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2 Health REC (Human Research) SOP, Stellenbosch University. May 2010. V3.3
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RESEARCH ETHICS COMMITTEES: APPEALS AND COMPLAINTS
Generic Standard Operating Procedure

Appendix 1

Appendix 2

List of References / Source Documents

Acknowledgements:

With thanks to Prof Doug Wassenaar, Chairperson BREC, University of Kwa-Zulu Natal who allowed extensive use of the draft Biomedical Research Ethics Committee of UKZN, Terms of Reference and SOP document, including copying of certain sections, particularly ‘Informed Consent’. 
A. TERMS OF REFERENCE

1) The Health Research Ethics Committees (hereafter referred to as HREC 1 & 2 or HREC) (international equivalent titles: Institutional Review Board (IRB), Independent Ethics Committee) are mandated to fulfill their function by the Senate of the University of Stellenbosch through the Senate Research Ethics Committee, to which HREC 1 & 2 will report at least annually in writing.

2) The essential purpose of HREC 1 & 2 is to protect the dignity, rights, safety, and well-being of all human participants in health-related research. HREC 1 & 2 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.

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

4) The HREC 1 & 2 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.

5) The HREC functions in compliance with, but not limited to, the following documents and guidelines:
   • The SA National Health Act. No. 61 of 2003.
   • Declaration of Helsinki (Current version)
   • The Belmont Report,
   • the US Office of Human Research Protections 45 CFR 461 (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 1 & 2 will ensure that the proposed research is nonetheless in keeping with the spirit of the declarations and codes.

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

7) The HREC has the authority from time to time, to appoint, a standing or adhoc subcommittee to investigate or finalise certain matters under its jurisdiction, in compliance with applicable norms, rules and regulations.

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

4 Health REC (Human Research) SOP, Stellenbosch University. May 2010. V3.3
   Approved by Senate REC: 5th August 2010
B. APPOINTMENT AND MEMBERSHIP

Appointment

- The Health Research Ethics Committees (HREC) is appointed biennially, with a letter of appointment, by the Senate Research Ethics Committee (SREC).
- Members may serve more than one term.
- The Chairperson and Vice Chairperson (s) will be elected by the members.
- All members will be asked to sign a non-disclosure agreement.
- Stellenbosch University will obtain professional liability insurance to cover both affiliated and non-affiliated members when carrying out any professional duties under the auspices of HREC 1 & 2

Membership

The composition of HREC 1 & 2 will be in accordance with the provisions of the Department of Health (2004) Ethics in health research: Principles, structures and processes and (2006) South African Good Clinical Practice Guidelines. These include:

1) Members of HREC 1 & 2 should collectively have the qualifications, experience and expertise to review and evaluate the scientific, medical, legal, psychosocial and ethical aspects of research proposals.
2) Appointment to the committee will be by nomination and co-option. The total number of committee members must be no less than 9.
3) All members are expected to provide the HREC administrative office with an abbreviated CV at the beginning of their term.
4) A quorum will be considered present if “50% plus 1” members are in attendance, but must include one non-affiliated member and one nonscientific 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.
5) Members will be persons of good standing who have a working knowledge of the ethical codes and guidelines mentioned previously.
6) Be representative of the communities it serves and, increasingly, reflect the demographic profile of the population of South Africa;
   Include members of both genders, although not more than 70% should be either male or female;
7) Include at least two lay persons who have no affiliation to the institution, are not currently involved in medical, scientific or legal work and are preferably from the community in which the research is to take place;
8) Include at least one member with knowledge of, and current experience in, areas of research that are likely to be regularly considered by HREC 1 & 2
9) Include at least one member with knowledge of, and current experience in, the professional care, counseling or treatment of people. Such a member might be, for example, a medical practitioner, psychologist, social worker or nurse);
10) Include at least one member who has professional training in both qualitative and quantitative research methodologies;
11) Include at least one member who is legally trained.
12) Ensure that the membership is equipped to address all relevant considerations arising from the categories of research likely to be submitted to it.
13) 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.

14) Members not attending 2 consecutive meetings without a valid written reason, and without submitting their reviews, risk termination of their membership of HREC 1 or 2.

15) HREC 1 & 2 members will be required to have continuous personal development in research ethics.

16) HREC 1 & 2 may co-opt expert members and other representatives as voting members as required by particular protocols. Voting status is to be confirmed by the HREC in advance on a case by case basis.

17) On invitation or request, HREC meetings may be attended by bona fide students, researchers and other interested parties 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.

