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**THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL  
HUMAN RESEARCH ETHICS COMMITTEE (HREC)  
STANDARD OPERATING PROCEDURES**

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## **1. AUTHORITY**

- 1.1 The South African Medical Research Council (SAMRC) Human Research Ethics Committee (HREC) was established as set out in its Research Ethics Policy and Terms of Reference.
- 1.2 Its authority has been conferred upon it by the SAMRC Board.

## **2. ROLE OF THE SAMRC HREC**

- 2.1 The SAMRC HREC functions as the official Human Research Ethics Committee of the SAMRC. The objective of the Committee in reviewing research involving human research participants is to contribute to safeguarding the dignity, rights, safety and well-being of all research participants and to ensure that the goals of research do not override the best interests of the research participants. The HREC is committed to ensuring high-quality scientific and ethical research by the SAMRC, therefore protecting the professional interests of the researchers as well. The SAMRC HREC aims to provide independent, comprehensive and timely review of the ethics of proposed studies conducted by SAMRC intramural units. Monitoring is conducted by annual and ongoing reporting.

## **3. MEETINGS**

- 3.1 The SAMRC HREC will have about 10 meetings per year, i.e. February to November. Meetings will be either face-to-face meetings or via video/telephone conference. The Committee will endeavour to hold meetings in the last week of the month. A schedule of the meeting dates of the year will be available from the SAMRC Human Research Ethics Office and on the SAMRC website.
- 3.2 At least 50%+1 of the members are required to compose a quorum.
- 3.3 At the discretion of the Chairperson, in consultation with the Committee members, and subject to their observing the confidentiality of the meeting, applicants may attend meetings to clarify points of issue but will not be present and part of the decision-making.
- 3.4 Poor meeting attendance impacts on the quorum and can result in a meeting being cancelled. To ensure timely and efficient review of research proposals, Committee members are expected to attend meetings punctually and regularly.

3.5 The agenda of a meeting will list the protocols, major amendments, annual status reports, serious adverse event reports and responses to queries to be discussed, and will be sent to the members, together with the study documents. The final agenda will be sent to members at least **5 (five)** working days before the meeting.

#### **4. PROTOCOL APPLICATION FOR APPROVAL BY THE COMMITTEE**

4.1 Researchers in South Africa have the ethical responsibility to ensure that their research is relevant both to the broad health and development needs of the country and to the individual needs of those who suffer from the diseases and concerns under study. The findings of the research must be translatable into mechanisms for improving the health status and reducing the burden of disease among all South Africans.

4.2 The Human Research Ethics Office will make available a comprehensive checklist (revised from time to time) to guide the researchers when making submissions. Researchers must submit written applications for ethics clearance and provide stipulated supporting documents (research protocol, information sheet, informed consent, questionnaire, investigator's brochure, budget, etc.).

4.3 All documentation must be submitted to the Human Research Ethics Office **NO LATER than 30 (thirty) working days** before the scheduled date of the meeting.

4.4 A research proposal must include the following:

4.4.1 A statement of the ethics considerations involved in the proposed research. The Committee must be satisfied that the research protocol gives adequate consideration to participants' welfare, rights, beliefs, values, customs and cultural heritage.

4.4.2 A clear community engagement plan outlining how stakeholders and community members will be consulted and involved in the research lifecycle process. Researchers need to follow the SA Community Advisory Board guidelines.

4.4.3 The process of obtaining informed consent and assessing understanding of the consent information should be included in the protocol. Special attention should be paid to participants' understanding and appreciation of the information provided prior to making decisions to join the research.

- 4.5 Researchers are encouraged to include capacity and skills development outcomes within the submission of protocols to the SAMRC HREC. This includes opportunities for postgraduate studies and development of young scientists.
- 4.6 Research conducted for PhD and Masters degree purposes should first obtain approval from a registered research ethics committee of the institution where the degree will be obtained, before the application is sent to the SAMRC HREC for noting.
- 4.7 All documents and other material used to inform potential research participants must be approved by the SAMRC HREC, including plain-language information sheets, consent forms, questionnaires, advertisements and letters.

## 5. NEW PROTOCOL SUBMISSIONS

- 5.1 An application for review of the ethics of proposed biomedical research should be submitted by a qualified researcher responsible for the ethical and scientific conduct of research.
- 5.2 The following documentation should be submitted to the Human Research Ethics Office **30 (thirty)** working days before the next meeting (one unbound hard copy plus an electronic copy emailed to the Secretariat):
- Signed and dated checklist. The clinical trial application form must be signed by ALL applying principal investigators.
  - Letter stating that the science of the protocol has been reviewed and approved within the Unit.
  - Protocol of the proposed research (clearly identified & dated), together with supporting documents and annexes. Provision must be made for a protocol signature page signed by all local principal investigators.
  - PI-generated summary, synopsis, or diagrammatic representation (flowchart) of the protocol.
  - Diary cards, questionnaires and computer-based surveys intended for research participants.
  - Proposed **English** written informed consent form and consent form updates, clearly identified and dated (final informed consent document translated in other languages accompanied by a letter from an official translator).

