Researchers must ensure that they use the current version of the HREC application form at www.sun.ac.za/rds Applications on outdated HREC application forms will be not be accepted.

SECTION 1: DETAILS OF APPLICANT/PRINCIPAL INVESTIGATOR		
Title, First name, Surname:	**SU number:**	***PROJECT ID NUMBER*** *(HREC office use only)*
Professional Status:		
University DIVISION:		
University DEPARTMENT:		
Complete Postal Address:		
Telephone No:	**E-mail address:**	
Registration with HPCSA* ☐Yes ☐No	**Registration #:**	

Note:
- *or equivalent statutory health council registration no. as appropriate*
- *if registration is pending, submit proof of application*
- *if a non-medically trained PI is overseeing research which involves medical procedures, the application must include a medical doctor registered with the HPCSA as a co-investigator*

SECTION 2: TITLE OF STUDY	
Title of Research Project:	
Sponsor's Protocol No (if applicable)	
Sponsor's Details (if applicable)	
Is this a sub-study linked to an existing/main study? ☐ Yes ☐ No	**If yes, HREC #:**

SECTION 3: STUDY FOR DEGREE PURPOSES	☐ Yes ☐ No
Name of Degree:	**Supervisor:**
Division:	**Contact No:**
Department:	**E-mail:**

SECTION 4: DETAILS OF COLLABORATING INVESTIGATORS		
Name and Title	**Position and role**	**Division AND Department**
1.		
2.		
3.		
4.		

SECTION 5: DETAILS OF SUB-INVESTIGATORS		
Name and Title	**Position and role**	**Division AND Department**
1.		
2.		
3.		

SECTION 6: WHERE WILL THE STUDY BE CONDUCTED?	
1. Tygerberg Hospital	
2. Stikland Hospital	
3. Karl Bremer Hospital	
4. Faculty of Medicine and Health Sciences	
5. Other: please list	

SECTION 7: HUMAN SUBJECTS RESEARCH PROTECTION	
1. Does the Research involve Human Subjects who are Alive?	☐ Yes ☐ No
Dead (includes identifiable tissues specimens)?	☐ Yes ☐ No
Medical records only?	☐ Yes ☐ No
Students, staff or alumni of Stellenbosch University *(If yes, please contact, and submit to, the Division of Institutional Planning)*	☐ Yes ☐ No
2. Will any medicine be tested during the investigation?	☐ Yes ☐ No
2.1 If Yes to question 2, is the medicine approved by the Medicines Control Council?	☐ Yes ☐ No
2.2 If yes to question 2.1, is the medicine registered for the dose which will be used in this specific project?	☐ Yes ☐ No
2.3 If Yes to question 2.1, is the medicine registered for the indication(s) which will be used in this specific project?	☐ Yes ☐ No
2.4 If No to question 2.1, is the medicine approved by the Medicines Control Council for your use in this specific project?	☐ Yes ☐ No
2.5 If No to question 2.2 and/or 2.3, is the medicine approved by the Medicines Control Council for your use in this specific project?	☐ Yes ☐ No
3. Will any radioactive material be administered to the patient during the investigation?	☐ Yes ☐ No
4. Is any biohazardous material (*) involved in the project? (*) *"Biohazardous material" refers to recombinant DNA molecules, viruses, fungi, parasites, bacteria and all other potentially biohazardous material or products that are dangerous to both the experimental patient and the researcher.*	☐ Yes ☐ No

SECTION 8: RESEARCH WITH CHILDREN		
1. Does your research involve children? *(A child is defined as a person younger than 18 years*		☐ Yes ☐ No
If no, please continue to section 9		
If yes, please specify the age range of potential child		
1.1 Indicate whether the child research is *Therapeutic* or *Non-therapeutic* *(Please check [✓] the appropriate box below and provide a brief justification)*		
1.1.1 **Therapeutic research** = Interventions that hold out the prospect of direct health-related benefit for the child participant; OR		
1.1.2 **Non-therapeutic research =** Interventions that 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 child participant's condition.		
1.1.3 Brief justification:		
1.2 Indicate which risk category is applicable to your research involving children (Please check [✓] the appropriate box below and provide a brief justification)		
1.2.1 "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);		
1.2.2 The research poses more than minimal risk but holds out the prospect of direct benefit for the child participant.		
1.2.3 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;		
1.2.4 The research does not meet the conditions for the risk categories above but presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.		
1.2.5 Brief justification:		
1.3 This research is essential research for children and presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.		☐ Yes ☐ No

