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THE SOUTH AFRICAN MEDICAL ASSOCIATION RESEARCH ETHICS COMMITTEE

(SAMAREC)

STANDARD OPERATING PROCEDURES AND GUIDELINES FOR THE ETHICS EVALUATION OF CLINICAL TRIALS IN HUMANS

(UPDATED February 2015)

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STANDARD OPERATING PROCEDURES AND GUIDELINES FOR THE ETHICS EVALUATION OF CLINICAL TRIALS

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A. DEFINITIONS AND INTERPRETATIONS

In this document, unless the contents otherwise requires:

1. **Doctor** refers to a medical practitioner (or dentist, when appropriate), as defined in terms of the Health Professions Act, no. 56 of 1974 (as amended),

2. **Study doctor** refers to a doctor (or dentist, when appropriate), participating in the clinical trial / study. The words **study investigator, investigator, sub-investigator, co-investigator, trialist or researcher** may be used interchangeably, as long as the person is a clinician, where applicable. Whichever term is used, it must be used consistently throughout the documents.

3. **Principal Investigator** is a person responsible for the conduct of the clinical trial at a trial site.

4. **Associate Investigator** refers to a member of the health care team involved for specific investigations which are required for the conduct of the clinical trial / study. This will be in accordance with their relevant field(s) of expertise and training e.g. ophthalmologist or psychologist responsible for specific aspects but not taking clinical responsibility as sub investigators for trial participants.

5. **Sub-Investigator** – any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions.

6. A **Clinical Trial** is a prospective biomedical or behavioural research study of human subjects that is designed to answer specific questions about biomedical or behavioural interventions (vaccines, drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

7. **Study Staff** collectively refers to the investigators, study coordinators, study nurses, pharmacists, raters, and any other people rendering support to the investigator

8. **Study site** is the location(s) where trial-related activities are actually conducted.

9. **Participant** means the person participating in the clinical trial / study and/or receiving treatment, including receiving blood or blood products, or using a health facility or establishment, as a result of participation in the clinical trial / study. The words **research participant or participant** may be used interchangeably, where applicable.
   Where the participant is a patient with a clinical condition, the word "patient" should be used. (**"Research subject", may be used but is not SAMREC preferred wording.)**

10. **Research** means the creation, preservation, accumulation and improvement of knowledge by means of scientific investigations and methods in the field of the medical and related sciences as well as those sciences the application of which is important for the promotion of health or the combating of disease, and includes the acquisition, development and transfer of expertise and technology. The word **researcher** shall have a corresponding meaning and the term experiment or, clinical trial may be used interchangeably with the word **research**, when applicable.

11. **Clinical Research** is usually conducted with patients in a medical setting (e.g. hospital, clinical or private consulting rooms) to obtain information on the natural history or pathogenesis of a

condition that could assist with improving strategies for diagnosis, treatment or prevention of disease.

12. Any reference to the singular includes the plural and vice versa;

13. Any reference to natural persons includes legal persons and vice versa;

14. Any reference to a gender includes the other gender;

15. The clause headings in the Standard Operating Procedures have been inserted for convenience only and shall not be taken into account in interpreting this SOP.

16. '**Physician**' means – a medical practitioner registered as a specialist in internal medicine and this should not be used as an alternative term when referring to a family doctor/ general practitioner.

17. **Amendments –** if required to be changed in the PID to be forwarded to SAMAREC in the most recently approved PID of SAMAREC. All changes must be indicated with track changes (colour/highlighted).

18. **Witness** is someone who witnesses the signing by the participant and not the consent procedure. However, when the participant is illiterate the meaning of witness changes and it means someone who witnesses the consent procedure.

B. PART ONE: INTRODUCING SAMAREC

1. LEGISLATIVE FRAMEWORK

National Health Act

The South African Medical Association Research Ethics Committee (SAMAREC) was established by the SA Medical Association (SAMA) in 1992 to evaluate the ethics of research protocols developed for clinical trials to be conducted in the private healthcare sector. In terms of national and international regulatory requirements, all health research involving human participants must undergo an independent ethics review. The National Health Act, 61 of 2003, as amended, (NHA), provides for the establishment of a National Health Research Ethics Council (NHREC) with which all research ethics committees are required to be registered. SAMAREC is registered on the Department of Health (DOH) National Research Ethics Council database.

The main responsibility of SAMAREC is to ensure the protection and respect of the rights, safety and well-being of participants involved in clinical trials and to provide assurance to the public of that protection, *inter alia,* by reviewing, approving and providing comment on clinical trial protocols, the suitability of investigator(s), facilities, methods and procedures used to obtain informed consent. The Bill of Rights which is entrenched in the Constitution of South Africa provides that everyone has the right not to be subjected to medical or scientific experiments/research without their informed consent.

In terms of the NHA "clinical trials" means a systematic study, involving human participants that aims to answer specific questions about the safety or efficacy of a medicine or method of treatment.

Research can be broadly classified as therapeutic and non-therapeutic. Therapeutic research is a clinical investigation designed to determine the efficacy and safety of a therapeutic or diagnostic method. The interventions are not applied solely to enhance the well-being of the individual participant.

The objective of therapeutic research is to increase general knowledge (i.e., test a hypothesis and draw conclusions) and at the same time provide the patient with a needed health benefit. Accordingly, the duties of the study doctors are to take into consideration the fact that the patient is also a research participant.

In contrast to therapeutic research, non-therapeutic research is an investigation that has no intent of producing a diagnostic, preventive, or therapeutic benefit to the research participant, who is usually healthy and is not seeking nor expecting a health benefit from the research.

In the execution of its responsibilities in evaluating the ethics of research protocols, SAMAREC is guided by the relevant South African law, research and ethics guidelines, professional standards, international standards and guidelines and codes of practice.

The NHA provides that health research ethics committees (RECs) must be established by every institution, health agency and health establishment at which health research is conducted, or they must have access to a health research ethics committee, which is registered with the National Health Research Ethics Council.

"The NHA further provides that a health research ethics committee must-

(a) review research proposals and protocols in order to ensure that research conducted by the relevant institution, agency or establishment will promote health, contribute to the prevention of communicable or non-communicable diseases or disability or result in cures for communicable or non-communicable; and

(b) grant approval for research by the relevant institution, agency or establishment in instances where research proposals and protocol meet the ethical standards of that health research ethics committee."

*The **National Health Research Ethics Council** was established by the Minister of Health after consultation with the National Health Council. The Minister appoints as members of the NHREC not more than 15 persons nominated by interested parties at the invitation of the Minister by notice in the Government Gazette.*

In terms of the NHA the National Health Research Ethics Council must:-

(a) determine guidelines for the functioning of health research ethics committees;

(b) register and audit health research ethics committees;

(c) set norms and standards for conducting research on humans and animals, including norms and standards for conducting clinical trials;

(d) adjudicate complaints about the functioning of health research ethics committees and hear any complaint by a researcher who believes that he or she has been discriminated against by a health research ethics committee;

(e) refer to the relevant statutory health professional council matters involving the violation or potential violation of an ethical or professional rule by a healthcare provider;

(f) institute such disciplinary action as may be prescribed against any person found to be in violation of any norms and standards, or guidelines, set for the conducting of research in terms of this Act;

(g) advise the national department and provincial departments on any ethical issues concerning research."

According to the Guidelines for Ethics in Health Research, published by the Department of Health, ethics review provides an objective appraisal of the research proposal as it affects the prospective participants and the general day to day functioning of the health system.

In March 2002, SAMAREC became a registered Research Ethics Committee at the Department of Health and Human Services (DHHS) of the USA.
(REC: 0000 2235)

In May 2002, Federal Wide Assurance was also obtained from the Office of Human Research Protection (Office of Human Research Protection-Group) of the USA.
(FWA: 0000 2567)

American Food & Drug Administration (FDA) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Guidelines for Good Clinical Practice

SAMAREC follows the standards adopted by the latest version of the FDA and ICH Guidelines for Good Clinical Practice; and conforms to the guidelines laid down by the World Medical

Association, in particular, the Declaration of Helsinki, the Belmont Report, the National Department of Health, the South African Medicines Control Council (MCC) and other relevant statutory bodies involved in the healthcare sector.