C. APPLICATION PROCEDURE

- Application forms and guidelines for submission are available from the Division of Research Development and Support (RDSD) of the Faculty of Health Sciences or by visiting the website at www.sun.ac.za/rds/
- Two copies of each of the following documents should be submitted to the HREC office (bolded documents are obligatory) Documents in italics are applicable to drug/medical device trials only:

  1) Standard Application Form
  2) Covering letter (optional, unless an expedited review is requested)
  3) Checklist ( “General” or “Clinical Trials”)
  4) Study Synopsis or Summary (NB this is essential and should be between 750-1500 words and include a clear and concise summary of research objectives and methods.)
  5) Research Protocol
  6) Patient information leaflet and consent form OR motivated request for a waiver of informed consent.
  7) Budget
  8) Short CVs (maximum 2 pages) of all investigator/s and supervisors
  9) Investigator Declaration/s and supervisor declaration where applicable.
  10) Proof of Insurance (if necessary e.g. for a clinical trial)
  11) Letter of indemnity for SU/ Tygerberg.
  12) Material for distribution to patients, including diary cards, QOL questionnaires etc (if applicable)
  13) Recruitment material and advertisements (if to be used)
  14) SA approved package insert for registered comparators
  15) Investigators Brochure.
  16) GCP certificates for investigators (clinical trial)
  17) Contract or financial agreement, (if research is to be funded by an external party)
  18) Proof of Registration on the SA National Clinical Trials Register (clinical trial)
  19) MCC approval or proof of application to the MCC.
Please note:

1) Applications can be submitted on a rolling basis, but must be received a minimum of 2 weeks prior to any specific meeting date to appear in the Agenda of that meeting (if this can be accommodated. If not, the application will appear at the next meeting).
2) The supervisor of undergraduate projects will be regarded as the Principal Investigator and the project will be registered under his/her name.
3) The dates of meetings are available from the RDS administrative office and website at www.sun.ac.za/rds (click on Ethics at left of screen) and are distributed to all departmental heads at the beginning of the year.
4) The application will be checked for completeness by the administrative team. If incomplete, the applicant/supervisor will be informed accordingly and requested to make any corrections or forward the missing documents. (See Review Process for more information)

D. REVIEW PROCESS

REVIEW CRITERIA:

Research studies will be reviewed within the context of aforementioned regulations and guidelines. HREC, in reviewing a protocol, must consider any and all factors that may influence the scientific validity and ethical acceptability of the protocol. The following criteria will be used to review projects:

1. Social and scientific value of project

HREC must consider the project to have relevance to the community involved and/or the greater South African and African community.

2. Scientific validity

HREC must ensure that the proposed research is scientifically valid. (Patients and volunteers may not, ethically, be exposed to potential risks and burdens where the project will not generate the intended knowledge). This requirement includes ensuring that the researchers are suitably qualified to undertake the research.

3. Risk-benefit ratio of project

In order to approve research covered by this policy, HREC shall determine that all of the following requirements are satisfied:

- Risks to participants are minimised:
  - Using procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk, and
  - Whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

- Risks to participants must be reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, HREC shall consider only those risks and benefits that may result from the research (as
distinguished from risks and benefits of therapies participants would receive 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 that fall within the purview of its responsibility.

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

4. **Fair selection of subjects**

1) Selection of participants is equitable. 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 problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons (see Appendix A).

2) When some or all of the participants are likely to be vulnerable to undue influence or coercion, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these participants (see Appendix I).

5. **Informed consent processes**

1) Informed consent will be sought from each prospective participant or the participant’s legally authorized representative, in accordance with, and as required by Sections E of this document.

2) Informed consent will be appropriately documented, in accordance with, and as required by Section E-4 of this document.

6. **Respect for participants:** The research protocol demonstrates respect for participants throughout the course of the project e.g. there are adequate provisions to protect the privacy of participants and to maintain the confidentiality and security of data. Participants may withdraw from the study at any time without prejudice etc.

7. **Respect for communities:** The proposed research demonstrates respect for communities by appropriate community interaction and feedback of results.

Additional points of note:

1) All researchers submitting protocols for ethics review should be 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. 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.
2) All international collaborative research will have a local principal Investigator.

3) 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.

EXPEDITED REVIEW

A New research study may be considered suitable for a “fast track” ethical review process only if it involves “minimal risk” research:

Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research, is not greater in and of themselves than those ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests.

See Appendix I for projects considered suitable for expedited review according to US-HHS requirements. HREC adheres to the requirements stipulated in this document except for those related to clinical drug/device trials.

Note that in addition, the following projects are considered by HREC to be not suitable for fast track review and should (except in exceptional circumstances) be reviewed by a full committee.

- All clinical trials involving drugs/medical devices or other therapeutic interventions.
- Multi-institutional collaborative research projects
- International grant funded research

A “fast track” (expedited review) procedure for minimal risk research may be used, at the discretion of the HREC chairperson, or any other person delegated this responsibility by the chairperson, under the following circumstances:

- All minimal risk research, for the purposes of a degree or diploma (under or post graduate).
- When an investigator specifically motivates for and justifies a “fast track” approval process.
- Any minimal risk project identified as suitable by the chairperson or any other person delegated by the chairperson for this purpose.

