

**HOSPICE PALLIATIVE CARE ASSOCIATION
OF SOUTH AFRICA : (HPCA)**

RESEARCH ETHICS COMMITTEE

(Registration no. : REC-250408-005)

STANDARD OPERATING PROCEDURES

- 1 Research Ethics Committee (REC)
 - 1.1 Meetings will be scheduled to be held at least quarterly by teleconference or face-to-face. Members will be notified of the scheduled dates no later than the second week of January.
 - 1.2 Minutes of meetings will be circulated to members within 14 days after the meeting.
 - 1.3 The agenda for scheduled meetings will be circulated to members at least 14 days prior to the meeting.
- 2 Composition of the REC will be in accordance with the Department of Health – Republic of South Africa : Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.

Members of the REC should collectively have the qualifications, experience and expertise to review and evaluate the scientific, medical and ethical aspects of research proposals.

Ideally, the REC should be representative of the communities they serve and reflect the demographic profile of the South African population.

Ideally, not more than 70% of the REC should be of one gender only.

Appointment on to the Committee will be by nomination and co-option. The total number of Committee members will be at least 9 as per DoH guidelines. Members will be required to have continuous personal development in research ethics.

- 2.1 Membership
 - (i) Chairperson;
 - (ii) Two Deputy Chairs;

- (iii) At least two laypersons with: -
no affiliations with the institution;
not currently involved in medical, scientific or legal work;
should preferably be from the community.
- (iv) At least one member with knowledge of and current experience in research areas that are regularly considered by the REC;
- (v) At least one member with knowledge of and current experience in professional care, counselling or treatment (e.g. General Practitioner, Psychologist, Social Worker, Nurse);
- (vi) At least one member who is legally trained.

2.2 Quorum / Voting:

The Committee will make its decisions at announced meetings at which at least a quorum of 60% is present. Scheduled meetings will only be conducted when a quorum is present. Co-opted members are included in the decision on the quorum. Decisions will be determined by consensus (general agreement). Where general agreement does not exist, consensus will be undermined and the decision will be arrived at by vote.

2.3 Compliance

The REC functions in compliance with, but not limited to the Department of Health – Republic of South Africa : Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa, Declaration of Helsinki, The Belmont Report, the Office of Human Research Protections 45 CFR 46, 21 CFR 50, 21 CFR 56, CIOMS, ICH-GCP-E6 Sections 1-4 and the International Conference on Harmonisation and Technical Requirements for Registration of Pharmaceuticals for Human Use i.e. the ICH Tripartite.

When strict compliance with the letter of a particular requirement of these Declarations and Codes is not possible, the Committee will ensure that the proposed research is none-the-less in keeping with the spirit of the Declarations and Codes.

3 REVIEW PROCESS

- 3.1 All researchers submitting protocols for ethics review will be registered with the Health Professions Council of South Africa (HPCSA) or any other statutory health council in South Africa as appropriate. For non-South African citizens who are students, proof of registration to an equivalent body in their home country and in South Africa will be necessary.
- 3.2 All collaborative research will have a local Principal Investigator.
- 3.3 Studies that have a substantive clinical component, and the Principal Investigator is not a clinician, a Co-Investigator, registered with the HPCSA, must be appointed to the study.
- 3.4 The Committee will obtain the following document/s from the researcher:
 - Trial/study protocol(s)
 - Written informed consent form(s)
 - Participant recruitment procedures

- Written information to be provided to participants
- Researcher's brochure (IB) (if applicable)
- Safety information (if applicable)
- Researcher's current curriculum vitae and / or other documentation evidencing qualifications
- Any other documentation that the Committee may require to fulfil its responsibilities

Further documentation may be required after initial ethics approval has been granted such as Data Safety Monitoring Boards (DSMBs) reports or other monitoring Committee / Board reports; updated documentation where applicable.

3.5 The review process will be:

1 week for the administrative process

3 weeks for Committee review. A reviewer will, at the REC meeting give a synopsis of the study together with the positive and negative aspects of the proposed research.

Hence, a protocol that is ethically and scientifically sound will have a review time of 30 days. Committee members who, for any reason, are unable to attend the forthcoming meeting will inform the Ethics Administrator at least 3 weeks before the meeting.

Protocols need to be submitted by the 7th of each month and will be reviewed either at a face-to-face meeting or if this is not possible, via teleconferencing on the last Tuesday of each month.