- Participant recruitment procedures, education material (e.g. advertisements) and any other written information to be provided to participants.
- Information about reimbursements to participants, including costs to participants for study participation. This includes any refreshments, tokens of appreciation, or incentives for retention. The NHREC document on reimbursement should be used as a guideline; it is available at:  
<http://nhrec.health.gov.za/index.php/grids-preview>
- The process for obtaining informed consent at the various sites.
- Details of financial agreements/study budget with investigators **signed and dated**.
- A motivation for the use of a placebo control (where applicable).
- Post-research treatment explanatory document (where applicable).
- A list of site details, including the site address and names of the PI, sub-investigators, study coordinators, registered pharmacists and all other research team members.
- Investigator's brochure/registered package insert/available safety information.
- Principal Investigator's and Co-/Sub-investigator's current Curriculum Vitae in the required format and/or other documentation evidencing qualifications and professional registration (updated, signed and dated), including the signed and dated MCC Declaration by the PI.
- A copy of the insurance certificate covering the protocol (1 copy).
- MCC application/approval letter (if applicable) (1 copy).
- South African National Clinical Trials Registration Forms (if applicable).

5.3 If an approved study is not initiated for whatever reason, the Committee must be informed.

## 6. PRINCIPAL INVESTIGATOR AND CO-PRINCIPAL INVESTIGATOR

6.1 Communication between the SAMRC HREC and the investigators should be directed through the Principal Investigator (PI).

6.2 The PI must be resident in South Africa and is *inter alia*, responsible for the following:

6.2.1 Complying with the SA and ICH GCP guidelines;

6.2.2 Submitting an application to the SAMRC HREC and the South African Health Products Regulatory Authority (SAHPRA) where applicable (both of these reviewing institutions must approve the project before the study may commence);

6.2.3 The scientific and ethics aspects of the study; and

6.2.4 Communication with the SAMRC HREC.

6.3 Once a study is in progress, all reports of adverse events and management issues dealt with by the Sponsor should be transmitted to the Committee, ideally through the PI or Co-PI, who should be fully informed of these issues.

6.4 PIs must inform the Committee of the number of projects in which they are involved and the percentage time spent on each with every new submission to SAMRC HREC.

## **7. CLINICAL RESEARCH AND TRIALS**

7.1 All clinical trials must be conducted according to ICH GCP guidelines and SA GCP guidelines.

7.2 A clinical trial may not commence before receiving a national study number from the Department of Health's National Clinical Trials Register and approval from the South African Health Products Regulatory Authority (SAHPRA).

7.3 The information in the South African National Clinical Trials Register should be available publicly, with the reservation that it be limited to information that would not jeopardise commercial interests. It will include:

- Title of research project.
- Duration of the project.
- PI name and institutional affiliation.

7.4 A regular update of an anonymised research profile from the database may be placed on the Department of Health's website with information such as:

- The number and proportion of studies by type (for example, trials or non-trials) and study site.
- Total sponsorship by type of study and study site.

7.5 The Curriculum Vitae of the PI, co-investigators and key personnel responsible for the safety and well-being of the participants must be submitted for consideration by the Committee.

7.6 The investigator's brochure must be part of the submission where applicable.

7.7 In the event of rapid staff turnover at a clinical research site, the Committee must be assured that new investigators have the requisite experience and training in clinical research and that participant safety and wellbeing will not be compromised.

## 8. PARTICIPANT INFORMATION AND INFORMED CONSENT REQUIREMENTS

8.1 Separate participant information and informed consent documents must be submitted for:

- The main study
- HIV testing
- Pharmacogenomic research
- Genomic research
- Consent/assent for minors (children under the age of 18 years who are 7 years and older)

8.2 For vulnerable participants, the *Ethics in health research: principles, structures and processes*, Department of Health, 2015 stipulates as follows: “In South Africa, researchers must be particularly aware of the vulnerability of prospective participants in terms of access to health services and education levels. Research details must be provided in a clear, simple and culturally appropriate manner. If a participant lacks capacity to exercise an informed choice to participate, an appropriate person to make the choice for them must be identified by the investigator. A participant is free at any time to withdraw consent to further involvement in the research, without having to face any unfair negative consequence or disadvantage”.

8.3 The following essential elements must be understood and appreciated before a participant is capable of giving informed consent.

- That consent is being given to participate in research.
- The purpose of the research.
- The expected duration of the participant’s involvement.
- A description of the procedures to which the participant will be subjected, including any experimental procedures that are innovative and have not been used in medical practice.

8.4 The informed consent document should be at grade 6 literacy level.

8.5 Prospective participants should be helped to arrive at an informed decision by, for instance, use of appropriate language, selection of a non-threatening environment for interaction, and the

availability of peer counselling. Participants may find information about the following points useful:

- The investigators' qualifications.
- Explanation of participants' responsibilities.
- Description of foreseeable risks or discomforts.
- Description of benefits to the participants or to others, both during and after the research.
- Disclosure of alternative procedures or courses of treatment.
- Description of the extent to which confidentiality will be maintained.
- Statement that sponsors of the study may be able to inspect research records.
- Statement that the research has been approved by an accredited research ethics committee.
- Contact details of research ethics committee representatives.
- Explanation regarding compensation for research-related injuries.
- Explanation regarding the consequences of injury, including medical treatments.
- Explanation of who to contact in the event of research-related injury.
- Statement that participants' data may be added to a big database of journals/funders/researchers/sponsors. Participants may decline consent to data sharing.
- Statement on benefit sharing (see guidance at paragraph 25 below)

8.6 Investigators must assure potential participants that participation is voluntary, and that refusal to participate, or a decision to discontinue participation, will not involve any form of penalty. The approximate number of participants should be disclosed. Details of treatment must be supplied and, where appropriate, the possibility of random assignment to various treatments or procedures must be made clear. The nature of experimental and control groups must be explained, as well as circumstances that might lead to the termination of participation. Unforeseeable risks obviously cannot be anticipated, but participants must be informed of the nature and extent of risks – including financial risks – attendant on participation. Participants must be made aware of their right to be informed of relevant new findings, and of the consequences of their withdrawal from research. They should know, too, whether the investigator might terminate participation. Educational materials should be developed where possible.