Post graduate research for degree and diploma purposes:

1. The investigator should submit all necessary documentation for a new application as well as a covering letter motivating for a “fast track” review process. 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 Masters and Undergraduate research projects.

2. The administrative team will ensure all documents are in order and complete and contact the researcher to request missing information if necessary.
3. The chairperson, or an HREC member appointed by the chairperson, will review the research study and provide the chairperson with a written report. The chairperson will at his discretion:—

1) **Approve** the study.
2) **Request modifications** prior to approval.
3) **Defer approval** - i.e. refer the study to a full sitting of the HREC for consideration.

4. If modifications are requested then all requested changes must be made before a final letter of approval will be issued. The member delegated to do the original review will check that the response/ changes are acceptable.

5. The investigator may start the project only once an approval letter has been received.

6. The approval will be considered for ratification by the HREC, at the following meeting.

7. Reports of reviewers and all written comments by the chairperson will be made available to all committee members in the printed agenda at this meeting.

8. HREC has the authority to suspend the approval of any project approved via an expedited process and request further changes or additional information. All research activities must cease until this process is concluded.

**PhD projects:**

- PhD projects will usually (preferably) be reviewed by a full HREC. However if there is a good reason why expedited review is required, then a covering letter of motivation requesting expedited review should be submitted with the project.
- **NB:** All PhD projects should preferably have undergone a scientific review process first before being submitted for ethics review and approval. The final version of the protocol should be submitted, not the first version.

**Under-graduate student projects:**

Many undergraduate students are required to complete small research projects during the course of their studies. Supervisors of undergraduate research projects should please note the following points:

- The scope and ethical sensitivity of the project should be carefully chosen and considered. Students are often inclined to choose projects which interest them, but which may well involve sensitive or ethically challenging issues and with which they are often poorly equipped to deal. e.g. Termination of pregnancy, drug abuse in pregnancy etc.
- It is the supervisor’s responsibility to decide whether or not the project requires formal ethical clearance. Are the students actually conducting a research project i.e. a systematic investigation that will lead to generalisable knowledge? If 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 students own classroom environment then the exercise is an educational exercise rather than a research project and may well not require ethics approval. Supervisors are advised to seek confirmation on this issue from the HREC Chairperson or a delegated member.
• A research project conducted by students in the public domain e.g. in a school or hospital environment, using scholars or patients as participants, should be submitted for ethics approval.

• If the intention from the outset is to conduct health research with a view to presentation of results external to the classroom environment e.g. at a conference, or possible publication in a journal, then ethics approval is required.

• Many undergraduate research projects do in fact 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.

**Application Procedure for Undergraduate Projects:**

1. Students should submit the written protocol they have developed as part of their course requirements as well as an application form and a check list.

2. The HREC will regard the supervisor as the Principal Investigator or Applicant, who assumes ultimate responsibility for the project. The project will be registered under the name of the supervisor and all correspondence will be addressed directly to him/her, not to the student. The supervisor’s CV and supervisor declaration must accompany the submission.

3. 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. The same expedited approval procedures as described above will be followed.

5. The HREC administrative office will attempt to ensure that this process is completed in a maximum of 10 working days. However this is subject to capacity, and the timing of the application.

6. If modifications are required, then all requested changes must be made before a final letter of approval is issued.

7. The approval will be considered for ratification by the HREC, at the next meeting.

**CONVENED (FULL) MEETING REVIEW**

The HREC will convene on a monthly basis, except January and July to review and consider:

• New research proposals and all supporting documentation such as participant information sheets, consent documents, advertising and recruitment material, all instruments, questionnaires etc.

• New proposals approved via an expedited review mechanism, for ratification of approval.

• Major protocol amendments;

• Adverse events reported in previously approved studies;

• Continuing Review Reports (both progress and final) on research projects

• General and policy matters.

• Consider allegations of misconduct in research or other complaints.

**Pre-meeting processes**

• New applications must be received at least 12 working days before a meeting. (Agenda closure dates are published in conjunction with meeting dates but do not guarantee that applications will be on a specific agenda.)

• An administrative review will be completed by the administrative staff who may request additional information.
• Projects are distributed to two members of the committee, at least one week prior to the meeting for evaluation and review.
• The chairperson may, at his/her discretion, co-opt an external consultant for a particular protocol, if he/she feels the committee does not have the necessary expertise to adequately evaluate all aspects of a particular protocol.
• Copies of the application form, study synopsis and patient information and consent form will be made and distributed to all committee members at least one week prior to the meeting as part of the meeting “Agenda” file.
• Reviewers will make written comments available to the chairperson, prior to each meeting, if they are unable to attend the meeting.