A REC should consider the following issues when reviewing a proposal for a clinical study:

- the scientific relevance of the clinical study;
- the suitability of the investigator(s) for the proposed study in terms of his/her availability, qualifications, experience, supporting staff, and available facilities;
- the relevance of the study rationale and the appropriateness of the inclusion / exclusion criteria to the South African context;
- the suitability of the study application in relation to the objectives of the study; i.e. the potential for reaching sound conclusions with the smallest possible exposure to risk of participants, and the justification of predictable risks and **inconveniences** weighed against the anticipated benefits for the participants and/or others;
- the suitability of the study population, whether they constitute a vulnerable group, if so whether justified and whether sufficient measures to protect their interest are in place;
- that the number of participants to be recruited is adequate to demonstrate the predicted effect;
- the risk-benefit analysis takes full cognisance of benefits and harms beyond the life of the study itself, particularly in relation to chronic life-threatening conditions;
- if placebos are to be used, whether their use can be justified;
- that by their participation in a clinical study the participants are not denied timely access to medical personnel, investigations, equipment or procedures;
- The means by which initial recruitment is to be conducted and by which full information is to be given and how informed consent is to be obtained.
- The adequacy and completeness of the written information to be given to the participants, their relatives, guardians and, if necessary, legal representatives. All written information for the participant and/or legal representative must be submitted in its final form;
- that the application allows the participants and/or their representatives adequate time to consider the patient information document before informed consent is sought;
- the content of any advertisements or public notices which will be used to recruit participants to a study;
- the study protects participants' rights to privacy and confidentiality;
- the provision of compensation/treatment in the case of injury or death of a participant if attributable to a clinical study, and the insurance or indemnity to cover the liability of the investigator and sponsor;
- the extent to which investigator(s) and participants are to be compensated for participation in the study;
- making specific recommendations regarding the continuation of treatments beyond the duration of the study, or mechanisms to ensure that participants' access to treatment are fairly protected and not unduly compromised;
- the demographic information available to assess whether the patient population is adequate to support the study;
- whether there is no cost to the participant, medical schemes or insurance for trial specific procedures;
- whether the product will be made available to participants after the trial ends, and if so whether there is any cost to the participant to continue treatment post-trial;
- whether any restrictions will be placed on the publication of results by the investigators after completion of the trial;

- the adequacy of the statistical methods proposed to evaluate the data generated; and whether the study is advancing knowledge in the research field.

SAMAREC reviews health research involving human participants, prior to initiation of such research and focuses on the ethical implications relating to the clinical research. Ensuring protection of the rights and welfare of the participants is the Committee's primary concern. Based on the above-mentioned standards and guidelines, SAMAREC will advise and make suggestions to study doctors and applicants, when requested.

2. COMPOSITION OF SAMAREC

Research ethics committees must consist of members who collectively have the qualifications and experience to review and evaluate the science, health and legal aspects, and ethics of proposed research. Committees must be independent, multi-disciplinary, multi-sectorial and pluralistic. The composition of SAMAREC complies with the prescriptions of the Department of Health Guidelines for Ethics in Health Research and consists of members as approved by the SAMA Board of Directors.

The current composition of SAMAREC is as per annexure 5

2.1 The SAMAREC Composition will be updated as and when changes occur.

2.2 The Committee may request other individuals to assist in the review of complex issues outside the expertise of the members, but such individuals may not vote on matters requiring a decision to be taken;

2.3 Curricula vitae of the Committee members and external experts (if applicable) are available on request.

3. CONTACT DETAILS

The SAMAREC Officer (co-ordinator) may be contacted at:

Telephone	:	(012) 481 2046
Fax	:	(012) 481 2095
Postal Address	:	P O Box 74789 Lynwood Ridge 0040
Physical Address	:	Castle Walk Office Park, Block F, Nossob Street Erasmuskloof Ext.3 Pretoria 0183
E-mail	:	samarec@samedical.org

4. FEES

Details of the fees charged by SAMAREC for evaluation of protocols appears on Annexure 7 hereto.

All applications should be accompanied by a proof of payment on submission. Applications without proof of payment will not be processed.–The specific protocol in respect of which payment is being made must be clearly indicated on the proof of payment.

The amount can be deposited or transferred electronically into the bank account of the SA Medical Association at Nedbank, Account Number: 1602237387, Branch Code: 160245, Current Account, Reference Number: (Insert Protocol Number or Invoice Number). The deposit slips should be e-mailed for the attention of the SAMAREC Co-coordinator at **samarec@samedical.org**.

No refunds will be given should the protocol, once evaluated, not be approved. Administrative changes, report-back and adverse event reports will not be charged for. Major and minor amendments to a protocol, an application for continuing review and additional sites will attract an additional fee as per Annexure 7.

C PART TWO

PROCEDURES AND ADMINISTRATIVE GUIDELINES

1. MEETINGS

- SAMAREC meets on the second Wednesday of each month, unless circumstances require otherwise.
- Applications for consideration must be submitted to the SAMAREC Co-ordinator at the offices of the South African Medical Association at least one month before the next scheduled meeting.
- Agendas for the meetings are prepared by the Committee Co-ordinator in consultation with the Chairperson and circulated, together with all applications and other supporting documents, as well as a protocol evaluation form for each application, to members before meetings.
- A written response regarding decisions is usually forwarded to applicants within 10 working days after the meeting.
- 60% of the Committee constitutes a quorum.
- Confidentiality of the content of applications, the protocols and the procedures of SAMAREC, is maintained as far as is reasonably possible.

(A list of the scheduled meetings for the current year is annexed as Annexure 1)

2. SUBMISSION OF RESEARCH PROTOCOLS

All submissions to SAMAREC should be done electronically (via e-mail, on a CD or a memory stick).

For new applications, the following documents relevant to the proposed study need to be submitted: -

- Covering letter
- Protocol summary/synopsis
- Covering letter
- Protocol
- SAMAREC Checklist (attached as Annexure 2)
- Patient Information and Informed Consent Document (PID) (pro forma attached as Annexure 4)
- Investigator's Brochure
- Letters of information,
- Questionnaires (if any)
- Copy of the insurance certificate
- MCC approval or notification or letter of submission
- Proof of NHREC registration
- Details and breakdown of financial arrangements with study doctors, and
- Information pertaining to patient recruitment e.g. advertisements, bulletins and information placed on the Internet. (Guidelines attached as Annexure 6)
- Justification for the use of a placebo
- Curricula Vitae of all study personnel according to the Medicines Control Council (MCC) format (as a minimum format / requirement) copy of format attached as Annexure 3)
- Declarations by Trialists

- Proof of personal malpractice indemnity cover of study doctors, nurses and pharmacists
- GCP certificates
- Dispensing licence (if applicable)

All documentation should be properly indexed, with the protocol number clearly visible on all the sections of each document. All relevant attachments with regard to the study staff **should be put together per person**, i.e. CV, Declaration, HPCSA / SANC Registration, Malpractice Insurance, GCP Certificate, Dispensing Licence etc. The manual and computer filing systems of the SAMAREC are based on the protocol number and not the name of the drug involved.

3. COVERING LETTER

The covering letter must give a brief summary of the protocol and indicate the study doctor's assessment of any potential additional risk or discomfort to the participants. Only the names of investigators/sub-investigators and all study staff in the private healthcare sector, on behalf of whom the application is made, must be listed in the letter with an indication of their submitted documents (example attached as Annexure 9).

4. DECLARATIONS

Declarations by all study staff , must reflect the name of the sponsoring company, protocol number and title, as well as the study staff's name and designation (pro forma attached as Annexure 8) Declarations must be properly completed and signed

5. CURRICULUM VITAE

Although the Curriculum Vitae of all study personnel should be, as a minimum requirement, according to the MCC format, the format shown in Annexure 3 would be preferred when submitting protocols to SAMAREC for evaluation.

The approval criteria for Principal Investigators are:

- must be a suitably qualified health care professional ;
- must have participated in two completed trials as Sub-Investigator;
- must have proof of valid GCP training in the last 3 years; and
- The trial must be within the Principal Investigator's scope of practice.
- Note the Specialist Regulations of the HPCSA, states that:
  "A medical practitioner or a dentist who holds registration as a specialist in terms of the Act, shall -
  (a) in the case of a speciality, confine his or her practice to the speciality or related specialities in which he or she is registered;
  (b) in the case of a sub-speciality, confine his or her practice mainly to the sub-speciality in which he or she is registered."

The approval criteria for Sub-Investigators are:

- must be suitably qualified health care professional such as a qualified medical doctor;
- must have proof of valid GCP training in the last 3 years or the intention to attend GCP training when required by the nature of the study/trial ; Proof of completion thereof must be submitted before commencing the trial (same for PI).

- if not previously involved in a trial, they should work under the supervision of the Principal Investigator; and
- the trial should be within the Sub-Investigator's scope of practice.
- Note, the Specialist Regulations of the HPCSA, states that,
  "A medical practitioner or a dentist who holds registration as a specialist in terms of the Act, shall -
  (a) in the case of a speciality, confine his or her practice to the speciality or related specialities in which he or she is registered;
  (b) in the case of a sub-speciality, confine his or her practice mainly to the sub-speciality in which he or she is registered."

6. MALPRACTICE INSURANCE

All healthcare professionals (psychologists, pharmacists, nurses or other health professionals) who are clinically involved with the participant must, at all times act within their specific Scope of Practice. They must also provide proof that they have adequate malpractice insurance; either independently, through a professional association (e.g. Denosa) or as an employee of a medical practice (i.e. named under the malpractice insurance of the relevant practice).

7. ABBREVIATIONS

Abbreviations may not be used without initially writing the words out in full with the appropriate abbreviation in brackets. Words need to be written out in full in the PID, in the first instance, even if abbreviated elsewhere in other documents included in the application for approval. Only South African English abbreviations for Standard International (SI) units must be used (e.g. ml not mL).