8.7 The above points may be regarded as essential elements of informed consent, and all should be incorporated in an informed consent form or document. Informed consent is a vital requirement

in ethical conduct of research, and is valid only when it is obtained without deceit or misrepresentation. The informed consent requirements are not intended to pre-empt the laws of the country, which may require that additional information be provided to participants. The moral duties of the medical practitioner or other investigator are in no way limited by these requirements.

8.8 The Committee requires the following information on the **informed consent process with each new application**:

- i. A description of the process for obtaining informed consent, including the process for ascertaining understanding and appreciation of the information provided.
- ii. The adequacy, completeness, and understandability of written and oral information to be given to the research participants, and when appropriate, e.g. for unconscious participants, or participants with dementia or any other condition where it may be applicable, their legally acceptable representatives. Clear justification for the intention to include in the research individuals who cannot consent, and a full account of the arrangements for obtaining consent for such individuals.
- iii. Assurances that research participants will receive information that becomes available during the course of the research relevant to their participation.
- iv. The provisions made for receiving and responding to queries and complaints from research participants or their representatives during the course of a research project.
- v. In all instances **verbal and written** informed consent, and assent in the case of minor participants, should be obtained, unless there are good reasons to the contrary, such as a situation of coma, emergency, or mental incapacity.
- vi. Verbal consent, **where the participant is illiterate**, should be obtained in the presence of and countersigned by a literate, independent **witness confirming that all the relevant information was provided to the research participant in an understandable manner**.
- vii. For **minor participants under the age of 18 years**, consent from the **parent or legal guardian** must be sought.
- viii. In addition to the consent of the parent or legal guardian, consent must also be obtained from the minor participant if the minor is capable of understanding. Maturity, psychological state of mind and age should be taken into account. Special care should be taken to create an informed consent document that will be understandable to minors. Where a minor is not competent to consent, assent from the minor may be obtained

however, in all such cases, the protocol must provide sufficient information outlining the steps that will be taken to obtain the child's assent and how it will be documented.

- ix. Following approval of original English versions, all translations with authenticity certificates (or other method used to confirm accuracy) must be submitted to the Committee for information and filing.
- x. Information regarding the insurance for the study should be included.
- xi. Readability scores and tests of understanding should be included.

For more information, refer to the *Ethics in Health Research: Principles, Processes and Structures. Second Edition. Department of Health, Republic of South Africa, 2015*

## **9. VULNERABLE PARTICIPANTS**

9.1 *Ethics in Health Research: Principles, Processes and Structures. Second Edition. Department of Health, Republic of South Africa, 2015* describes the following vulnerable groups:

- Minors (children and adolescents)
- Women
- Adults with incapacity to provide informed consent
- Persons in dependent relationships
- Persons highly dependent on medical care
- Persons with physical disabilities
- Prisoners
- Collectivities

9.2 The Committee must pay special attention to protecting the welfare of certain classes of participants:

- Minors – children and adolescents
- Persons with intellectual or mental impairment
- Disabled persons
- Persons in dependent relationships
- Persons participating in research as groups (referred to as collectivities)
- Pregnant women
- Prisoners
- People whose first language is not English

- Traumatized and comatose patients
- Terminally ill patients
- Elderly or aged patients
- Minorities
- Students
- Employees

9.3 The Committee may impose additional measures to protect the welfare of participants, especially with regard to informed consent.

9.4 The Committee may make it mandatory to conduct post-research investigations to review whether there was compliance with the additional measures imposed. If compliance was defective, the Committee may withdraw approval for the research investigation concerned.

9.5 Types of research that need additional attention include:

- Research involving indigenous medical systems
- Emergency care research
- Innovative therapy or interventions
- Research necessitating ambiguity of information for participants

## 10. REVIEW OF APPLICATIONS AND APPROVAL PROCESS

10.1 Review of an application is undertaken in two separate steps, i.e. scientific review prior to meetings, and ethics review.

10.2 *Scientific review:* Each application is sent to at least two independent reviewers who are experts in the field. The reviews are conducted according to a set review form. The scientific reviewers have to approve any changes requested or recommended by them before the application is submitted for ethics review by the Committee. Applicants do not suggest their own reviewers. Local scientific review is important in terms of relevance within local circumstances, irrespective of reviews for funding. Protocols will not be considered for ethics review in the event that it has not passed the scientific review process.

10.3 *Ethics review:* The Committee will consider all aspects of the protocol and must be satisfied that the research satisfies the following criteria: collaborative partnership, social value, scientific validity, fair selection of study population, favourable risk-benefit ratio, informed consent, respect

for recruited participants and study communities, and research translation. There must be justice and beneficence for the participants in all research projects.