Meeting

The meeting proceeds as follows:

1. The chairperson opens the meeting.
2. A quorum, as described earlier must be present for all decision making.
3. The secretary records those present and also notes apologies.
4. The minutes of previous meeting are corrected and accepted.
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:
   - Matters arising from the previous meeting.
   - Project progress reports/re-approvals
   - New applications:
     - Clinical Trials
     - Other new applications
   - Resubmission of “referred back” projects
   - Ratification of projects approved by expedited review
   - Substantial amendments for discussion. (A substantial amendment is one that may alter the risk benefit assessment of the study or result in significant change in study procedures)
   - Ratification of substantial amendments approved via an expedited review process. NB Minor amendments such as minor changes to ICFs; administrative protocol changes; do not need to be ratified by the committee. (See section J for further details)
   - Serious adverse events (SAEs)
   - Other documents for noting/approval
   - General items

6. New applications are introduced by the chairperson. The primary reviewer presents a review of the study to the committee. The second reviewer adds comments. Discussion is then opened to the full committee.
7. If the investigator is a member of the committee he/she may answer any specific queries that members wish to address but should voluntarily recuse him/her prior to discussion and decision-making. This recusal should be recorded in the minutes.
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.
9. The chairperson facilitates discussion and summarises the perceived viewpoint of the committee.
10. The committee attempts to reach a decision by consensus.
One of the following decisions must be made:

- Approval with no changes.
- Modifications required (The project has no major ethical concerns but a number of clarifications or methodological changes are required that can be finalised by an expedited review process i.e. without having to serve before the HREC again)
- Deferred (The project has major ethical concerns and requires considerable revision. It will need to be reconsidered after changes, at a full HREC sitting)
- Rejected

11. If a consensus is not reached, because of disagreement, then the HREC will vote on a proposal as summarized by the chair.
12. Voting will be recorded as number for, against and abstaining.
13. The secretary records all decisions in the minutes and the method by which they were made. All discussion points, issues of controversy and reasons for decisions will be 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.
14. A protocol that is scientifically and ethically sound will have an average review time (from submission to approval) of 30 days. It may take considerably longer to finalise approval with respect to protocols that are scientifically and ethically flawed.

COMMUNICATION OF REVIEW DECISIONS

Decisions taken at the HREC meeting, or via an expedited review process, are communicated in writing to the applicant. 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. On occasion, a research study may be rejected completely.

1. Investigators can address any queries to the HREC secretary or Cluster Head: Research Ethics or, who will attempt to resolve problems and liaise with the chairperson when necessary.
2. It is the responsibility of the investigator 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 by 6 months.
3. All requested protocol and ICF changes must be clearly marked. The tracked changes facility on the word processor should be used.
4. The primary 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.
5. If correct, the said documentation will be forwarded to the chairperson for final approval.
6. 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 did not give a conditional approval ("modifications required" decision) to the protocol, but requested major alterations to the protocol i.e. DEFERRED or "Referred Back" the protocol, it must be resubmitted to a full sitting of the committee.
7. 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 2 months before expiry of approval.

8. Please note the final approval date will be recorded as the start date and approval will expire in 1 year from this date. However 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 starting date of the project. Project re-approval must occur within 1 year of this date.

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

### E. INFORMED CONSENT

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. 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. The information that is given to the participant or the representative shall be in language understandable to the participant or the representative. No informed consent, whether oral or written, 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.

- One of the primary justifications for a local review process with respect to multi site/multi national clinical trials is to ensure that the participant information and consent form is adapted to the requirements of the local community and potential participants.
- Written informed consent should always be obtained unless an alternative process is clearly justifiable.
- The process of recruitment and documentation of informed consent must be clearly described in the study protocol.

### 1. BASIC ELEMENTS OF INFORMED CONSENT

Except as provided in section 3, in seeking informed consent the following information shall be provided to each participant:

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;
2) a description of any reasonably foreseeable risks or discomforts to the participant;
3) a description of any benefits to the participant or to others which may reasonably be expected from the research;
4) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant;
5) a statement describing the extent to which confidentiality of records identifying the participant will be maintained;
6) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7) 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; and
8) 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
9) a statement that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

2. ADDITIONAL ELEMENTS OF INFORMED CONSENT.

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

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;
2) anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent;
3) any additional costs to the participant that may result from participation in the research;
4) the consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant;
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
6) the approximate number of participants involved in the study.

3. VARIATIONS OF CONSENT PROCEDURES (including waiver of informed consent):

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:

1) the research involves no more than minimal risk to the participants;
2) the waiver or alteration will not adversely affect the rights and welfare of the participants;
3) the research could not practicably be carried out without the waiver or alteration; and
4) Whenever appropriate, the participants will be provided with additional pertinent information after participation.

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

• 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.

• The participant must, having been fully informed, be asked to give his/her free and voluntary consent to inclusion in the study. Where a relationship of dependence exists between participant and researcher (e.g., service provider/service recipient), consent should ideally be obtained by an independent person.