SECTION 9: STUDY TYPE			
1. Industry Sponsored Clinical Trial		**2. Self Initiated Clinical Trial**	
3. Retrospective Record Review		**4. Laboratory-Based Research**	
5. Qualitative Research		**6. Prospective Descriptive Study**	
7. Other		**8. Please state type if 'Other':**	

SECTION 10: HOW IS THIS RESEARCH FUNDED? *(State approximate total budget)*			
1. Industry	**R**	**2. NIH/US government**	**R**
3. Internal departmental budget	**R**	**4. Other International grant**	**R**
5. Self funded	**R**	**6. External SA Grant (MRC, NRF etc.)**	**R**

SECTION 11: DISCLOSURES	
1. Have you acquainted yourself with the code of conduct regarding the Ethics of research at this Institution and do you undertake to fully comply with it at all times?	☐ Yes ☐ No
2. Has this study been, or is it likely to be, submitted to any other Research Ethics Committee?	☐ Yes ☐ No
2.1 If yes, please name the Committee(s) and provide outcome i.e. approved/rejected. *(If approved, attach approval letter)*	
3. Has the Principal investigator or any of the co-investigators been previously/or are presently being investigated for alleged research misconduct?	☐ Yes ☐ No
3.1 If yes, please provide details and dates	
4. Are any of your intended research participants in other research studies and/or trials?	☐ Yes ☐ No
4.1 If yes, please provide details	
5. Are you presently a Principal Investigator (PI) in other research and/or clinical trial activities?	☐ Yes ☐ No
5.1 If yes, please provide details and % of your time allocated to each	
6. Have you completed a payment instruction form and attached proof of payment to this application?	☐ Yes ☐ No
7. Does this protocol comply with the Helsinki Declaration of 2013? *(See http://www.wma.net/en/30publications/10policies/b3/)*	☐ Yes ☐ No
7.1 If no, please explain with full justification	
8. Does the protocol provide insurance for research-related adverse events?	☐ Yes ☐ No
a. If yes, please describe:	
b. If no, please justify:	
c. Is the provision of insurance compliant with SAGCP Section 4.11? *(See p.41 of http://www.kznhealth.gov.za/research/guideline2.pdf)*	☐ Yes ☐ No
d. If no, please justify:	

SECTION 12: SIGNING OF APPLICATION		
Applicant	**Supervisor** *(only for student research)*	**Head of Division**
…… Print name	…… Print name	…… Print name
…… Signature	…… Signature	…… Signature
…… Date	…… Date	…… Date

Kindly see overleaf for REQUIRED documentation to accompany all HREC applications…

DOCUMENTS REQUIRED FOR ALL SUBMISSIONS
1. Application form
2. Checklist
Complete either the General or Clinical Trial Checklist, whichever is applicable.
3. Payment instruction form (human/health research or Clinical Trial) **AND Proof of payment** (human/health research)
4. Study Protocol
5. Protocol synopsis or summary
Please provide a protocol synopsis or summary of the proposed research, in addition to the full protocol, **no longer than 2 pages**. The Protocol Synopsis or summary should contain the following: ▪ Title ▪ A short introduction, motivation and literature overview (1 paragraph only) ▪ Research question or hypothesis ▪ Aims and Objectives ▪ A concise summary of the methodology ▪ Description of subject population including characteristics, age range and number of subjects ▪ If the research will require blood draws, bone marrow biopsy samples, other biopsies or the collection of tissues, etc., performed solely because of participation in the research, please indicate the exact amounts and frequency with which the samples will be taken. ▪ Anticipated risks as well as the precautions taken to minimize risk ▪ Anticipated benefits ▪ Ethical Considerations
6. Participant Information and Consent Form (ICF)
The ICF can be submitted in either English or Afrikaans. Once the requested changes, if any, have been made, then the HREC requests the researcher to submit translations in English, Afrikaans and Xhosa, along with a translation certificate or letter of authenticity. *Note: if it has been decided that translated consent forms are not necessary for the particular study, then the applicant is required to specifically justify this in the protocol under "Ethical considerations."*
7. Short Curriculum Vitae (CV) of all investigators
Submit a short CV for the principal investigator, co-investigators, and sub-investigators. Each CV should not comprise more than 2 pages.
8. Investigator Declaration for all investigators
Complete and sign and "investigator declaration" and declare any conflict of interest for the principal investigator, co-investigators, and sub-investigators. If the study is for degree purposes, a supervisor declaration should be signed by the study supervisor.
9. Budget & Financial contract
Submit a budget (if not included in the protocol) and financial contract (if applicable i.e. external funding)
ADDITIONAL DOCUMENTS REQUIRED FOR CLINICAL TRIAL SUBMISSIONS ONLY
If you are submitting a clinical trial application, please see the list below for *additional* documentation that must accompany clinical trial applications: 1. Cover letter 2. Flow chart 3. A description of the study site, including the available infrastructure and the roles and responsibilities of study staff 4. MCC approval or proof of application (if applicable) 5. NHREC approval or proof of application 6. Proof of insurance for participants (if applicable) 7. Letter of legal indemnity, extended to Stellenbosch University and Tygerberg/ Stikland Hospital (if applicable) 8. Material for distribution to patients, including diary cards, QOL questionnaires etc. 9. Recruitment material and advertisements (if applicable) 10. Proof of GCP training 11. SA approved package insert(s) of registered comparators 12. Investigator's brochure 13. Payment instruction form