- 10.4 The Chairperson will allocate one protocol for comprehensive review to two members of the Committee with requisite experience. These members will present their findings to the Committee. All members will be required to familiarise themselves with the synopsis and the consent forms for all protocols.
- 10.5 Notwithstanding the above, all Committee members will participate on an equal basis in a democratic open deliberation process regarding the science of the protocol, the risks and benefits, the value of the research, fairness in participant selection, the informed consent document, and any other ethical issues.
- 10.6 The Committee, after considering inputs from the reviewers of a submission, will make one of four decisions by consensus: approval; require minor amendments; require major amendments; or rejection.
- 10.7 Proposals requiring minor amendments may be approved outside the meeting by a sub-committee comprising the Chairperson or Vice-chairperson, with additional members where necessary and noted/ratified at the next meeting. Proposals requiring major amendments will need to be resubmitted to the full Committee. Rejected submissions may be resubmitted for fresh review by the full Committee.
- 10.8 Decisions are recorded in writing and will include reasons for rejection.
- 10.9 The applicant will be informed of the approval, approval with stipulations, requirement for modifications, deferral, or rejection<sup>1</sup> within **15 (fifteen)** working days after the meeting. No verbal feedback will be given.
  - **Approval:** The proposed research is approved in its current form, with no changes required. The date of approval is considered the date that all conditions were determined to be met.
  - **Approved with stipulations:** The proposed research is approved with minor alterations required.

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<sup>1</sup> From: Health Research Ethics Committee 1 and 2 Human Research Standard Operating Procedures And Guidelines June 2016 V4.3, University of Stellenbosch

- **Modifications required:** The proposed research has no major ethical concerns but a number of clarifications or methodological changes are required. The research applicant must resubmit the revised research application. The review can be finalised by an expedited review process, i.e. without having to serve before the full Committee again.
- **Deferred:** The proposed research has major methodological and/or ethical concerns and requires considerable revision. The research applicant must resubmit the revised research application. The revised research application will be reconsidered at a convened (full) Committee meeting.
- **Rejected:** The proposed research may not be resubmitted.

10.10 **No recruitment, screening or enrolment on a study may take place before the Committee issues its written approval. This includes written approval for amendments and renewals.**

10.11 The Committee will not grant retrospective ethics approval for completed research, or for research submitted to another research ethics committee in the absence of prior arrangement.

10.12 REC may suspend the study if it is not being conducted in accordance with the approved protocol.

10.13 Should applicant not respond to comments/queries raised by the HREC within a period of 6 months after the latest feedback, such application may lapse at the discretion of HREC. If lapsed, fresh application should be submitted.

## 11. EXPEDITED REVIEW PROCEDURES

11.1 In exceptional cases, the Chairperson, Vice-Chairperson or an *ad hoc* committee will evaluate a request for expedited review. However, all such requests must be well motivated. The timeframe for the expedited review will be at the discretion of the HREC, but should occur in no more than 10 working working days from receipt of request.

11.2 Categories of research that may qualify for an expedited procedure include those involving no **more than minimal risk to the participants**, as well as **minor changes to research, or amendments that are urgent**.

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

**risk research**<sup>2</sup>: the probability and magnitude of harm or discomfort anticipated in the research, is not greater, in and of itself, than that ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests.

11.4 **Minor amendments**<sup>3</sup> do not change the risk benefit profile of the study in any way. Examples of typical minor amendments:

11.4.1 Additional Investigators or study sites

11.4.2 Small changes in the consent process

11.4.3 Change in background information or update of literature review

11.4.4 Extension of period of study

11.4.5 Other changes that do not affect study design and will not affect study outcomes or results

11.4.6 Administrative changes

11.4.7 Stricter inclusion or exclusion criteria.

11.5 **Major amendments**<sup>4</sup> require a change(s) to the study methodology or procedure that may result in an alteration of the risk benefit profile of the study. Examples include:

11.5.1 Change in study aims, objectives or design

11.5.2 Resulting changes to consent documents

11.5.3 Additional study procedures

11.5.4 Easing of inclusion or exclusion criteria

11.6 The expedited review may be carried out by the Chairperson of the Committee or by an *ad hoc* committee convened by the Chairperson. The decisions will be ratified by the full Committee during the next meeting. Administrative changes that will have no impact on the study may be approved by the Secretariat.

11.7 In general, research with potential to cause physical or psychological harm will not be considered for expedited review. This includes research involving experimental medicine or surgical interventions, research involving invasive procedures, and research involving sensitive personal or cultural issues.

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<sup>2</sup> From: Health Research Ethics Committee 1 and 2 Human Research Standard Operating Procedures And Guidelines June 2016 V4.3, University of Stellenbosch

<sup>3</sup> From: Health Research Ethics Committee 1 and 2 Human Research Standard Operating Procedures And Guidelines June 2016 V4.3, University of Stellenbosch

<sup>4</sup> From: Health Research Ethics Committee 1 and 2 Human Research Standard Operating Procedures And Guidelines June 2016 V4.3, University of Stellenbosch

## 12. PROTOCOL AMENDMENT

- 12.1 An amendment is a change that is administrative in nature or has an impact on the safety or integrity of the participants, alters scientific value of the research or interpretation of the results, affects validity of data, the design of the study, planned statistical analyses or significantly alters other aspects of the research. Changes in clinicians, pharmacists and any staff member who is involved with safety of participants on a clinical trial also constitute an amendment, and applications for such amendment should include information on the role and tasks of the persons involved. The nature and examples of **minor and major amendments** are discussed in sections 11.4. and 11.5 above.
- 12.2 Protocol amendments received will be tabled as part of the agenda at the next Committee meeting for review by the full Committee. Administrative amendments may be approved by the Committee administrator.
- 12.3 The following documentation should be submitted to the SAMRC Ethics Office **15 (fifteen)** working days before the next meeting as applicable:
- i. Cover letter explaining the nature of and reason for the amendment
  - ii. Application form that includes a justification for each amendment
  - iii. Revised protocol with tracked changes
  - iv. Revised informed consent document with tracked changes
  - v. Any other relevant material that was revised with the amendment

## 13. CONTINUING REVIEW / ANNUAL RENEWAL

- 13.1 Continuing review of research will be conducted at appropriate intervals but **not less than once per year**. Continuing review can be done more frequently if the Committee requests it.
- 13.2 The Committee must receive an application for annual renewal at the latest **ONE YEAR after approval**.
- 13.3 A request for renewal must reach the Committee at least two months before the expiration of the current approval. It will be the responsibility of the PI to ensure that renewal is granted before the current ethics approval expires.