8. PUBLISHING OF RESULTS

In the interest of transparency, it is preferable that the Principal Investigator may independently publish his or her results, subject to internationally approved conditions. However, where this is not the case, the agreed upon procedure for publishing the results, should be explicitly stated in the application. The sponsor must be identified in all research publications.

9. LANGUAGE

The Committee will only consider and approve English documentation. South African English spelling should be used in all documents, including the Patient Information Documents. Should translations be required, the sponsor or investigator(s) (in non-sponsor driven research), must obtain the services of a professional translator, and keep a record of their certification as to the accuracy of the translation. Where research involves the participation of persons unfamiliar with the language in which the research is to be conducted the PID and related documentation must be translated into the participants' language.

When utilising the services of an interpreter, the investigator must ensure that the participant's informed consent is obtained and that an interpreter is present during discussions with the participants about the research study. As a rule, the interpreter should be an independent person and the patient should consent to the presence of the interpreter.

10. MEDICINES CONTROL COUNCIL (MCC) APPROVAL

Where MCC approval for the trial is required, a copy of the approval letter must be submitted. If MCC approval is pending, proof of application to the MCC must be included. Where only MCC notification is required, a copy of the notification must be submitted.

11. AMENDMENTS

They must be submitted to and will be approved by the Chairperson, Vice-chairperson or the SAMAREC Amendments Subcommittee, unless otherwise indicated. Such approvals will also be ratified by the full committee at the subsequent meeting.

Covering letters accompanying amended PIDs must state the date of their original approval. Amendments must be shown on the latest SAMAREC approved document containing the changes recommended by SAMAREC, and the changes should be highlighted to facilitate review.
All amendments must be submitted electronically.

12. PRESENTATIONS

Presentations at meetings by sponsors and/or researchers, who wish to explain and elucidate complicated and/or sensitive trials, will be allowed upon request to, and at the discretion of SAMAREC. SAMAREC may also request the sponsor to present should they have some concerns regarding the trial.

13. REPORTING OF ADVERSE REACTIONS

The timeframes and format for reporting of serious adverse events, adverse events and drug reactions are described in the MCC guidelines and should be strictly adhered to.

Reports of serious adverse events to SAMAREC MUST include a recommendation by the Principle Investigator regarding the continuance of the study trial, together with a brief motivation.

An unexpected serious adverse event means an event in which the specificity or severity is not consistent with the current investigator brochure (i.e., investigational drug or device). Unexpected serious adverse events may be classified as “related” or “possible related”. An adverse event, which is related to the use of the drug, device or intervention, is one for which there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. A “related” serious adverse event has a strong temporal relationship to the study drug, device or intervention and an alternative aetiology is unlikely or significantly less likely. A “possible related” serious adverse event is one that may have been caused by the drug, device or intervention; however, there is insufficient information to determine the likelihood of this possibility. If an unexpected serious adverse event proves terminal, SAMAREC must be notified immediately.

In addition to SAMAREC reporting requirements the study doctor must promptly report to the sponsor any unexpected adverse clinical event that may reasonably be regarded as caused by, or probably caused by the drug or device. If the adverse event is serious, the study doctor must report the adverse event immediately to the sponsor who, in turn, will notify the Medicines Control Council (MCC).

In the event of providing a report on SAEs – the PI must also give an indication on whether, in his/her opinion, the SAE is trial related or not, and reasons for his/her opinion.

A serious adverse event is any untoward medical occurrence that, whether drug related or not:

- Results in death,
- Is life threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity or
- Results in a congenital anomaly/birth defect (see the ICH Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting)

14. REPORTS AND MONITORING

Following approval of a protocol, six-monthly reports on the trial must be submitted to SAMAREC. Failure to forward these reports will result in suspension of approval for the protocol, without any prior notification by SAMAREC. Any decisions taken by SAMAREC after the review of progress reports will be conveyed to the investigator.

Once the study has been completed the final study report must be submitted in due course. Copies of the MCC reports will suffice.

SAMAREC would also appreciate copies of relevant publications arising from reviewed work. All information will be placed on record and kept confidential at the offices of the SA Medical Association for at least three years after the completion of a trial.

15. CONTINUING REVIEW OF RESEARCH PROTOCOLS

Protocols are approved for a maximum period of one year only. For projects, which continue beyond one year, it is the responsibility of the principal investigator and the sponsor to submit to SAMAREC an Application for Continuing Review supported by the study progress report. The SAMAREC Application for Continuing Review must be submitted in time to allow for review and approval no later than 12 months from the initial review date. Upon receipt of the application for Continuing Review SAMAREC will review and approve, if appropriate, continuation of the project for the subsequent approval period.

Continuation of projects beyond five years requires submission of a revised, updated SAMAREC Application, protocol and consent/assent documents. The Application for Continuing Review must also be submitted to SAMAREC for approval.

16. REPORTING PROPOSED CHANGES IN A RESEARCH PROTOCOL.

Any proposed change in a protocol which affects participants or patients must be reviewed and approved by SAMAREC prior to implementation except where an immediate change is necessary to eliminate a hazard to the participants. Study doctors/sponsors should submit a document detailing the amendment(s) and a revised Patient Information and Informed Consent Document (PID) as required. Minor changes during the period for which approval is in force will be reviewed by way of an expedited review procedure.

If a change in protocol is relatively minor e.g. changes in statistical analysis, it is not necessary to have a revised PID or an addendum to the PID. If, however, the change is not minor and therefore changes the content of the originally signed PID, (e.g. addition of an intervention not addressed in the original PID, disclosure of a previously unidentified risk) the study doctor should have all new participants sign a revised PID. All currently enrolled participants should sign the revised PID or an addendum to the originally signed PID.

17. EXPEDITED REVIEW PROCESS

SAMAREC has established procedures for expedited review of research when this is in the public interest. In general, research with potential to cause physical or psychological harm would not be considered for expedited review. This includes drug trials, research involving invasive procedures and research involving sensitive personal or cultural issues. Expedited review and approval may be considered for research where participants have a disease that may be rapidly fatal.

18. COMPLAINTS PROCESS

Complaints may be lodged, in writing, with the SAMAREC Officer (co-ordinator) who will submit such complaints to the Chairperson as soon as possible for investigation.

19. APPEALS AGAINST DECISIONS

Appeals against decisions should be lodged, in writing, to the full committee, who will then investigate the complaint and endeavour to deal with it to the satisfaction of the complainant.

20. EDUCATION

Research ethics committees must ensure that their members receive initial and continued education in research ethics and GCP training, and are kept aware of current issues and developments in the broad area of research ethics and science.

The current members of SAMAREC are qualified and experienced in these aspects and are afforded the opportunity of attending ethics and research ethics related courses, workshops and conferences as indicated.

D. PART THREE

THE SAMAREC REVIEW PROCESS

1. INTRODUCTION

The following description of the SAMAREC review process reflects the various ethical principles and regulatory requirements that study doctors should consider during the design phase of their project. In order to approve a research project involving participants, SAMAREC must assure itself of the following:

Study Design

- The experimental design of the study is sound;
- Any risks associated with the research project are minimised to the greatest extent possible;
- The potential benefits are maximised to the greatest extent possible;
- The risks to the participant are outweighed or balanced by the potential benefits;
- The prospective participant population is appropriate in terms of characteristics and number;
- The investigators have the appropriate qualifications, experience and facilities to conduct the research;
- Monitoring requirements are reviewed and adequate;
- Any other factors deemed appropriate.

Volunteer Participation

- The recruitment of participants is free of coercion;
- The method used to obtain informed consent is ethically and legally acceptable;
- The degree to which confidentiality is maintained is acceptable;
- Injury compensation is provided in accordance with the Association of British Pharmaceutical Industry (ABPI) Guidelines;
- Any other factors deemed appropriate.

2. REVIEW OF THE PROSPECTIVE PARTICIPANT POPULATION

The prospective participant population must be appropriate with respect to the nature and goals of the research. In addition, the study doctor should be guided by the principles that lead to an equitable selection of participants with regard to the potential risks and benefits of the research. Therefore, SAMAREC will examine carefully the characteristics of the participant population. Factors such as the required number of participants, age range, sex, ethnic background and health status will be considered. The utilisation of any vulnerable classes of participants such as foetuses, prisoners, children, mentally incompetent persons, non compos mentis persons, persons living with HIV / AIDS, the frail and terminally ill persons, and persons of low socio-economic status must be clearly justified.

3. REVIEW OF METHOD(S) OF PARTICIPANT RECRUITMENT

SAMAREC will review the method of prospective participant identification and recruitment in order to be assured it is ethically and legally acceptable. Advertisements used to recruit participants are considered an extension of the recruitment and informed consent processes, and

therefore, must be reviewed by SAMAREC. All advertisements must adhere to the SAMAREC Guidelines for Clinical Trial Advertisements (Annexure 6).

4. REVIEW OF EXPERIMENTAL DESIGN

SAMAREC will review the experimental design in order to be assured that it is scientifically sound and that the potential risks to the participants are minimised and the potential benefits maximised by using procedures consistent with acceptable research design.