4. DOCUMENTATION OF INFORMED CONSENT:

1. Except as provided in section 3 above, informed consent shall be documented by the use of a written consent form approved by HREC 1 or 2 and signed by the participant or the participant’s legally authorized representative. A copy shall be given to the person signing the form.

2. The written consent document must include the elements of informed consent required by Section 5 (a). 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.

3. HREC may waive the requirement for the investigator to obtain a signed consent form for some or all participants if it finds either:

   a. 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.

   b. 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.

4. The HREC provides 3 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.

   • General
   • Paediatric research or research on incompetent participants
   • An assent template suitable for use in a 7-12 year old age group.
   • An ICF template in the form of a letter. (Suitable for research involving peers, nurses, students etc)
   • Research that involves genetic analysis.

5. These forms are available electronically from RDS. Contact 021-938 9207, or visit the RDS website at www.sun.ac.za/rds/
5. Once the participant has agreed to participate, at least 2 copies of the signed form will be made. The original is to be kept by the principal investigator. One copy may be kept in the participant’s medical records when appropriate; and one copy will be given to the participant.

TRANSLATION OF PATIENT INFORMATION AND CONSENT FORM

Multi-lingualism is challenge to any research within a South African context. In a country that has 11 official languages, the task of translating and effectively communicating information to, and obtaining consent from patients in several languages is daunting and costly. However epidemiological shifts in disease burden and prevalence, in various populations groups within South Africa, are occurring because of urbanisation and dietary and lifestyle changes. The principle of justice requires that potential research participants of all local language groups should be afforded the opportunity to participate in research.

1. In the Western Cape information and consent documents should be available in 3 languages i.e. English, Afrikaans and Xhosa. An exemption of this requirement must be specifically requested and justified and approved by HREC 1 or 2.
2. 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 Afrikaans and Xhosa 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.
3. Once completed, the translations must be returned to the HREC office accompanied by either a certificate of translation or letter from the PI declaring that the translation is an accurate reflection of the approved English version.
4. The committee will acknowledge receipt of translations. However only the original English or Afrikaans version will be officially approved.
5. The committee reserves the right to check translations and delay approval of the study, if the translations are deemed to be of poor quality.
6. Investigators and sponsors are encouraged to ensure that Information and Consent documents are translated into BOTH Afrikaans and Xhosa particularly in circumstances where the unavailability of a Xhosa ICF document may act as an unjustifiable barrier to recruitment.

F. RESEARCH INVOLVING CHILDREN

1. A “Child” is defined as someone younger than 18 years in the Bill of Rights of the Constitution of South Africa.
2. 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.
3. Research involving children must conform to ethical guidelines and the law.
4. Unless contrary to South African laws and regulations, research involving children should be determined by HREC as falling into one of the following categories:
   a. Research not involving greater than minimal risk to the children
   b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child participants involved in the research
c. Research involving greater than minimal risk and no prospect of direct benefit to the individual child participants involved in the research, but likely to yield generalisable knowledge about the participant’s disorder or condition provided that the risk represents a minor increase over minimal risk.
d. Research that HREC believes does not meet the conditions above but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

5. Adequate provision should be made for obtaining assent of the children and consent from their parents or legal guardians.
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.
7. US DHHS funded research with children must comply with US 45 CFR 46.404-407 in addition to relevant South African legislation and regulations.

G. COMMUNITY / PRISON BASED STUDIES

HREC must ensure that, particularly with regard to research involving communities, those communities’ traditions and values are respected. This applies particularly with regard to obtaining consent to participate in the 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.

When reviewing non-expedited studies involving prisoners, HREC must ensure that:
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,
2. at least one member present shall be a non-scientist,
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,
4. the Investigator has complied with the conditions specified in the South African DoH (2004) Ethical Guidelines (Section. 5.11),
5. 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.
6. 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.

H. GENETIC RESEARCH

(Refer to Chapter 9 of the Dept of Health “Ethics in Health Research: Principles, Structures and Processes" for detailed ethical guidelines. Page references in this section are from this guideline)

HREC requirements for a research protocol that includes genetic analysis
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.

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.

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.