4.0 The Committee's review of a protocol will lead to

- approval
- approval conditional to modifications required by the Committee
- rejection

4.1 The Committee must document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

- approval;
- modifications required prior to its approval;
- rejection; and
- termination or suspension of any prior approval.

The Chair will inform the researcher in writing of the Committee decision.

4.2 The Committee will conduct continuing review of each ongoing study at intervals appropriate to the degree of risk to human participants, but at least once per year. (Appendix C).

4.3 Should changes in circumstances make it necessary, the Committee may at any time withdraw approval of a protocol previously approved by it.

4.4 Sub-Committee decisions may be implemented from the date of the sub-Committee review. All sub-Committee decisions will be taken to the monthly Research Ethics Committee meeting for ratification.

- 5.0 The Committee has the responsibility of ensuring that the proposed research is scientifically valid. (Patients and volunteers may not, ethically, be asked to accept risk or discomfort arising from a project that is not scientifically valid). This requirement includes ensuring that the researcher/s is/are suitably qualified to undertake the research.
- 6.0 The Committee, in reviewing a protocol, has regard to any and all factors that may influence the ethical acceptability of the protocol.
- 7.0 All participants of a proposed research project must be given the fullest information regarding the purpose of the research, the procedures that will be involved, the expected or possible benefits to the participant and/or to the community and the risks and/or discomforts that will be experienced by the participant, as well as any other facts that could influence the participant's decision to consent to participate.
- 7.1 The participant must, having been fully informed, be asked to give his/her free and un-coerced consent to inclusion in the study. Where a relationship of dependence exists between participant and researcher (e.g. doctor/patient relationship) consent should be obtained by an independent person. The participant must understand that refusal to participate will not entail any adverse consequences for the participant, such as reduction in the level of care offered to the participant. The Committee must ensure that inappropriate or undue inducements to consent, financial or other, are not offered to the participant.
- 8.0 Where the protocol indicates that prior consent of the trial participant or the participant's legally acceptable representative is not possible, the Committee must determine that the proposed protocol and/or other document(s) adequately address/es relevant ethical concerns and meets applicable regulatory requirements for such trials.
- 9.0 The Committee must be fully informed regarding the degree of risk and/or discomfort that patients/volunteers will undergo.
- 9.1 The Committee must ensure that, where a research protocol involves significant risk or discomfort to participants, no feasible alternative exists that could provide the answer sought.
- 9.2 The Committee must satisfy itself that there is an acceptable balance between the risk/discomfort that the participant is asked to undergo, and the benefit that is expected to result from the research.
- 9.3 The Committee must ensure that patients are not deprived of recognised benefits as a result of being included in the "placebo" arm of a trial.
- 9.4 The Committee must be informed of the benefits that may be expected to result from the research, including
- potential benefits to participating participants.
 - anticipated benefit to categories of individuals (e.g. sufferers from particular diseases).
 - anticipated benefit to society and/or particular communities.
- 10.0 The Committee must review the amount and method of compensation to participants to assure that neither presents a problem of coercion or undue

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

- 10.1 The Committee must ensure that information regarding compensation to participants, including the methods, amounts and schedule of payment to trial participants is included in the written informed consent form and any other written information that is provided to participants. The way in which compensation will be prorated must be specified.
- 10.2 The Committee must satisfy itself that, where substantial expenditure of public (i.e. the Community's) funds will be incurred, the importance and potential benefit of the research will be proportionate.
- 11.0 The Committee must ensure that absolute confidentiality regarding the identity of participants of research is maintained at all stages of the research, and particularly in regard to published results of research.

12.0 Research involving children:

“Child” is defined as someone younger than 18 years in the Bill of Rights of the Constitution of SA.

Research in children should be undertaken only when the research cannot be carried out equally well on adults, and the research question will not be answered using adult participants. The purpose of the research will be to obtain knowledge relevant to the health needs of children.

Research involving children will have to be in conformity with the ethical and legal doctrines of informed consent.

- 13.0 The Committee must ensure that, particularly in regard to research involving communities, those communities' traditions and values are respected, particularly in regard to the obtaining of consent to participation in the research. However, "blanket" consent given by a community's leaders must never absolve the researcher from also obtaining the fully informed consent of the individual participant.
- 14.0 The Committee must ensure that all co-professionals who are actively involved in the care of participants of research, particularly nurses, are fully informed of the nature and purpose of the research.