5. REVIEW OF THE POTENTIAL RISKS

A risk is a potential harm (injury) associated with the research that a reasonable person would be likely to consider significant in deciding whether or not to participate in the research. The concept of risk includes discomfort, burden, or inconvenience a participant may experience as a result of the research procedures. Underlying the consideration of risk is the implicit moral guideline that all study doctors have a duty not to harm their participants and must minimise potential risk to the greatest extent possible.

The five major types of risk are: -

- **Physical risk** (e.g. pain, bruising and infection associated with venipuncture, adverse reactions to drugs, muscle soreness and pain as a consequence of exercise testing, heart attack induced by maximal exercise test);
- **Psychological risk** (e.g. depression and confusion as a result of administration of drugs, feelings of guilt precipitated by a sensitive survey);
- **Social risk** (e.g. invasion of privacy, loss of community standing);
- **Legal risk** (e.g. compromising medical scheme benefits); and
- **Economic risk** (e.g. loss of employment, loss of potential monetary gain, cost to state or patient or medical scheme). Financial reimbursement of site or study doctor must not be excessive so as to result in a conflict of interest.

Risk can also be classified as minimal, greater than minimal and significant. The USA Federal Regulations define minimal risk, as “The probability and magnitude of harm or discomfort anticipated in the research are 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”. The term “minimal risk” is used as a base or standard by which the risk associated with research is judged.

Examples of “minimal risk” procedures include collection of urine, collection of perspiration, weighing, pulse measurement, blood pressure measurement, voice recordings, electrocardiography, collection of blood by venipuncture from adults who are not pregnant, magnetic resonance imaging, skin fold body composition measurements, and any standard psychological testing with no stress.

Examples of a “greater than minimal risk” procedure include the administration of drugs, intravenous (IV) catheterisation, radiology examinations (x-ray, CT scan), maximal exercise testing and stressful psychological testing.

Examples of “significant risk” procedures include chemotherapy, radiation therapy and major surgery.

6. REVIEW OF POTENTIAL BENEFITS

A benefit is a valued or desired outcome. Benefits associated with participation in research can be classified generally as those that accrue to the participant directly (e.g., improvement of the participant's health status; acquisition by the participant of knowledge considered of value) and those that accrue to society (e.g., additions to the knowledge base). SAMAREC will review the anticipated benefits to both the participants and to others. In addition, SAMAREC will consider whether the benefits are maximised to the greatest extent possible through proper protocol design. Therefore, an underlying moral notion of "beneficence" should guide the study doctor.

Financial and other forms of compensation are not considered a benefit to be derived from research participation. Although the patient may consider financial compensation a desirable outcome this fact will not be used in the risk-benefit analysis and should not be mentioned in the PID. For example, the fact that patients may receive a sum of R150 per visit to defray travel expenses cannot be reflected as a benefit (see MCC Guidelines). Please note that it may be stated in the protocol document that the patient would receive an exact amount for travel and / or other costs. However, the exact amount of R150 must not appear in the Patient Information and Informed Consent Document (PID) as this could be seen as coercive.

7. RISK-BENEFIT ANALYSIS

Once the potential risks and benefits are identified, an ethics review of research requires an examination of the relationship of the risks to the benefits. Risks and benefits cannot be considered parallel constructs and, therefore, no formula is applicable. The various ethical codes and regulations, however, require a favourable balance between harm and benefit. To assist the study doctor and SAMAREC in assessing the risk-benefit relationship the following is a series of principles, which take into consideration whether or not the research is therapeutic in nature:

1) In research that has no likelihood or intent of producing a diagnostic, preventive or therapeutic benefit to the participant (non-therapeutic research), the potential risk to the participant must be outweighed or balanced by the potential benefit to the participant and/or by the potential benefit to society.

2) In research involving the study of the efficacy of a therapeutic or diagnostic method and the intervention is, therefore, not designed solely to enhance the well-being of the participant who is seeking a health benefit (therapeutic research), the potential risk should be primarily outweighed or balanced by the potential benefit to the participant. In addition, the relation of the anticipated benefit to the risk must be at least as favourable to the participant as that presented by alternate standard therapies available to the participant in the non-research context. No participant is allowed to continue participating in a research protocol if therapy of proven superior nature becomes available to the participant.

3) In research where a standard therapy, not part of the research protocol, is employed, the anticipated benefits of the therapy must not be used to justify exposing participants to the risks associated with the research procedures. Such risks can only be justified in light of the potential benefits of the research procedures to the participant. However, the risks associated with the research procedures should be used in determining the risk-benefit ratio.

8. REVIEW OF PARTICIPANT COMPENSATION AND ASSESSMENT OF FINANCIAL ARRANGEMENTS

SAMAREC will review the amount of compensation (monetary as well as other forms) paid to the participants in order to ensure that the payment is not coercive (or deemed to be an enticement) and only covers reasonable actual expenses, e.g. relating to travel.

Financial arrangements involving participants and study doctors form part of the assessment by the Committee. Where participants or their medical schemes are requested to accept liability for any trial related costs, this must be clearly stipulated in the PID. Clear explanation of what are trial related costs and normal treatment (standard care) costs should be provided, and where participants are required to be responsible for normal treatment costs, this should be explained in terms of a cost breakdown in the PID or as an annexure to the PID.

Fees charged for dispensing medicines must be charged in accordance with the prescribed legislation (and regulations). Professional fees may only be charged by the health professional rendering the professional service.

9. REVIEW OF CONFIDENTIALITY

SAMAREC will review the methods to be used to preserve confidentiality. If research data and participant identifiers will be made available to persons other than the listed study doctors or the sponsor, SAMAREC will review the justification for sharing this data and determine acceptability.

10. REVIEW OF THE PATIENT/PARTICPANT INFORMATION AND INFORMED CONSENT DOCUMENT (PID) PROCESS

The Bill of Rights states that –
"Everyone has the right to bodily and psychological integrity, which includes their right - (c) not to be subjected to medical or scientific experiments without their informed consent"

Therefore, no research may be carried out on a person without his/her consent or the consent of the person's legally authorised representative prior to the person's participation in the experiment. The principal reason for informing participants about the experiment is that they have a right to know what would be done to them and what risk this entails, before they give their consent. Persons are regarded as autonomous and the requirement of informed consent is designed to uphold the ethical principle of "respect for persons". The use of humans as research participants is a privilege and a favour granted to the researcher. The researcher has no right to carry out health research without informed consent. An experiment differs from the usual medical practice where interventions are done solely for the benefit of the patient.

SAMAREC takes the view that clinical trials compare to medical procedures and therefore, accepts that patients/participants older than 18 years may independently consent to participate in clinical trials. Patients/participants younger than 18 years may NOT consent independently to participate in clinical trials.
Persons younger than 18 years are regarded as a vulnerable group and applications for clinical trials involving them will be carefully considered by SAMAREC in order to safeguard their interests. Such persons need to be assisted by their parents or their legal guardians. Where the

research does not involve greater than minimal risk to the child and direct benefit is foreseen, SAMAREC may consider the consent of one parent sufficient. Exceptions to this rule would be where one parent is deceased, unknown, incompetent, and not reasonably available or only one parent has legal care and custody of the child. No other person, such as a caregiver or grandparent may give consent on behalf of parents or legal guardian. In addition to the PID to be signed by the parents or legal guardian, appropriately worded **Patient Information and Assent Document** is needed to be read and signed by those minors who can observe and understand the circumstances relating to the clinical trial**. (See page 38)**

In order for consent to be ethically and legally valid it must meet the requirements stated in the Principle (I) of the Nuremberg Code, which states, "The voluntary consent of the human patient is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the patient matter involved as to enable him to make an understanding and enlightened decision."

The PID and informed consent documen3t is a legal document proving that informed consent was obtained. By signing the document the participant declares that he/she gives consent to participate in the clinical trial. The study doctor signs the document to declare that he/she has guided the participant through the PID and explained the content to the satisfaction of the participant. The witness signs the document to testify that the participant and study doctor concerned have signed the PID. Where a participant is illiterate, verbal consent must be obtained and such verbal consent must be properly recorded. A witness must also confirm by signing the verbal consent document, that the participant understands the contents of the PID and has given free consent to participate in the trial. **(See Annexure 4).** The ethical and, indeed, legal validity of consent is, however, dependent upon the process of informed consent which requires the study doctor to engage in dialogue or negotiation with the prospective participant. The study doctor as an instrument to guide the negotiations with the prospective patient, therefore, should use the PID for this purpose. The SAMAREC will review both the PID and the process of informed consent in accordance with the provisions of the Guidelines for Good Practice in the Conduct of Clinical Trials published by the Department of Health in order to ensure acceptability.

The signatory section of the PID must be continuous with the rest of the PID to ensure that it is one document.

Note that tick boxes are not suitable for participants' acceptance of various clauses in the PID. The clauses should rather be initialled by the participant.