4. A researcher must not transfer genetic material and related information to another research group unless:
   a. There is a formal collaboration that has been approved by a HREC and a Material Transfer Agreement has been signed by the appropriate authorities
   b. The genetic material and information is transferred in a form that ensures participants cannot be identified. (Prima facie principle)

**Informed Consent**

The Participant Information and consent document for genetic research must be separate from the main consent form. Participants must be informed of the following:-

1. That they are free to refuse consent without giving reasons and still take part in the main trial.
2. An explanation of the genetic research study in simple layman’s terms, including justification for the study must be given.
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.
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.
5. Be told whether or not feedback or results will be available and if not, an explanation must be given.
6. Be asked whether or not they wish to be told of research results that could be of relevance to them as individuals?
7. Give details about involvement of other family members, if applicable and must give consent for researchers to approach other family members.
8. Be assured that material and information will not be released for other uses without their consent.
9. Consent for storage should be requested. Information as to where and for how long should be provided.
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.
Request for Waiver of Individual Consent for genetic analysis

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. (Pg 44) Before granting a waiver of consent an REC must determine:

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

I. STORED TISSUE

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).
2. Only HREC approved analyses may be done.
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.
4. Specimens may not be shared with any party unless approved by HREC in advance.
5. Where tissue samples are to be exported, a valid current export permit is required.
6. A separate consent form or section of the informed consent form, for storage of additional or residual samples is required.
7. A separate consent form for genetic testing is required.
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.

J. AMENDMENTS AND PROTOCOL DEVIATIONS

All research should be conducted according to an ethically approved, written protocol.

The difference between a protocol deviation and a protocol amendment:

- 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.

- Amendments, sub-studies or addendums to studies are planned changes to a study protocol, made in advance.

The following points apply to all planned changes to approved study protocols:

1. These changes should be submitted to the HREC 1 OR 2 as a requested “study amendment” using the application form for substantial/major amendments and not implemented prior to HREC approval.
2. 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.
3. **Minor amendments** do not change the risk benefit profile of the study in any way. Examples of typical minor amendments:
   - Additional Investigators or study sites
   - Small changes in the Informed Consent
   - Change in background information or update of literature review
   - Extension of period of study
   - Other changes that do not affect study design and will not affect study outcomes or results
   - Administrative changes
   - Stricter inclusion or exclusion criteria.

4. **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:
   - Change in study aims, objectives or design
   - Resulting changes to consent documents
   - Additional study procedures
   - Easing of inclusion or exclusion criteria

5. 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.

**Protocol deviations:**

Significant protocol deviations that are likely to adversely effect participant well-being or data integrity should be reported to the HREC 1 OR 2 within a maximum of 15 days. Minor protocol deviations can be listed with the annual progress report.

**K. SERIOUS ADVERSE EVENT REPORTING**

The term Serious Adverse Event (SAE) is usually used within the context of clinical or drug trials. However an Adverse Event (AE) or SAE can occur in non-pharmaceutical research as well. 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.

DEFINITION OF A SERIOUS ADVERSE DRUG EVENT (FDA TITLE 21 PART 312, 32): - Any adverse drug experience, occurring at any dose that results in any of the following outcomes:

- Death
- A life threatening incident
- Inpatient hospitalisation or prolongation of existing hospitalisation,
- Significant or persistent disability/incapacity,
- Congenital abnormality/birth defect.
- 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.
- 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.

1. All significant adverse events occurring at the investigator’s site must be reported to the Health Research Ethics Committee (1 or 2), by the investigator within a maximum of 21 days. However any event which in the opinion of a reasonable and competent investigator, could have serious negative consequences for research participants, research team members, the project as a whole, or the university, should be reported to the HREC 1 or 2 within 48 hours of the investigator becoming aware of the event.

2. All SAEs occurring at other sites should be reported to the HREC 1 or 2, if deemed necessary by the investigator, i.e. significant or unexpected.

3. A standard reporting form for drug related SAEs must be completed and submitted. This 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.

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

5. SAEs that are unexpected or repeated will be investigated further and appropriate action taken, if deemed to be necessary by the HREC 1 or 2

L. GUIDELINES FOR ROUTINE CONTINUED REVIEW (PROGRESS REPORTS)

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

1. Ethics approval is valid for one year only. A progress report is an application for renewal of ethics approval and must be submitted annually, at least 2 months before the ethics approval expiry date, so that the progress report can be reviewed and the project re-approved prior to the expiry date. No research may continue without this process and re-approval. Six monthly progress reports may occasionally be requested if the HREC deems the project to be of particularly high risk.

2. The progress report must be submitted on the HREC progress report form.
3. 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.

4. For multi-centre studies the information in the progress report must pertain specifically to SU sites. All clinical trials falling under the jurisdiction of the MCC must submit a progress report to the MCC six monthly and should provide the REC with a copy of this report. However a site specific progress report must be submitted annually, for ethics reapproval, preferably using the HREC progress report form.

5. 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. Copies of published abstracts, may be submitted as attachments, and may replace text required in Section G of the report form, if appropriate and self-explanatory.

7. 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.

8. 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

Main points to be included are:

- 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.

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

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

11. 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.
12. 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.

13. 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.

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

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

M. CONFLICT OF INTEREST POLICY FOR INVESTIGATORS

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.

Investigator conflicts of interests are of particular importance when an unacknowledged or undisclosed interest, financial or otherwise, may negatively affect the well being of research participants. It is this aspect of COI's that is of concern and relevance to the HREC.