15 MODUS OPERANDI

- 15.1 In addition to the researcher's protocol and brochure (if such exists) the researcher must complete a detailed ethics application protocol produced by the Committee, which is designed to allow evaluation of all aspects of the ethical acceptability of the proposal. Any member of the Committee may study the detailed original protocol of the research proposal, if he/she should feel this to be necessary, in addition to examination of the ethics application protocol. A separate, abridged application form is to be used where expedited review is requested.
- 15.2 All researchers are required to submit annual progress reports for purposes of recertification. In special circumstances, more frequent reports may be called for.

- 15.4 Any proposed modification of a project already approved must be submitted to the Committee for further approval.
- 15.5 Reports on serious adverse events (SAE) should be reported within 7 days of the occurrence for local sites, one month for all South African sites and all SAEs worldwide should to be reported on a 6 monthly basis.
- 16.0 RESEARCH MISCONDUCT
- 16.1 Research misconduct encompasses inter alia :
- Fabrication, falsification, plagiarism in proposing, performing, reviewing or reporting research.
 - Deviation from or failure to adhere to the proposed protocol without proper permission from the REC (protocol violation)
 - Misrepresentation
 - Falsification of credentials
 - Deception in the research proposal
 - Deception in the carrying out of research
 - Piracy of materials
 - Failure of Informed Consent
 - Breaches of confidentiality
- 16.2 Incidents of research misconduct will be managed in accordance with the procedures contained in the HPCA Code of Ethics.
- 16.3 The identity of the individual who raises awareness of a protocol violation will be protected and will be made known to the Chair of the REC only. The report on the violation will however be discussed at a full sitting of the REC.
- 17.0 The Committee will perform its functions according to these written Standard Operating Procedures (SOPs), will maintain written records of its activities and Minutes of its meetings and will comply with GCP and the applicable regulatory requirements.
- 18.0 Ethical review will be done in compliance with the Regulatory Authority checklist as outlined in Appendix B.
- 19.0 The researcher may be called upon to provide information on any aspect of the study but may not participate in the deliberations of the Committee or in the vote / opinion of the Committee.
- 19.1 The Committee may consult with and/or invite non-members with expertise in special areas to their meetings.

- 20.0 The REC reserves the right to develop policy documents to cater for any complexity in ethics issues as they develop.
- 21.0 This document will be reviewed and updated annually.

APPENDIX A

DEFINITION VULNERABLE COMMUNITIES - UNAIDS AND DOH

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.

(In accordance with the Department of Health : Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa)

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)¹

The contents of a trial protocol should generally include the following topics. However, site-specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol-referenced documents, such as an Investigator's Brochure.

General Information

- Protocol title, protocol identifying number, and date. Any amendment(s).
- Should also bear the amendment number(s) and date(s).
- Name and address of the sponsor and monitor (if other than the sponsor).
- Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and the address and telephone number(s) of the trial site(s)
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and addressees) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.
- Written curriculum vitae of principal investigator, co-investigators and other persons designated by the principal investigator to be responsible for some aspects of the study.

2. Background Information

- Name and description of the investigational product(s).
- A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
- Summary of the known and potential risks and benefits, if any, to human participants.
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- Description of the population to be studied.
- References to literature and data that are relevant to the trial, and that provide background for the trial².

¹SOURCE: ICH Guidelines for Good Clinical Practice

²**Systematic Review:** The research protocol should demonstrate knowledge of relevant literature and wherever possible be based on prior laboratory and animal experiments. Investigators do not always take into proper account the results of existing research when planning new clinical trials. This constitutes unethical practice for several reasons. Firstly, if existing evidence is available that an active form of care is better than placebo, further placebo controlled research denies some patients effective treatment. Such research should only be considered where there is a need to evaluate additional important outcomes, including adverse effects. Secondly, failing to take into account evidence that a treatment is ineffective, or that it does more harm than good, inevitably exposes patients to inconvenience or unnecessary risk. Thirdly, conducting trials that address previously answered questions wastes limited resources.

Systematic review has evolved over the past decade as a rigorous methodology for synthesising the results of primary research. The process involves identification, appraisal and integration of the findings of

published and unpublished studies, with the aim of drawing conclusions from the totality of relevant evidence. All ethics committees must therefore:

- Insist on a well-conducted systematic review of relevant existing research as a precondition for approving new research.
- The review should provide convincing evidence that proposed research is necessary, that it will not expose patients to unacceptable risks or practices, and that it will not withhold care that is known to be effective.
- Require that investigators make available to potential trial participants a summary of the findings of the systematic review before requesting their consent. Both the possible benefits and the risks of treatment should be clearly stated.
- Help to minimise bias resulting from non-publication of negative studies by
 - (a) ensuring registration of clinical trials at inception and
 - (b) requiring a written commitment from investigators to publish the results of trials.