11. REVIEW OF INVESTIGATORS

SAMAREC will review investigators and must be assured that they:

- Have the appropriate qualifications;
- Are licensed with the Health Professions Council or other appropriate statutory bodies to carry out procedures involving human participants with an acceptable degree of risk;
- Maintain adequate malpractice insurance cover;
- Carry out procedures involved in the clinical trial within their speciality/sub-speciality, if they are registered in that speciality or sub-speciality; and

- Have adequate facilities and equipment to conduct the research with an acceptable degree of risk.

12. REVIEW OF MONITORING REQUIREMENTS

The SAMAREC will determine whether or not a research project requires review more often than annually and will establish an appropriate reporting and/or monitoring procedure which may include observation of the consent process, observation of on-going research and review of research records.

13. REVIEW OF INJURY COMPENSATION

Compensation for trial related injuries must be covered and set out in the PID. Compensation should be provided in accordance with the Guidelines of British Pharmaceutical Industry Compensation Guidelines (ABPI). Broadly speaking, these guidelines recommend that the sponsor, without legal commitment, should compensate you without you having to prove fault. This applies in cases where it is likely that such injury results from giving any new medicine or any procedure carried out in accordance with the protocol for the study. The sponsor will not compensate where such injury results from any procedure carried out that is not in accordance with the protocol for the study. Your legal right to claim compensation for injury where you can prove negligence is not affected. A copy of the ABPI Guidelines must be made available to the patient by the study doctor, on request.

All professionals must provide proof that they carry personal professional indemnity insurance cover.

14. CONFLICT OF INTEREST

SAMAREC ensures that no member of the committee adjudicates on a clinical trial in which that member has any conflict of interest in relation to the research project under consideration. Members should declare before each meeting any real or potential conflicts of interest with any of the studies to be evaluated and offer to recuse themselves from the evaluation of the study concerned. The Committee will consider the declaration and make a ruling regarding the presence/recusal and/or voting rights of the member recused.

15. ACCESS TO INFORMATION

Protocol and trial information and documentation are regarded as confidential and are treated as such by SAMAREC and SAMA. In terms of the Guidelines for Ethics in Health Research, published by the Department of Health, all records and documentation relating to the functioning of SAMAREC are open to the National Health Research Ethics Council. All other requests for access must be done in terms of the Promotion of Access to Information Act and the manual of the SAMA and procedures determined by the Association in this regard.

16 ANNEXURES

The following annexures set out further information and pro-forma documentation, for the guidance of study doctors and sponsors:

16.1 Annexure 1: SAMAREC Meeting Dates
16.2 Annexure 2: SAMAREC Checklist
16.3 Annexure 3: MCC Format of Curriculum Vitae of Trialists
16.4 Annexure 4: Guidelines Pertaining to the Patient Information and Informed Consent Document (PID) and SAMAREC Patient Information and Informed Consent Document (PID) (Including various consent annexures to be used as relevant to a particular clinical trial)
16.5 Annexure 5: Members of SAMAREC
16.6 Annexure 6: SAMAREC Guidelines for Clinical Study Advertisements
16.7 Annexure 7: SAMAREC Fees
16.8 Annexure 8: Declaration by Investigators
16.9 Annexure 9: List of Study Staff and their submitted documents.

Annexure 1

SCHEDULED SAMAREC MEETING DATES 2017

SUBMISSION DATE	MEETING DATE
05 January 2017	08 February 2017
01 February 2017	08 March 2017
01 March 2017	12 April 2017
05 April 2017	10 May 2017
03 May 2017	07 June 2017
01 June 2017	12 July 2017
05 July 2017	09 August 2017
02 August 2017	13 September 2017
06 September 2017	11 October 2017
04 October 2017	08 November 2017
01 November 2017	06 December 2017

NOTES:

- *Meeting dates may change at the discretion of the Chairperson.*
- ***Closing date** for submission of applications **is 4 weeks** before the date of next meeting.*

Co-ordinator: SAMAREC
Governance and Legal Unit
South African Medical Association
Block F Castle Walk Corporate Park
Erasmuskloof, Pretoria
Tel: 012 481 2046
Fax: 012 481 2095
E-mail: samarec@samedical.org

Annexure 2

CHECKLIST

Protocol Number: _____

Local coordinator / contact person:

Name _____

Phone _____

Fax _____

E-mail _____

Postal Address _____

_____

_____

General Information:
(Please note that this list reflects the requirements of the Research Ethics Committee, and the Patient Information and Informed Consent Document (PID) will be weighed against these criteria.)

1. Is the trial going to be conducted in the Private Sector?

2. Do you wish to make a presentation?

3. Have you submitted all the requested documentation electronically?

4. Is the protocol number clearly visible on all the documentation?

5. Have you included details of the financial arrangements with investigators and confirmed that patients will be reimbursed for expenses incurred?

6. *Will patients be expected to pay for anything?*

7. Placebo Justification – where applicable the placebo justification must be included in the cover letter.

8. What is your assessment of any potential additional risk or discomfort in respect of patients?

9. Are all relevant details (names of Investigators, Declarations of Trialists, etc.), filled in?

10. Do the Investigators' CV's include the following information?

- Name and Practice address
- Qualifications and tertiary institutions

- Clinical trials experience: Details of previous and current trials, dates, and whether completed or ongoing
- Conferences and/or Congresses attended
- Proof of personal indemnity insurance cover, i.e. MPS or other valid insurance membership number
- Health Professions Council of SA (HPCSA) registration number
- Date and signature
- GCP and / or Dispensing Licence

11. Does the protocol clearly stipulate that the investigator may independently publish his or her results?

Information concerning the Patient Information and Informed Consent Document (P I D)

12. Does the P I D indicate that the principles enunciated in the Declaration of Helsinki (last update: October 2013) are complied with?

13. Does the P I D state that neither the patients nor their medical schemes have to pay for trial related expenses?

14. Does the PID state that compensation for trial related injury will be paid in accordance with the guidelines of the ABPI?

15. Is the Patient Information and Informed Consent Document one continuous document?

16. Does the Informed Consent section provide for names of the patients, study doctor and witness to be both printed and signed?

17. Have you fully complied with the details in the attached guidelines?

18. Have you structured your P I D around the SAMAREC "ideal" example?

Any queries relating to the functioning of the SAMA Research Ethics Committee may be addressed to the following Co-ordinator of the SAMA Research Ethics Committee:

Telephone : 012 481 2046
Fax : 012 481 2095

Postal Address : P O Box 74789
Lynwood Ridge
0040

Physical Address : Castle Walk Corporate Park
Block F
Nossob Street
Erasmuskloof Ext 3
Pretoria
0183

Annexure 3

MCC FORMAT FOR CVS OF INDIVIDUALS PARTICIPATING IN THE CONDUCT OF CLINICAL TRIALS IN SOUTH AFRICA.

Trial:

Protocol:

Designation: (e.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Associate Investigator, Study Co-ordinator, Regional Monitor, Local Monitor, Contract Research Affiliate)

1. Personal Details
   Name:
   Work Address:
   Telephone Number:
   Fax Number:
   Cell-phone Number:
   E-mail address:
2. Academic and Professional Qualifications
3. Health Professions Council of South Africa (HPCSA) registration number if applicable (or other health professions body registration particulars if applicable – e.g. Nursing Council)
4. Current personal medical malpractice insurance details [medical and dental practitioners]
5. Relevant related work experience (brief) and current position
6. Participation in clinical trials research in the last three years (title, protocol number, designation) [If multiple trials, only list those with relevance to this application, or in the last year.]
7. Peer-reviewed publications in the past 3 years
8. Date of last GCP training (as a participant or presenter)
9. Dispensing Licence Registration number (if applicable)
10. Any additional relevant information supporting abilities to participate in conducting this trial. [briefly]

Signature: Date:

Annexure 4

Guidelines Pertaining to the Patient Information and Informed Consent Document (PID) and SAMAREC Patient Information and Informed Consent Document (PID) (Including various consent annexures to be used as relevant to a particular clinical trial)

1. It must be clearly indicated in the P I D that **the principles contained in the Declaration of Helsinki (last updated October 2013) and the South African Department of Health Clinical Trial and Ethics in Health Research Guidelines** are complied with, and that the study has been approved by the SAMAREC. The latest approved version of the Declaration of Helsinki is always applicable.

2. The PID must be written in layperson's language (with attention to grammar and South African English spelling).

3. Wherever patients are expected to consider or sign documents, and the age group involves minors, parents/legal guardian involvement, this must be clearly mentioned in the PID.

4. Where patients are *non compos mentis*, the involvement and capacity of the person who may legally consent on behalf of the patient must be clearly mentioned in the PID.

5. The Patient Information and Informed Consent Document is **ONE** continuous document, and may not be presented separately – i.e**., INFORMED CONSENT is merely another sub-heading in the document, in the same format as all other sub-headings, and does not start on a new page.**

6. In the informed consent section of the PID, names of patients, study doctor, parents/legal guardians and witnesses must be printed as well as signed. If someone other than the study doctor explains the informed consent, i.e. an interpreter, he/she must also sign a Declaration to this effect at the same time. This latter process must be witnessed by an independent witness.

7. Whenever generics are mentioned, please insert examples of South African trade names as well in brackets. This is useful information for patients reading the Patient Information and Informed Consent Document.