1. Investigators must consider the potential effects that a financial relationship of any kind may have on the research or on interactions with research participants.
2. All investigators are obligated to sign the Conflict of Interest Declaration that is part of the Investigator declaration.
3. In particular investigators should disclose the following potential conflict of interests to the HREC:
   - Equity or stock holding in a sponsor company
   - Proprietary interests in product- patent holding, intellectual property rights, trademark, and licensing agreements.
   - Grants paid speaking arrangements, retainers for ongoing consultations, sitting on “Pharmaceutical Advisory Boards” etc.
   - Travel/conference sponsorship
   - Recruitment fees or other personal payments that are linked to study outcome, in any way
   - Co-authorship of articles, where the co-author’s input has been minimal.
   - Funding for additional staff and facilities, especially if not directly linked to the research project.
   - Equipment for use in a study that will then belong to the department
   - Donation of equipment unrelated to study.
   - Contributions to a departmental budget not directly related to project expenses.

Please note 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.
N. CONFLICT OF INTEREST POLICY FOR HREC MEMBERS

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, "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."

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

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) Relationship to the research study: The HREC member (his/her spouse or immediate family member) is the principal investigator or co-investigator of the research protocol under review by the HREC.
3) 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.
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.

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.

- 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.
- 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.

RECUSAL

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.

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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.

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.

O. RECORD KEEPING

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 5 years post-clinical trial. The HREC retains all research study records for 15 years in accordance with GCP requirements.

Research projects

1) A HREC reference number is allocated to all new applications. This number is recorded on all correspondence and additional attachments/amendments.
2) A research ethics data base is used to capture project information such as name of investigators, title of project etc.
3) Hard copies of all research study related documents and correspondence are filed according to their reference numbers.
4) Hard copy records of all communication between investigators and the HREC office are recorded and filed using this reference number.

Meetings

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

1) Show attendance at the meetings
2) All actions taken by the HREC
3) Whether or not decision was reached by consensus or voting,
4) If by vote, then the number voting for, against and abstaining.
5) The basis for requiring changes to, or disapproval of research.
6) A written summary of the discussion of controversial issues and their resolution.

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.
P. GUIDELINE FOR CONDUCTING SITE AUDITS

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 REC has the authority to from time to time, conduct audits on any active research activities involving human subjects.

- 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.
- 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.
- 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:

A. Routine

1) Inexperienced sites;
2) High-recruiting sites;
3) Sites recruiting vulnerable patients;
4) Research that is more “risky”;

B. For Cause

1. Sites from which complaints have been received (whether by a participant, sponsor or some other 3rd party);
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.
   • 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.

Implementation of an Audit and Notification

1) Sites from Group A will be selected randomly by the HREC.
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.
3) A notification of Sites for proposed audits will be tabled at the next HREC meeting.
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.

The audit

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 subjects.

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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.

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.

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.

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)

**INVESTIGATOR’S STUDY FILE:**

- a) Confirmation of Regulatory Approval
- b) Signed funding agreement and copies of receipts or financial correspondence (where applicable)
- c) Signed copy of the final protocol and any amendments
- d) Specimen diary card, questionnaires, etc
- e) Dated, signed CVs of all study site personnel
- f) Specimen of signatures of site staff
- g) Responsibilities list
- h) Correspondence and communication with funders, and other authorities e.g. Provincial government authority
- i) Record relating to equipment loan during the study
- j) Equipment calibration logs
- k) Laboratory certification (including updates)
- l) Laboratory normal reference ranges (including updates)

**REC Compliance**

- a) Any correspondence with the REC
- b) List of Committee members
- c) Letter of REC approval and approval of any protocol amendments or other changes
- d) 6-monthly/annual progress report to REC
- e) Annual re-approval from REC
- f) Notification of end of study
- g) Insurance statement (if applicable)
- h) Signed indemnity letter (if applicable)
- i) Any advertisement used for subject recruitment
- j) Specimen subject information consent forms
- k) Signed consent forms
- l) Participant screening list
- m) Participant recruitment log
- n) Participant identification record
- o) Copies of serious adverse events

**PHARMACY AND DRUG RECORDS (IF APPLICABLE)**

- a) Dispensing dates match up with visit date
- b) Drug logs are complete
c) Tablet counts are recorded
d) All drug returns are counted
e) Boxes containing drugs for return are labelled for return
f) Drug storage is appropriately recorded

**CASE RECORD FORMS**

a) All CRFs are as complete as possible
b) All amendments are made correctly
c) Date of patient visits match recruitment logs
d) Laboratory result, x-ray results, etc
e) All trial details filed in appropriate place

**TRANSPORT LOGS**

**Additional Points of Note:**

- Interviews may be conducted with the PI and site personnel.
- 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.

**Reporting of Audit and Follow-up**

a) 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.
b) 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.
c) 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.
d) 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.
e) 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.
f) 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

**REC deliberations and decisions**

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.