3. Trial Objectives and Purpose

- A detailed description of the objectives and the purpose of the trial.

4. Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

- A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- A description of the measures taken to minimize/avoid bias, including:
 - (a) Randomization.
 - (b) Blinding.
- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
- The expected duration of participant participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- Maintenance of trial treatment randomization codes and procedures for breaking codes.
- The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

5. Selection and Withdrawal of Participants

- Participant inclusion criteria.
- Participant exclusion criteria.
- Participant withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
 - (a) When and how to withdraw participants from the trial/investigational product treatment.
 - (b) The type and timing of the data to be collected for withdrawn participants.
 - (c) Whether and how participants are to be replaced.
 - (d) The follow-up for participants withdrawn from investigational product treatment/trial treatment.

6. Treatment of Participants

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial.
- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- Procedures for monitoring participant compliance.

7. Assessment of Efficacy

- Specification of the efficacy parameters.
- Methods and timing for assessing, recording, and analysing of efficacy parameters.

8. Assessment of Safety

- Specification of safety parameters.
- The methods and timing for assessing, recording, and analysing safety parameters.
- Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
- The type and duration of the follow-up of participants after adverse events.
- Procedures for unmasking the identity of treatment.

9. Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
- The number of participants planned to be enrolled. In multicentre trials, the numbers of enrolled participants projected for each trial site should be specified.
- Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- The level of significance to be used.
- Criteria for the termination of the trial.
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- The selection of participants to be included in the analyses (e.g. all randomized participants, all dosed participants, all eligible participants, valuable participants).

10. Direct Access to Source Data/Documents

- The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, ethics committee review, and regulatory inspection(s), providing direct access to source data/documents.

11. Quality Control and Quality Assurance

12. Ethics

- Description of ethical considerations relating to the trial.

13. Data Handling and Record Keeping

14. Financing and Insurance

- Financing and insurance if not addressed in a separate agreement.

15. Publication Policy

- Publication policy, if not addressed in a separate agreement.

The approval process includes ratification by a full sitting of the HPCA REC

CONTINUING REVIEW PROCESS (Adopted from OHRP *Guidance on Continuing Review - July 11 2000*)

FULL REVIEW

For continuing review to be credible, it must be substantive and meaningful.

Continuing review by the convened HPCA REC with recorded votes on each study is required unless the research is otherwise appropriate for expedited review (see below). The procedures for continuing review may include a primary reviewer system.

The criteria to be satisfied at initial review in order for the HPCA REC to approve research have to be satisfied at continuing review as well. These criteria include among others, determinations by the HPCA REC regarding risks, potential benefits, informed consent and safeguards for human participants.

Members should at least receive and review a protocol summary and a status report on the progress of the research, including:

- The number of participants accrued;
- A summary of adverse events and any unanticipated problems involving risks to participants or others and any withdrawal of participants from the research or complaints about the research since the last HPCA REC review;
- A summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review;
- Any relevant multi-centre trial reports;
- Any other relevant information, especially information about risks associated with research; and
- A copy of the current informed consent document and any newly proposed consent document.

At least one member of the HPCA REC (primary reviewer) should also receive a copy of the complete protocol including any modifications previously approved by the HPCA REC. Furthermore, upon request, HPCA REC members should also have access to the complete HPCA REC protocol file and relevant HPCA REC Minutes prior to or during the convened HPCA REC meeting.

When reviewing the current informed consent documents the following should be ensured:

- The currently approved or proposed informed consent document is still accurate and complete;
- Any significant new findings that may relate to the participants' willingness to continue participation, are provided to the participant.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the HPCA REC, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

EXPEDITED REVIEW FOR CONTINUING REVIEW

This is limited to specific research categories, and to the review of minor changes in previously approved research during the period (of one year or less) for which approval is authorised.

An expedited review procedure may be used for the continuing review of research previously approved by the convened HPCA REC as follows:

(a) Where:

the research is permanently closed to the enrolment of new participants;
all participants have completed all research related interventions; and
the research remains active only for the long-term follow-up of the participants;

OR

(b) Where no participants have been enrolled and no additional risks have been identified;

OR

(c) Where the remaining research activities are limited to data analysis.

DATING OF CONTINUING REVIEW

The HPCA REC should decide the frequency of continuing review for each study protocol necessary to ensure the continued protection of the rights and welfare of research participants, to be done either on a bi-annual or annual basis.