8. Reference to "**clinic" or "hospital" is unacceptable, and should read "study doctors rooms" or "-facilities", in accordance with Health Professions Council of SA (HPCSA) rules**.

9. All trial related injuries must be covered and a copy of the insurance certificate must be furnished. Arrangements for compensation and insurance must be included in the PID, and **it must be stated clearly that compensation to patients will be in accordance with the ABPI guidelines**. A copy of the guidelines must be available.

10. All tests done on blood, urine and other samples taken from patients must be specified, and the nature and purpose of such tests explained in layperson's terminology in the PID e.g. urine sample for pregnancy test or for kidney functions.

11. It should be stated that there will be no trial-related costs to the patient or his/her medical scheme. Any costs to be borne by the patient must be clearly stated in the PID.

12. Once the full term “The Patient /Participant Information and Informed Consent Document” (PID) has been used, it can thereafter be referred to as “this document.

13. Tick boxes– the use of tick boxes is not encourage and participants should rather initial when they may have to reflect a choice

Pro Forma

PATIENT INFORMATION AND INFORMED CONSENT DOCUMENT

(Each patient must receive, read and understand this document before the start of the study)

TRIAL NUMBER: .....

TRIAL TITLE: .....

SPONSOR: ……

INTRODUCTION
You are invited to take part in a research study. This document is needed to help you to decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study. If you have any questions that are not fully explained in this document, do not hesitate to ask the study doctor. You should not agree to take part unless you are completely happy about all the procedures involved and possible risks. In the best interests of your health it is strongly recommended that you discuss with or inform your personal doctor (general practitioner) of your possible participation in this study. The study doctor will also be notifying your personal doctor in this regard, unless you disagree that notification takes place.

THE PURPOSE OF THIS TRIAL
You have been diagnosed as suffering from..... and the study doctor would like you to consider taking part in the research of a new drug, called..... . (***Where possible, include the trade name and/or examples of the drug in brackets after the word. Details of the study population and age must also be furnished)***

During the study you will receive …… ***(Explain the intervention, e.g.……either the active drug or a placebo. A placebo is an inactive substance; it does not contain any of the drugs which are to be used in this trial.)***

THE DURATION OF THIS TRIAL
If you decide to take part in this trial you will be one of approximately ..... patients. The study will last for up to..... (days/weeks/months/years). You will be asked to visit the study doctor ..... times as per the following schedule:.....
At each visit you will undergo the following examinations and tests:

Visit 1 – (week?):
Visit 2 – (week?):

(Give the exact reasons for the blood, urine and other tests, Electrocardiograms (ECG), and all other tests must be stated, indicating what tests will be done and why it is necessary to do them, in layperson's terms)

It is important that you let the study doctor know of any medicines (both prescriptions and over-the-counter medicines), alcohol or other substances that you are currently taking.

ETHICS APPROVAL OF TRIAL

The Protocol of this clinical trial was submitted for approval to the South African Medical Association Research Ethics Committee (SAMAREC), a research ethics committee registered with the National Health Research Ethics Council. Written approval has been granted by SAMAREC for the conduct of the trial. The study has been structured in accordance with the Guidelines on Clinical Trials and Ethics in Health Research, published by the Department of Health and the Declaration of Helsinki (last updated October 2013), adopted by the World medical Association (WMA), which deals with the recommendations guiding doctors in biomedical research involving human participants. Copies of these documents may be obtained from the study doctor should you wish to review it.

YOUR RIGHTS AS A PARTICIPANT IN THIS TRIAL

Your participation in this trial is entirely voluntary and you can refuse to participate or you can stop at any time without stating any reasons whatsoever. Your refusal to participate in or your withdrawal from this clinical trial will not affect your access to other medical care. The study doctor, however, retains the right to withdraw you from the study if it is considered to be in your best interest, in which event reasons will be provided for withdrawing you from the study. If it is detected that you did not give an accurate history or did not follow the guidelines of the trial and the prescriptions of the trial facility, you may be withdrawn from the trial at any time.

ALTERNATIVE TREATMENT

Alternative treatment in the form of..... is often used to treat (this condition)..... If you decide not to take part in this study it is possible that your personal doctor may treat you with this, or another suitable treatment. ***(If the option of "no treatment" is an alternative, this should be stated.)***

TRIAL PROCEDURES MAY RESULT IN DISCOMFORT OR INCONVENIENCE

(**Example)**: Venipunctures (i.e. drawing blood) are normally done as part of routine medical care and presents a slight risk of discomfort. Drawing blood may result in a bruise at the puncture site, or less commonly fainting, swelling of the vein, infection and bleeding from the site. Procedures are performed under hygienic conditions by experienced personnel. A total of ..... ml of blood (i.e. ….. tablespoon) will be collected over the course of the entire study.

THE RISKS INVOLVED IN THIS TRIAL

All medicines carry some risk, however small. In previous studies some patients have reported experiencing side effects which included ....., ..., and.....

(Medical terminology should be explained in layman's language in brackets.)

PREGNANCY / BIRTH CONTROL

Safety of the study medication in pregnancy and lactation as well as the effects during fertilisation of the egg cell has not been established. There might be unknown risks to the unborn child if a female patient is pregnant, or becomes pregnant during the study or if a male patient fathers a child whilst on study medication

MALE PATIENTS

If you are a man who can father a child, suitable contraceptive measures should be used during the study.

FEMALE PATIENTS

If you are a woman of child-bearing potential:

- You must not participate in this study if you are pregnant, or plan to become pregnant during the research study period, or are breastfeeding.
- You must use acceptable methods of birth control during this study (for example, a condom or a diaphragm plus spermicide; hormonal contraceptives that are injected, implanted or taken orally, or an intrauterine device.
- A pregnancy test will be done to confirm that you are not pregnant before your participation in this study.
- By signing this document, you confirm to the best of your knowledge that you are not pregnant now, breastfeeding and you do not intend to become pregnant during this study.

If at any time during this study you think you might be pregnant, or later learn during the study that you are pregnant, you must contact the study doctor immediately for further instructions regarding your participation in this study and follow-up.

DISCONTINUATION OF TRIAL TREATMENT

Uncontrolled discontinuation of trial medication is not advisable. Special care needs to be taken for the discontinuation of this trial medication. The study doctor will supervise any discontinuation with your health as first priority. In the event of withdrawal from the study by study doctor, the study doctor will provide you with reasons.

COSTS AND FINANCIAL ARRANGEMENTS

Neither you nor your medical scheme will be expected to pay for any study medication, study-related visits or trial procedures. **(If it is a requirement that a patient is responsible for any non-trial related costs, i.e. for usual treatment costs, this must be indicated clearly, giving details of what these responsibilities are and the estimated amount(s)**).

You will not be paid for participation in this study. However, a reasonable amount to cover your travel expenses will be paid out to you. Please discuss further details in this regard with the study doctor before commencement of the trial. There will be no costs to you or your medical scheme.

INSURANCE AND COMPENSATION

The Sponsor has obtained insurance for you and the study doctor in the event of trial related injuries. The Sponsor assumes no obligation to pay for the medical treatment of other injuries or illnesses not related to the studies. Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from the study doctor should you wish to review it. Any compensation will be paid in accordance with the Association of the British Pharmaceutical Industry (ABPI) Guidelines on Compensation, which guidelines adequately cover the compensation aspects relating to clinical trials. A copy of these Guidelines is available from the study doctor on request.

Your medical scheme should receive pre-notification of your possible participation in the trial and provide clarity on non-trial-related costs to be borne by them.

(This sentence is applicable where study doctors initiate studies or for studies where the patients' medical scheme will be expected to pay for certain costs. All costs to be borne by the patient or the medical scheme should be specified and the patient should be made aware of it).

You must notify the study doctor immediately of any research or other related complications, side effects and/or injuries resulting from the trial, and the nature of the expenses to be covered.

By signing this document, you do not waive any of your legal rights should a research-related injury occur.

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical trial. Our information to date is that it should not affect any life insurance policy taken out. Nevertheless you are strongly advised to clarify this with the insurance company concerned.

SOURCE OF ADDITIONAL INFORMATION

For the duration of the trial, you will be under the care of the study doctor, Dr..... If at any time between your visits you feel that any of your symptoms are causing you any problems, or you have any questions during the trial, please do not hesitate to contact him/her. The telephone number through which you can reach him/her or another authorised person is …….. and/or……

CONFIDENTIALITY

All information obtained during the course of this trial is strictly confidential and will be maintained as such. Data that may be reported in scientific journals will not include any information that identifies you as a patient in this trial.

In connection with this trial, it might be important for domestic and foreign regulatory health authorities, such as the Department of Health, the National Health Research Ethics Council, the Food and Drug Administration of the United states of America, the South African Medical Association Research Ethics Committee (SAMAREC), the South African Medicines Control Council (MCC), as well as authorised persons on behalf of the Sponsor, to be able to review your medical records pertaining to this trial. Therefore, by signing this document, you authorise your study doctor to release your medical records in appropriate circumstances to the Sponsor, its employees or agents, domestic and foreign regulatory health authorities, the MCC and the SAMAREC. You understand that these records will be utilised within reason by them only in connection with carrying out their obligations relating to this clinical trial.