The REC will decide either by consensus or by vote to:

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.
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.
3) Withdraw study approval AND/OR
4) Refer the matter to line management, the Deputy Dean: Research or the Senate REC for further investigation and action where appropriate.

- 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.

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.

Q. FEES

1) The Health Research Ethics Committees has a graded administrative fee structure in place, which is revised annually. Certain projects are exempt from fees.
2) The current administrative fee structure is available on the website or can be obtained from Mr Franklin Weber at 021 938 9657.
3) Fees must be paid immediately on receipt of an invoice. Invoices will be issued on receipt of a new application or amendment.
4) Approval letters will not be issued unless all outstanding amounts have been settled.
5) Payments made directly into SU bank account must contain the invoice number as a reference.
6) Please fax proof of payment to 021931 3352.
7) 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.

RESEARCH ETHICS COMMITTEES: APPEALS AND COMPLAINTS
Generic Standard Operating Procedure
Approved by the Senate Research Ethics Committee 9th February 2011

A. DEFINITIONS

Appeals arise because a Research Ethics Committee (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.

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

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1 Health Research Ethics Committee (REC) 1 and 2, Non-medical REC; Animal Care and Use REC; Biosafety REC
2 Health REC (Human Research) SOP, Stellenbosch University. May 2010. V3.3
3 Approved by Senate REC: 5th August 2010
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.

B. APPEAL PROCESS

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.

B1. APPEAL PROCESS (REC LEVEL)

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.
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 appropriate. The subcommittee may have the same powers as the REC, if so constituted by the REC concerned.
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.
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.
5. In the event of an (a) or (b) outcome, the decision of the REC (or REC-subcommittee) is final.
6. 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.
7. 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 appeal1.

B2. APPEAL PROCESS (SENATE RESEARCH ETHICS COMMITTEE LEVEL)

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 (SREC) no later than 10 working days of the decision of the REC.
2. The SREC is expected to have a mechanism whereby a PI may appeal the SREC’s decision. The chairperson of the SREC must appoint a subcommittee to revisit the substance of the appeal together with any additional information put forward by the PI. The subcommittee must obtain at least one independent, external, expert review of the research project and the substance of the appeal. Additional reviews should be obtained if deemed appropriate. The subcommittee may have the same powers as the SREC, if so constituted by the SREC concerned.
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.
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 National Health Research Ethics Council

5. In the event of an (a) or (b) outcome, the decision of the SREC (or SREC-subcommittee) is final.
6. If the SREC or SREC-subcommittee refers the matter to the National Health Research Ethics Council (NHREC) it undertakes to adhere to any decision taken by the NHREC, regarding the matter.
7. Researchers conducting ‘health research’ retain the right to appeal to the National Health Research Ethics Council in the event that they remain dissatisfied with the outcome of the appeal1.

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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.
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.

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.

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).

B2.1 Composition of Appeal Panel

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

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.

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.

B2.2 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.

B2.3 Powers of Appeal Panel

The appeal panel is empowered

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

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.

C. COMPLAINTS PROCESS

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.

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.
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.

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.

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.

6. The PI shall be notified of the outcome of the SREC investigation.
Appendix I


Vulnerable communities are defined as having some or all of the following characteristics:

- Limited economic development;
- Inadequate protection of human rights and discrimination on the basis of health status;
- Inadequate community or cultural experience with the understanding of scientific research;
- Limited availability of health care and treatment options;
- Limited ability of individuals in the community to provide informed consent;
- Culturally marginal groups
- Persons involved in illegal activities or livelihoods

2. RESEARCH REQUIRING ADDITIONAL ATTENTION: (SA GCP Guidance, DoH, 2006)

- Minors: Children and adolescents
- Women: Women and Pregnancy
- Foetuses in-utero
- Foetuses ex-utero
- Persons with mental disabilities
- Persons with substance abuse related disorders
- Persons in dependent or subservient relationships (e.g., students where the investigator is directly involved in their training; employees where the investigator has line authority over them).
- Prisoners
- Persons highly dependent on medical care
- Intensive care
- Neonatal intensive care
- Terminal care
- Persons with impaired capacity to communicate
- Unconscious persons
- Specific social collectivities
- Persons in indigenous medical systems
- Emergency care research
- Innovative therapy or intervention
- HIV/AIDS clinical and epidemiological research
Appendix II

Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure

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 children2, 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.

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).

REFERENCES / SOURCE DOCUMENTS

Codes and Guidelines

1. WMA Declaration of Helsinki 2002
3. Code of Federal regulations CFR Title 21 Food & Drugs revised as of April 1 2003
4. CFR Title 45 Public Welfare as of April 2003
9. CIOMS International Ethical Guidelines for Biomedical research Involving Human Subjects. 2002

Books/Articles


Other


Genetic Research