APPENDIX V: 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. **(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 anesthesia 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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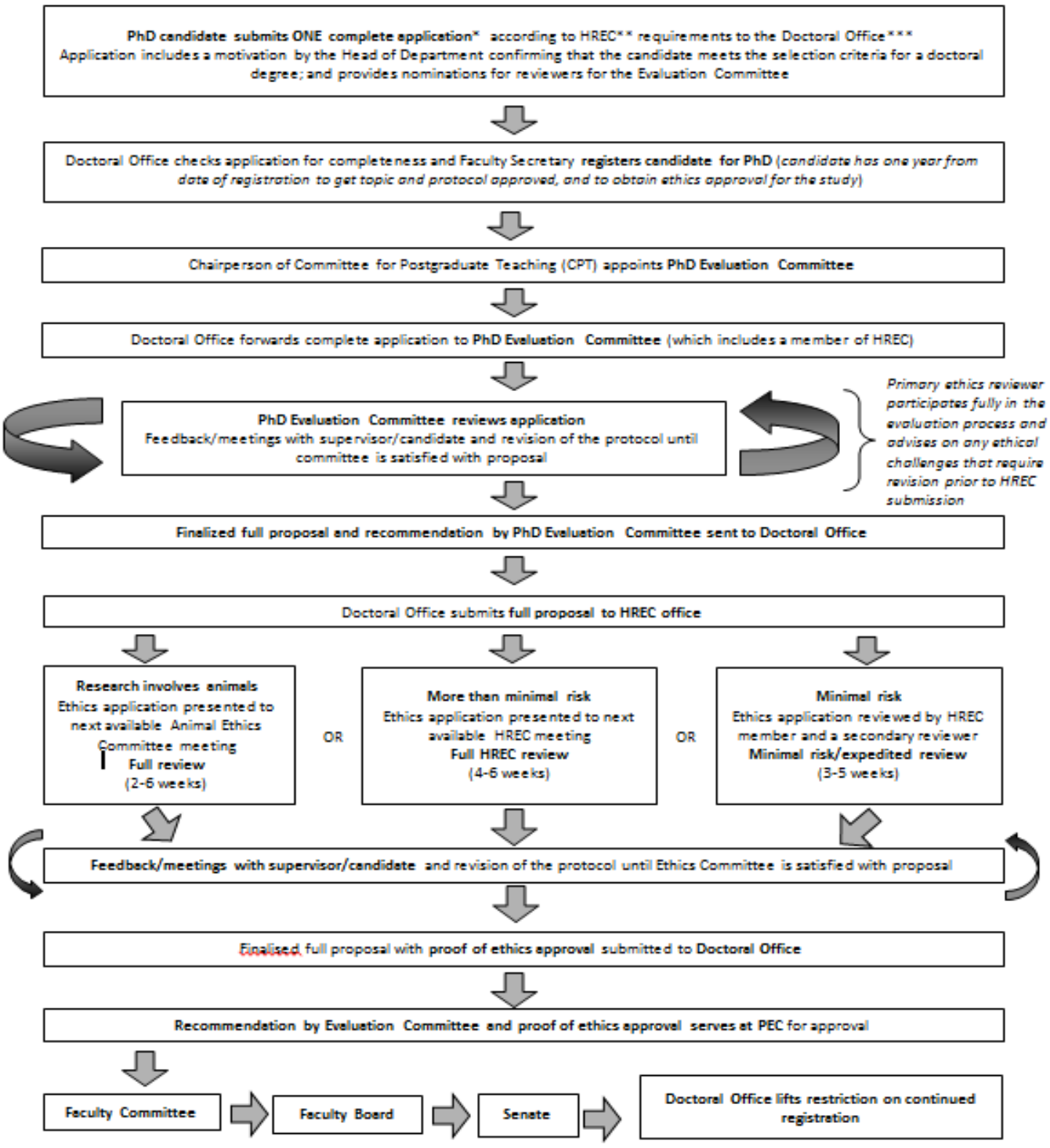
[1] An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.
[2] Children are defined 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 VI: PHD REVIEW PROCESS