Any information uncovered regarding your test results or state of health as a result of your participation in this trial will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this trial but this information will not be disclosed to any other than those mentioned above without your written permission. The only exception to this rule will be in cases where a law exists compelling us to report incidences of communicable diseases. In this case, you will be informed of our intent to disclose such information to the authorised state agency.

The results of this research study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.
The information collected during this study may be added to research databases and used in the future by the sponsor and its affiliated companies to study better measures of safety and effectiveness, study other therapies for subjects, develop a better understanding of disease included in the study or improve the efficiency, design and study methods of future clinical trials. Such information will not identify you by name.

INFORMED CONSENT

- I hereby confirm that I have been informed by the study doctor about the nature, conduct, benefits and risks of this clinical trial.

- I am aware that the results of the trial, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a trial report, but that some of my health information may be reasonably disclosed to the Sponsor and/or authorities under certain circumstances.
- I may, at any stage, without prejudice, withdraw my consent and end my participation in the trial.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the trial.
- I have read and understood the contents of the document.
- I understand that I shall receive a signed copy of this document.

Patient:

_____

Printed Name Signature Date

I, Dr ..... herewith confirm that the above patient has been informed fully about the nature, conduct and risks of the above trial.

Study Doctor:

_____

Printed Name Signature Date

Witness:

_____

Printed Name Signature Date

(Witness' signature confirms that he/she has witnessed the relevant signatures at the time of signing. Witness name, signature and date must be completed by the witness at the same time that this document is signed and dated by the patient and the Study Doctor. A competent witness is a person 16 years or older and of sound mind and not involved with the trial.)

VERBAL PATIENT INFORMED CONSENT

(This section is applicable when patients cannot read or write and should replace the previous Informed Consent section)

I, the undersigned study doctor, Dr ....., hereby confirm that:

- I have read and explained fully, to the patient, named..... as well as the witness who signed below, with the consent of the patient, the content of this document, indicating the nature and purpose of the trial in which I have asked the patient to participate.
- I have explained both the possible risks and benefits of the trial and the alternative treatments available for his/her illness.
- The patient has indicated that he/she understands the contents of the document and also that he/she will be free to withdraw from the trial at any time without giving any reason or jeopardising his/her subsequent treatment.
- I have informed the patient on the existence of relevant compensation arrangements in case of an injury attributable to the drug(s) used in the clinical trial, to which he/she agrees.
- The patient has had sufficient opportunity to ask questions.

- The patient has voluntarily agreed to participate in this trial.

Patient:

_____

Printed Name Signature or mark Date

Study Doctor:

_____

Printed Name Signature Date

I, the witness who signed below, confirm that the study doctor has explained fully the content of this document to the patient.

Witness:

_____

Printed Name Signature Date

The Patient Information and Informed Consent Document is a legal document; therefore the role of the witness is to confirm the signatures of the parties involved. In other words, the witness confirms that the parties involved signed the document. The witness can be somebody over the age of 16 and of sound mind, who is not directly involved with the trial e.g. the receptionist, the cleaner or even other patients waiting to see the doctor.

INFORMED CONSENT FOR PARENTS/LEGAL GUARDIANS

(This section must be used where parents/legal guardians give consent on behalf of minors under 18 years old. The PID can be worded to include reference to the parent(s)/legal guardian and the child or **it can be stated at the beginning of the PID that: "You" will read "you/your child".)**
I/we, the parent(s)/legal guardian of …..... hereby confirm that:

- I/we have also been given an opportunity to discuss the possibility of my/our child's/ward's participation in the trial.
- The study doctor has given me/us the opportunity to ask any questions concerning both the medicine and the trial.
- It has been explained to me/us that I/we will be free to withdraw my/our child/ward from the trial at any time, without any disadvantage to future care.
- I/we have understood everything, including the nature, risks, benefits and purpose of the trial, that has been explained to me/us and I/we give consent for my/our child/ward to participate in this clinical trial.
- The study doctor will provide me/us with a copy of this signed document.

Patient:

_____
Printed Name Signature (where child can write) Date

Parents/Legal Guardian:
1. Mother:

_____
Printed Name Signature Date

2. Father:

_____
Printed Name Signature Date

(The Research Ethics Committee will indicate whether one parent may give consent on behalf of the patient younger than 18 years, or both parents must give consent)

3. Legal Guardian (in cases where one has been appointed by the court)

_____
Printed name Signature Date

(Minors competent to understand must participate as fully as possible in the entire procedure)

Study Doctor:

_____
Printed Name Signature Date

Witness:

_____
Printed Name Signature Date
(Witness's signature confirms that he/she has witnessed the relevant signatures at the time of signing. Witness name, signature and date must be completed by the witness at the same time that this document is signed and dated by the patient and the Study Doctor)

This Pro Forma should be used together with the PID for the parent(s)/legal guardian)

PATIENT INFORMATION AND ASSENT DOCUMENT
(Minor patients under 18 years of age, who are capable of understanding the nature and extent of the research/treatment, must receive and sign a copy of this document)

TRIAL NUMBER:……..

TRIAL TITLE:

SPONSOR:

INTRODUCTION
You have been diagnosed with…... a disease of the ……, and are invited to participate in a study to evaluate the effect of (the drug) on your disease.
The purpose of the study is to find out what effects the drug has on people like you and to learn more about how to treat your illness. This treatment may or may not help you.
If you are not completely truthful with your study doctor about your health history, you may harm yourself by participating in this study.
You will be one of ……..patients participating in the study in ……. centres world-wide. The length of your participation in the study will be …… (Days/weeks/months/years).
If you decide to participate in this study you will be treated …….. ***(Explain nature of study in simple terminology)***
If you choose to participate in this study you will need to visit the study doctor's rooms for……..times which visits will take about ……hour each.
There will also be tests that you must undergo and for these tests it will be necessary to draw blood from a vein and to obtain urine. The study doctor will explain these tests to you.

(Optional paragraph – include if applicable:
If it is possible for you to become pregnant, a urine/blood pregnancy test will be done before receiving the first doses of medication. As it is not known what effects the medicine you will be taking could have on an unborn baby, it is important to find out whether you are pregnant or not before you start taking the medication. Should you be pregnant or become pregnant during the course of the study, you will be taken off the study.)

You may have some side effects from the medicine you will be taking. These effects may make you feel ill. You must tell the study doctor of any side effects. The study doctor will then stop the medication if indicated. The most common side-effects are…….

You may ask any questions about the study and should you wish to ask more questions in future please do not hesitate to call the study doctor on……or ask her/him next time you visit her/him.

You understand that you do not have to agree to participate in this study and that your parents/legal guardian or study doctor cannot force you to be in the study. Your parents/legal guardian will have to give consent on behalf of you to participate in this study to make it legal. They are also being informed by the study doctor about the study before they will give consent. However, their consent will be worthless if you do not agree to participate in the study.

If you change your mind in future and you do not wish to continue to participate in the study, you may withdraw and usual medical care will be given to you. Please also discuss this with your parents/legal guardian.

The study doctor will tell you if they find new information (good or bad) that they did not know about when they first explained this study to you.

All information collected about you for this study will be kept confidential (will not be told to anyone not involved in the study) and your name will not be used in study reports. Persons working on the study may look at your medical records, but they will not share your name with anyone. When the study is finished the study doctor will write a report about what was learned. The report will not name you or say that you were in the study.

If you sign this document you agree/assent to be in the study. You will be a given copy of this document to keep after you signed it. Your parent(s)/legal guardian will also sign this document in addition to the Patient Information and Informed Consent document that they will sign to give consent on behalf of you to participate in this study.

Patient:

_____

Name Signature Date

Parent(s):

Mother:

_____

Name Signature Date

Father:

_____

Name Signature Date

Legal Guardian:

_____

Name Signature Date

Study Doctor:

_____

Name Signature Date

Witness:

_____

Name Signature Date

(Witness's signature confirms that he/she has witnessed the relevant signatures at the time of signing. Witness name, signature and date must be completed by the witness at the same time that this document is signed and dated by the patient and the Study Doctor.)

Annexure 5

Members of SAMAREC

Prof JR Snyman MBChB, M Pharm Med, MD	Male, Pharmacologist, SAMA member, (Chairperson)
Dr M Groenewald MBChB, DCH (SA), PG Dip Int Res Ethics	Female, General Practitioner, SAMA member
Prof M Kakaza BSc, MBChB, Mmed (Neurology)	Female, Neurologist, SAMA Member
Mrs BM Fineberg, BSc (Hons); H.D.E.	Female; Educator
Mrs U Behrtel, BLC.LLB, Cert Med Law	Female, Attorney
Dr S Franzsen MBCH.B, M. Med (O& G) , ACAM (Chel), BA(Theo)	Female, General Practitioner, SAMA Member
Dr S G Motuba MBCHb, FILPA, MBA, Dip Fin Management, CoP in Short Term Insruance, Dip in Digital Marketing	Male, SAMA Member
Ms W Massangaie LLB	Female, Attorney

Annexure 6
SAMAREC Guidelines for Clinical Study Advertisements and Notifications in Health Research

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PART A

ADVERTISEMENT AND NOTIFICATION TO THE PUBLIC

INTRODUCTION

In terms of the Standard Operating Procedures (SOPs) of the South African Medical Association Research Ethics Committee (SAMREC) :
All advertisements and notifications to the general public and prospective research participants, or other persons or organizations, must be approved SAMAREC. In assessing such advertisements, SAMAREC will give consideration to the Guiding Principles enunciated hereunder.