- 13.4 Annual re-approval will only be given for the study to continue on receipt of a satisfactory annual progress report.
- 13.5 In conducting continuing review, all members will receive and review a protocol summary and a status report on the progress of the research at the sites approved by the Committee.
- 13.6 At the end of the study a **final close-out report** must be submitted for each site together with the publication, MCC and DoH communication, the close-out procedures and results dissemination plans.
- 13.7 The following documentation should be submitted to the Human Research Ethics Office **15 (fifteen)** working days before the next meeting:
- i. The application form
  - ii. Covering letter
  - iii. The protocol summary
  - iv. The **status report per site**
- 13.8 Status reports must be completed **per site** and must be signed and dated by the Principal Investigator. The status report should include the following information:
- i. The number of participants entered **per site**
  - ii. A summary of serious adverse events and unanticipated problems **per site**, including the outcome of the SAEs and their relationship to the study medication
  - iii. The number of withdrawals and the reason for the withdrawals per site
  - iv. Any relevant new information
  - v. All relevant line listings
  - vi. Community engagement outcomes
- 13.9 **Failure to submit annual progress reports/application for renewal will lead to deregistration of the study.**

#### 14. **RESUBMISSIONS**

- 14.1 Major deficiencies will usually result in a refusal to approve the protocol or amendment. A new submission will have to be made.

14.2 Minor deficiencies in the submission of protocol/amendment will result in **conditional approval** with a request for changes or additional information.

## 15. **SERIOUS ADVERSE EVENTS (SAEs) AND ADVERSE DRUG REACTION REPORTING**

15.1 All serious adverse events (all deaths or serious, unexpected, adverse drug reactions which are fatal or life threatening) should be reported electronically and in hard copy to the Committee within **two business days of becoming aware of the event**. This includes related and unrelated SAEs.

15.2 All **supporting information related to the SAEs** (i.e. follow-up reports, CIOMS reports, etc.) must be forwarded in writing to the Committee within **48 (forty eight) hours** of the sponsor receiving this information. When general abnormalities in participants are reported in SAEs, information on whether they had been exposed to drugs should be included.

15.3 A designated SAE Committee consisting of the chairperson and members of the Committee will review all SAEs.

15.4 All decisions will be ratified by the full Committee.

15.5 The Committee will acknowledge receipt of all SAEs in writing.

15.6 Every 3 months a line listing of all SAEs must be submitted to the Committee in the required format, available on the Internet at <http://www.mrc.ac.za/research/ethics/submission-documents>. This should include a report summarising the salient points.

15.7 At least the following information should be included when an SAE is reported:

- Protocol number
- Protocol title
- Research participant number
- Date of birth of participant
- Event onset date – time of onset
- Diagnosis (most significant SAE being reported)
- Investigator's name
- Study product
- Description of event
- Event outcome

- Action taken with regard to study product
- Treatment and referral
- Relationship with study product

15.8 All adverse events must be reported to the Committee in line listing format on an annual basis in conjunction with the application for annual re-approval (see under SAEs).

15.9 Pertinent safety information must be reported in writing to the Committee as soon as possible.

15.10 All suspected serious, unexpected adverse drug reaction reports originating from worldwide clinical sites outside South Africa should be reported to the Committee in line listing format on an annual basis in conjunction with application for annual renewal.

- i. A designated SAE Committee consisting of the chairperson and members of the Committee will review all SAEs.
- ii. All decisions will be ratified by the full Committee.
- iii. Line listings will **only** be reviewed during the annual re-approval process and not on a bi-annual basis, unless otherwise specified by the Committee.
- iv. The Committee will acknowledge receipt of all SAEs in writing.

## 16. DOCUMENTS ACKNOWLEDGED BY THE COMMITTEE

16.1 The following documents will only be acknowledged by the Committee:

- **Translated** patient information sheets and informed consent forms (certificate of translation must be included)
- **Translated** questionnaires and patient diary cards (certificate of translation must be included)
- **Updated** investigator's brochures (a summary of the changes must be included)
- Data and Safety Monitoring Board (DSMB) messages, results dissemination messages

## 17. RECORDING AND ARCHIVING OF DECISIONS

17.1 The Committee will maintain a record of all research protocols received and reviewed.

17.2 The Committee will retain on file a copy of each research protocol and application submitted for approval. The file will include information sheets, consent forms and relevant correspondence, all in the form in which they were approved. A list will be kept of the Committee members who

were present during discussion of the application and when the final decision of the Committee was reached.

- 17.3 The Committee will retain one set of all submitted documents related to applications for a period of at least 15 (fifteen) years, following the completion of a study. This will include electronic and hard copies of the documentation.