BYLAE P

Draft PhD evaluation and ethics approval procedures for PhD applications in the Faculty of Medicine and Health Sciences of Stellenbosch University



** In cases where timing of provisional registration is of the essence (primarily for bursary disbursements and in the case of joint PhDs), a well-motivated application for a fast-track registration can be made to the Deputy-Dean: Education for consideration. Please note a full application for evaluation and approval still needs to be submitted after provisional registration. Details of this mechanism may be obtained from the Doctoral Office.*

*** HREC requirements include xxxxxxxxx*

**** The Doctoral Office is currently being set up and applications must in the interim still be submitted to the Faculty Secretary for processing.*

EXAMPLE ONLY!

Applicants must ensure that they use the current version of the HREC progress report form, available at www.sun.ac.za/rds

Applications on outdated HREC progress report forms will not be accepted.

	STELLENBOSCH UNIVERSITY **FACULTY OF MEDICINE AND HEALTH SCIENCES**	

HEALTH RESEARCH ETHICS COMMITTEE 1 & 2

ANNUAL PROGRESS/FINAL REPORT FOR CLINICAL TRIALS:

LOCAL SITE SUMMARY

(INFORMATION SHOULD BE TYPED)

This summary must be accompanied by your submission of the copy of the MCC progress report(s) for the same reporting period.

SECTION A: REPORT TYPE *(please check [x] appropriate box)*			
☐ **Final report** (to be submitted after study/site closure) ☐ **Annual progress report** (request for extension/renewal of ethics approval)			
Reporting Period: From dd/mm/yyyy **to** dd/mm/yyyy			
SECTION B: DETAILS OF PRINCIPAL INVESTIGATOR			
Title, First name, Surname:			
University DIVISION/CRO:			
University DEPARTMENT:			
Telephone number:	**E-mail:**		
SECTION C: PROJECT DETAILS			
Title of study:		**HREC Ref No:**	
Approval date:	**Start date:**	**Expected date of completion:**	
SECTION D: FUNDING – HOW IS THE PROJECT FUNDED? *(please check [x] appropriate box)*			
☐ Industry sponsored	☐ NIH/US Government		
☐ Internal (solely from department budget)	☐ Other International Grant		
☐ Self-funded	☐ External SA Grant (MRC, NRF, etc)		
SECTION E: PARTICIPANTS			
	Local Site	**South Africa**	**Global**

Expected number of participants (total)			
Number of participants screened to date			
Number of participants enrolled in this reporting period			
Number of participants enrolled to date			
Number of participants completed			
Number of participants withdrawn before completion			
Reasons for withdrawal			

SECTION F: SUMMARY OF PROGRESS TO DATE (Refer to recruitment, participant retention, withdrawals, unanticipated problems, adverse events, positive outcomes, etc.)
Recruitment process
Participant retention
Unanticipated problems
Adverse events (this does not include SAEs)
Positive outcomes
Publications
Dissemination of results
SECTION G: SERIOUS ADVERSE EVENTS

	Local Site	South Africa	Global		Local site	South Africa	Global
Number of SAE's for reporting period				**Total number of SAE's since start of trial**			

Summary of LOCAL SITE SAE's for reporting period					
Ref. No./ Participant No.	**Date**	**Event**	**Causality** (Related/ unrelated/ unknown)	**Outcome** (Resolved/ unresolved/ death)	**Previously reported to HREC** (Yes/No)

SECTION H: SIGNATURES	
Principal Investigator	**Study coordinator**
…… Print name …… Signature …… Date	…… Print name …… Signature …… Date

APPENDIX VIII: HREC REVIEW FEES

For the latest HREC review schedule, please consult www.sun.ac.za/rds

APPENDIX IX: 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 X: 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.