## **18. MONITORING**

- 18.1 The Committee will ensure that the conduct of all research approved is monitored. Monitoring is conducted by annual and ongoing reporting. An audit/review of a study or site may occur at the discretion of the HREC, should there be concern for participant safety or other factors that may jeopardize the integrity of the research.
- 18.2 The Principal Investigator/s will report on the progress of the project annually.
- 18.3 All monitoring reports, such as DSMB reports, SAE reports, etc. must be submitted to the Committee by the Principal Investigator/s.
- 18.4 For high-risk studies and changes in Principal Investigator/s, the Committee may request more frequent updates. It will be expedited to not hold up the study.
- 18.5 No changes to the protocol or study procedures should be initiated without prior written approval from the Committee. In cases of urgency, an expedited review process can be followed as set out above.
- 18.6 The Committee will adopt additional appropriate mechanisms for monitoring, including random inspection of research sites, data and signed consent forms and records of interviews where indicated.
- 18.7 It is required that researchers immediately report anything that might warrant a review of ethics approval of the protocol, such as Serious Adverse Events (SAEs), proposed changes in the protocol, or unforeseen events that might affect continued ethical acceptability of the project.
- 18.8 The Committee may ask to review site monitoring reports on an *ad hoc* basis as part of the monitoring process.
- 18.9 The Committee may also monitor high-risk studies on an *ad hoc* basis.

- 18.10 Researchers must inform the Committee, giving reasons, if the research project is discontinued before the expected date of completion.

## **19. COMPLAINTS AND SUSPENSION OR DISCONTINUATION OF RESEARCH**

- 19.1 The contact details of the Committee Chairperson and secretariat must be available to all research participants, community stakeholders and researchers in the event that they wish to forward a complaint. All complaints will be investigated as directed the HREC Chair and parties will receive a response from the Committee.
- 19.2 Where the Committee is satisfied that circumstances have arisen that a research project is not being conducted in accordance with the approved protocol and that the welfare or rights of participants are being compromised, the Committee may withdraw approval after following the process as provided for in the REP.
- 19.3 The Committee will inform the researcher and/or sponsor of its action and will recommend discontinuation or suspension. In such instances, the researcher must discontinue the research and comply with any special conditions required by the Committee. Principal Investigators should document SAMRC HREC withdrawal of study approval and report this to the relevant regulatory authorities/sponsors/collaborators.

## **20. INTERNATIONAL RESEARCH**

- 20.1 International studies that will be conducted in South Africa must have a local Principal Investigator. The researchers will seek legal guidance regarding the agreements governing the research grant and submit it with their application.
- 20.2 The Committee will review all applications from the perspective of South African law, under which the Committee operates and is held accountable.
- 20.3 The Committee will only review research conducted outside South Africa if an SAMRC researcher is involved.
- 20.4 There are challenges to approving research in another country, e.g. monitoring, regulatory issues, payment of participants, requirements regarding informed consent for children or parental consent, etc. If the country where the research is being conducted has an ethics

review system or research ethics committee, that committee must also approve the research.

The contact details on the informed consent forms must be local numbers. An email address of the South African PI must be included.

- 20.5 Decisions on these studies will be determined by the legislation, circumstances and context of the respective countries.

## 21. PLACEBO-CONTROLLED STUDIES

- 21.1 As a general rule placebo control will not be approved by the Committee as research participants in the control group of a research study of a diagnostic, therapeutic, or preventative intervention should receive an **established effective intervention. This is referred to as standard of care or standard of prevention.** However, the Committee will consider placebo-controlled studies in the following circumstances:

- Where there is no **established effective intervention.**
- When withholding an established effective intervention would expose participants to, at most, **temporary discomfort or delay in relief of symptoms.**
- Use of an established effective intervention as comparator would **not yield scientifically reliable results** and use of placebo would **not add any risk or serious irreversible harm to the participants.**
- In open label studies.
- Add-on study designs where all participants have **equal access to the appropriate standard of care or prevention.**

- 21.2 The Declaration of Helsinki (2013) states that the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: 1. Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or 2. Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

21.3 In all instances where placebo control is suggested, the Committee must receive a separate **motivation for the use of placebo for the submitted application.**

## 22. GENETIC RESEARCH

22.1 In the case of human genetic research, the Committee requires a sub-protocol or appendix to the main protocol, outlining the objectives and procedures to be followed.

22.2 The Committee will only allow genetic research within the scope of the protocol (study medication toxicity, metabolism and efficacy, and specific disease entity studied within the protocol), i.e. pharmacogenetic research. **No open-ended genetic research will be approved.** The following will be considered:

- Social and cultural significance of the research.
- The balance between the contribution of knowledge and the potential for harm to individuals or collectives.
- The confidentiality and privacy of stored genetic information or research results relating to identified or potentially identified participants.

22.3 The samples should be stored in South Africa. Clear information regarding place and length of storage of samples should be included.

22.4 If that is not the case, a separate motivation is needed explaining the reasons why it is necessary to store samples outside South Africa.

22.5 If samples are exported from South Africa, an Export Permit must be obtained via the Department of Health.

22.6 A separate informed consent for the specific collection of a blood sample for pharmacogenetic or pharmacogenomic research must be submitted. This document must note and/or contain at least the following information:

- The genetic research will be limited to the medication (specify name) and disease/condition (specify name) under investigation.
- No unspecified open-ended research will be conducted without prior consent from the participant and/or approval from the Committee.
- The costs of the research will be covered by the sponsor.
- Information on privacy and confidentiality.

- Information on compensation in the event of a study-related injury.
- If samples are to be exported to a central laboratory outside South Africa, the physical address of this laboratory must be specified.
- The period for which the samples will be stored (maximum 15 years).
- In the consent statement, participants must consent to their samples being shipped to a secure laboratory outside South Africa.
- In accordance with the DOH *Ethics in Health Research: Principles, Processes and Structures, 2015*, the following levels of informed consent must be included as applicable: **Narrow (restrictive) consent:** the donor permits use of the biological specimen for single use only; no storage of leftover specimen; and no sharing of data or specimens. This form necessitates new consent if further use is desirable. **Tiered consent:** the donor provides consent for the primary study and chooses whether to permit storage for future use, sample and data sharing. **Broad consent:** the donor permits use of the specimen for current research, for storage and possible future research purposes, even though the precise nature of future research may be unclear at present. The nature of the further usage should be described as fully as possible and should stipulate that further prior ethics review of the new study is necessary. Permission may be sought to re-contact the person if intended future use is outside the scope of the current consent.

22.7 If it is anticipated that participants will receive results from the genetic testing, they should be counselled about the possible consequences of doing so. Reference must be made to the counselling in the consent document.

22.8 Counselling can be provided at the time of obtaining consent or in the future, prior to the provision of feedback, where applicable.

## 23. NON-THERAPEUTIC RESEARCH ON MINORS

23.1 Section 71(3)(a)(ii) of the National Health Act (NHA) requires the Minister of Health to consent to 'non-therapeutic' health research with minors, only after considering whether the following four criteria are met: (i) in such manner and on such conditions as may be prescribed; (ii) with the consent of the Minister; (iii) with the consent of the parent or guardian of the minor; and (iv) if the minor is capable of understanding, the consent of the minor.

- 23.2 The Minister may delegate authority, in terms of s 92(a), to any person in the employ of the state, a council, board or committee established in terms of the Act to give this consent.
- 23.3 The Minister has delegated authority to provide Ministerial Consent for 'non-therapeutic' health research with minors to RECs who have been found to be compliant with the audit and have achieved full registration with the NHREC. Correspondence in this regard was sent to relevant RECs on 14 October 2014. As further RECs become fully registered, their authority to exercise the delegated power will be communicated by the NHREC through the Secretariat.
- 23.4 Regulations for research with human participants, published on 19 September 2014 (R 719) contain Form A that sets out the four criteria to be met for the additional review of 'non-therapeutic' health research with minors. Proper use of Form A should provide adequate evidence that these reviews are performed appropriately by RECs (there is a link to the form on the Committee's webpage <http://www.mrc.ac.za/research/ethics/submission-documents> ).

## **24. USE OF HUMAN TISSUE SAMPLES**

- 24.1 Where human tissue is to be used in research, researchers and the Committee must be satisfied that the research proposal conforms to the principles of ethical conduct and the prescribed regulations of the National Health Act, 61 of 2003.
- 24.2 Approval must be obtained from the Committee for collecting samples of human material for research.
- 24.3 New approval must be obtained for all research projects not specifically mentioned when consent was originally obtained.
- 24.4 The samples should be stored in South Africa. Researchers shall stipulate data management plan (DMP) on their protocols. The DMP will include but not limited to data collection, storage, security, compliance to legal requirements, adherence to ethical requirements, sharing and access.
- 24.5 If samples will not be stored in South Africa, a separate motivation is needed explaining the reasons why it is not possible and a draft MTA for consideration by the HREC must accompany the application. Once Ethics approval for this aspect has been obtained, it will be the responsibility of the Researcher to ensure that he/she, obtains an export permit from the National Department of Health(if applicable) before the biological samples are sent out of South Africa.

A copy of the export permit or proof of exemption therefrom must be submitted to the Ethics Office for record purposes. Research participants must provide consent for export of samples.

- 24.6 A researcher must not transfer genetic material and related information to another research group unless there is a formal collaboration that has been approved by a HREC, a Material Transfer Agreement has been signed by the appropriate authorities, and the genetic material and information is transferred in a form that ensures participants cannot be identified.

## **25. BENEFIT SHARING**

Regarding benefit sharing in research, please consider the following:

- 25.1 Could the proposed research result in downstream commercialisation / commercial exploitation (for example, biomarker research could form the basis of / result in the creation of diagnostic products)?
- 25.2 If so, does the protocol mention a benefit sharing plan for the study participant, host community, or country / region? In particular, does the protocol or accompanying supporting documents (such as a Material Transfer Agreement, Commercialisation Plan, or Benefit Sharing Plan) ensure that any / all of the above parties receives an equitable share of the benefits that arise from arising intellectual property or subsequent use / commercialisation of the samples or products, or the rights in those samples or products by the researcher, sponsor, third party (for example, a collaborator who may be granted access to those samples) and any subsequent parties. Such benefit can take the form of monetary compensation, post-trial access to the product for the participant and host community, sponsored universal access to the product for the host country, or royalty-free licence for the host country / region to use the invention / product. In some instances, where research is publicly funded (for example, NIH, SAMRC, etc.), such benefits may accrue automatically. Funders such as the Gates Foundation may also impose a Global Access Plan as a condition of funding, which allows for global benefit sharing.
- 25.3 If a participant is asked to waive their rights to any potential future commercial benefits, is the waiver request justified in the protocol? Is the host country assured of royalty-free access to any downstream invention? Is the waiver covered / mitigated by a funder-imposed Global Access Plan or equivalent (for example, publicly funded research may be governed by statute, which obliged public benefit accrual)?

## **26. MULTICENTRE RESEARCH AND HYBRID UNIT RESEARCH**

- 26.1 If research is conducted at more than two sites in South Africa, with the PI and Co-PIs from different institutions resulting in the involvement of more than two registered RECs, one REC may be designated the Committee of Record for that study. The RECs must be in agreement upfront. This will be determined on a case by case basis.
- 26.2 Hybrid units should obtain approval from one of the two institutions' registered HREC, informed by the institutional location of the Principal Investigator and project funding. In the case of protocols that have a social sciences or humanities focus, these need to be submitted to the relevant HREC.

## **27. PUBLICATION OF RESULTS**

- 27.1 Investigators have an obligation to disseminate research results, whether positive or negative, in a timely and competent manner. This is particularly important in clinical trials, where investigators are duty bound to ensure that findings are made public for all outcomes assessed. It is, however, important that the release of research findings be done in an ethical manner, to ensure that false expectations are not raised in a vulnerable population. Research results should not be prematurely released or published, or unreasonably delayed. It is advisable that the main results should be disseminated, using appropriate communication formats, to the participants and other interested members of the communities in which the study was conducted.
- 27.2 Results of a study, whether sponsored by government or industry, should be the intellectual property of the investigators, not the sponsor, and all results that have scientific merit should be published. Local investigators must have access to data as part of the protocol agreement. Requests to withhold findings, to change or tone down the content of a report are not acceptable in good ethics practice. However, sponsors or stakeholders should be afforded the opportunity to comment on research findings prior to publication, without any entitlement to veto, change the conclusions, or unreasonably delay publication of results. In collaborative research with pharmaceutical or other companies, the conditions of publication should be spelt out clearly in the protocol. The Committee should be satisfied that there is no interference with the right to publish results. Participants should always receive the results prior to the public release.

## **28. PRESS RELEASES**

28.1 Investigators have an obligation to communicate research results during press releases in an ethically responsible manner. Investigators should consult with the SAMRC Corporate Communications Department and adhere to all related policies. .

## **29. ADVERTISEMENTS**

29.1 Advertisements for recruitment purposes must be submitted to the Committee for review and approval and should comply with the following guidelines:

- The advertisement should be in line with the NHREC template for advertisements.
- The name of the medical practitioner should not appear in the advertisement for study participants, but the particulars of an independent contact person should be given.
- The advertisement may be published in any medium, printed or electronic, including the internet and television, provided all the rules pertaining to advertisements as laid down in this document are adhered to.
- There are no limitations on the size or number of times a notice may be published.
- Details of the clinical research may be published e.g. "A phase II clinical trial in hypertension".
- Purpose of the research and a summary of eligibility criteria.
- Straightforward and truthful description of the benefits to the subject, if any.
- Direct mailing of advertisements is permissible.
- Bulk distribution is not permissible.
- Advertisements may be made available for issue individually to existing patients at the rooms of health care professionals and also at local information centres.

## **30. EPIDEMIOLOGICAL RESEARCH**

30.1 All epidemiological research must be approved by the Committee and should be conducted according to written protocols that state the aims of the study, the data that is required and how the data will be collected, used and protected.

30.2 When the Committee considers a protocol for epidemiological research, it must be satisfied that:

- Relevant South Africa legislation and approved policies dealing with the privacy and confidentiality of data and the protection of personal information including but not limited to the provisions contained in the Protection of Personal Information Act (No 4 of 2013) will be complied with.
- Researchers have the necessary facilities and skills in epidemiology to conduct the research.
- Permission should be obtained from principal investigators or custodians of primary data if further research is to be conducted on that data.
- Access to medical or other records for research should be obtained from the custodian of the data according to Promotion of Access to Information Act (Act 2 of 2000).
- There is a scientifically acceptable process for the disclosure of information and dissemination of research results and, where there is to be selective disclosure of information, that there are scientifically justifiable reasons for doing so.

30.3 Informed consent of participants should be obtained for the use of identified or potentially identifiable data for all epidemiological research.

## **31. INSURANCE**

31.1 In respect of all clinical trials and where relevant, the following statements must be added to informed consent forms:

31.1.1 Insurance for the study provided by the sponsor:

If you fall ill, suffer any side effects or if you are injured in any study related manner, contact the investigator/researcher immediately. The sponsor of this study has taken out the necessary insurance to cover you as a research participant for bodily injuries sustain as a result of the clinical trial. This study is covered by (please indicate the name of the insurance company as well as the policy number).

31.1.2 Insurance for the study provided by the South African Medical Research Council (SAMRC)

If you fall ill, suffer any side effects or if you are injured in any study related manner, contact the investigator/researcher immediately. The SAMRC, as sponsor of this study, has taken out the necessary insurance to cover you as a research participant for bodily

injuries sustain as a result of the clinical trial. This study is covered by (please indicate the name of the insurance company as well as the policy number).

## 32. COMPLIANCE WITH APPLICABLE LAWS, PRINCIPLES AND GUIDELINES

32.1 The Committee, in granting its approval is in compliance with, and must be satisfied that the protocol conforms to the spirit of the following guidelines:

- The World Medical Association Declaration of Helsinki, 2013
- South African Constitution, 1996 (Act No.108 of 1996)
- National Health Act, 2003 (Act 61 of 2003)
- Department of Health: *Ethics in Health Research: Principles, Processes and Structures*, Second Edition, 2015
- Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa, 2006
- ICH GCP Guidelines E6(R2) 2016
- Council for International Organisations of Medical Sciences (CIOMS): International Ethical Guidelines for Health-related Research Involving Human, 2016
- The Association of the British Pharmaceutical Industry (ABPI) Compensation Guidelines
- FDA Code of Federal Regulations Parts 50, 56 & 312

**Level:** 3  
**Risk:** Strategic  
**Effective Date:** 1 February 2023  
**Review Date:** January 2026  
**Standard Operating Procedures Owner:** Chief Research Operations Officer  
**Policy Manager / Cognisant Person:** Research Integrity Officer  
**EMC Approval**

### Confirmation of Approval



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**Prof Glenda Gray**  
**President & CEO**

26 January 2023

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**Date**