PURPOSE

The purpose of these Guiding Principles is primarily to protect the fundamental rights of persons participating or considering participation in health research by providing guidance and governance in respect of advertisements and notifications relating to such health research.

Persons experiencing health problems are often particularly vulnerable to persuasive influence such as unprofessional advertising and are, therefore, entitled to protection from misleading or promotional advertising, or improper competitive actions.

It should also be noted that advertising in an unprofessional manner or canvassing and touting for research participants is, generally, regarded as unethical behaviour by health care personnel and health establishments, and could constitute a breach of professional conduct.

GUIDING PRINCIPLES

In light of the above, the following principles are hereby published to assist health care workers, researchers, health establishments, as well as sponsors, when compiling advertisements and notifications relating to health research:

1. It is generally permissible for sponsors undertaking health research, as well as health care providers and researchers participating therein, to advertise such research. However, the advertisements for recruiting research participants should be evaluated and approved by the same Research Ethics Committee (REC), such as SAMAREC that evaluates and approves the health research protocol.

2. Researchers intending to promote their participation in health research shall do so in a professional manner and always subject to the rules and ethical considerations of the statutory body with whom they are registered or the entity governing their specific profession.

3. The name of a sponsor company or individual researcher may not appear on advertisements and notices. However, the particulars of an independent person from the sponsor company may be stipulated as a contact person.

4. The telephone number stated on the advertisement should be that of an independent person or independent call centre, and must not belong to any researcher participating in the health research, or to any health research site.

5. The contact details must be that of a person able to respond to questions related to the study, and may also be the person engaged to undertake screening for the health research.

6. The person engaged to screen the phone calls may be reasonably reimbursed.

7. The advertisements and notifications may be published in any medium, printed or electronic, including the internet and television.

8. There are no limitations on the size or number of times an advertisement or notice may be published.

9. Factual information of the health research may be published e.g. “A Phase III Clinical Trial on Type 2 Diabetes...”

10. The selection / inclusion criteria may be mentioned e.g. “Are you between 18 and 70 years and suffering from Type 2 Diabetes?”

11. Any reference to drugs, which contain a substance appearing in Schedule 2 and above as defined in the Medicines and Related Substances Act (as amended from time to time), may be included in the advertisement; provided that the reference or sentence construction is not tantamount to promotion or advertisement of such drug.

12. Advertisements or notifications may be made available for distribution to existing patients of health care providers, at consulting rooms, clinics, hospitals, health establishments or at local information centres such as libraries and museums.

13. Graphics and photographs (even of an anatomical structure) on advertisements and notices are permissible but must not be indecent, deceptive, misleading or bring any profession into disrepute.

14. Payment details or reimbursement to research participants may not appear in the advertisement or notice for research participants.

15. All advertisements and notifications to be used for or in health research, must be approved by the relevant REC or by SAMAREC.

PART B

ADVERTISEMENTS AND NOTIFICATIONS AMONGST HEALTH CARE PERSONNEL

INTRODUCTION

It is common practice and should be encouraged amongst health care providers, to communicate the setting up of a practice or practice address changes to colleagues and in these communications to colleagues they may include information on their field of practice, e.g. “treatment of patients with AIDS”. It is likewise permissible for a health care provider or

researcher engaging in health research to advise colleagues, other health care providers and health establishments, that they are involved in health research and that they are looking for suitable research participants.

In the best interests of research participants, only health care personnel and researchers with demonstrable research capabilities should be recruited to conduct the required research. The health care personnel and researchers to be recruited would be held accountable, and could be convicted, for unprofessional and unethical behaviour on their part during health research.

PURPOSE

The purpose of these further Guiding Principles is to ensure that health care personnel and researchers intending to promote their participation in health research do so in a regulated and professional manner.

GUIDING PRINCIPLES

1. Health care personnel and researchers participating in clinical trials may communicate such information to colleagues, other health care providers and health establishments or relevant persons and entities, with the aim of obtaining referrals of potential research participants.

2. The advertisements and notifications may be published in any medium, printed or electronic,; provided that all relevant ethical rules and guidelines of the statutory body with whom they are registered or the entity governing their specific profession, are complied with;

3. Any further detailed or factual information on the health research, selection / inclusion or exclusion criteria may be included in the notification, to enable appropriate referral of potential research participants for screening;

4. It should be specifically mentioned in the advertisements or notification letter that the research participant referred for participation in the health research will remain the *bona fide* patient (person) of the referring health care provider i.e. as soon as the health research has been completed / or is terminated for whatever reason, such research participant would be referred back to the referee.

5. Health care providers or researchers who are liable for, and incur advertising costs for recruitment of research participants in health *res*earch, may be reimbursed.

6. Non-specific and generic information regarding payment details or reimbursement to potential research participants may appear in the advertisement or notice.

7. The Guiding Principles enunciated in paragraphs 8, 9, 10, 11, 12, 14, and16, of Part A above, shall apply *mutatis mutandis* to this Part B.

PART C

EXAMPLE OF ADVERTISEMENT/ NOTIFICATION

(Picture)

ADVERTISEMENT/ NOTIFICATION:

A Phase III Clinical Trial on Type 2 Diabetes

(NO RESTRICTION ON SIZE OR TYPESTYLE OR NUMBER OF TIMES PUBLISHED)

ARE YOU BETWEEN 18 AND 45 YEARS OLD?
ARE YOU SUFFERING FROM TYPE 2 DIABETES?
DO YOU HAVE THE FOLLOWING SYMPTOMS ……?

IF SO PLEASE PHONE THE FOLLOWING NUMBERS SHOULD YOU BE INTERESTED IN PARTICIPATING IN HEALTH RESEARCH WHEREIN A NEW DRUG WILL BE TESTED FOR THE CONDITION / DISEASE YOU HAVE

TEL: (012) 000-0000 OR TEL: 086 000 0000

The health research protocol was approved by ABC Research Ethics Committee on 01 January 2010, NHREC registration number XXX01/2010.

APPROVAL OF GUIDING PRINCIPLES

This document was approved by SAMAREC on 21 January 2015.

CONTACT DETAILS OF SAMAREC

Address: Block F, Castle Walk office Park, Nossob Street, Erasmuskloof Ext 3 Pretoria
Tel: (012) 481 2046
Fax: (012) 481 2095
E-mail: samarec@samedical.org

Annexure 7

SAMAREC FEE STRUCTURE

New Protocol	R13 300.00
Major Amendment	R6 600.00
Minor Amendment	R3 300.00
Application for Continuing / Annual Review	R3 300.00
Application for Additional Sites (Three or less sites)	R3 300.00
Application for Additional Sites (More than three sites)	R6 600.00
Genetic Sub Study	R4 000.00
Student/ Doctor Unsponsored Study	R3 000.00

The Fees will be updated 01 July 2016

Annexure 8

Declaration by Principal Investigator.

Name:

Title of Trial:

Protocol:

Site:

1. I have read and understood Item 1.5.5 on page 5 and Section 3 (pages 14-20) 'Responsibility of the Principal Investigator (PI) and Participating investigators ' of the *Clinical Trials Guidelines of the Department of Health: 2000.*
2. I have notified the South African regulatory authority of any aspects of the above guidelines with which I do not / am unable to, comply. (Details of non-compliance must be attached to this declaration.)
3. I have thoroughly read, understood and critically analysed (in terms of the South African context) the protocol, and all applicable documentations, including the investigator's brochure, and the Patient/Participant Information and Informed Consent Document(s).
4. I will conduct the trial as specified in the protocol.
5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.
6. I will not commence with the trial before written authorisations from the relevant ethics committee(s) as well as the South African Medicines Control Council (MCC) have been obtained.
7. I will obtain informed consent from all participants, or if they are not legally competent, from their legal representatives.
8. I will ensure that every participant (or other involved persons, such as relatives) shall at all times be treated in a dignified manner and with respect.
9. I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial. All conflicts of interest have been declared by me.
10. *Delete the inapplicable option below:*
    I have not previously been the Principal Investigator at a site which has been closed due to failure to comply with Good Clinical practice.

    OR

    I have previously been the Principal Investigator at a site which has been closed due to failure to comply with Good Clinical practice and attach the relevant explanatory documents to this declaration.
11. *Delete the inapplicable option below:*
    I have not previously been involved in a trial which has been closed as a result of unethical practices.

    OR

    I have previously been involved in a trial which has been closed as a result of unethical practices and attach the relevant explanatory documents to this declaration.

12. I will submit all required reports within the stipulated timeframes.

_____

Printed name of Principal Investigator Date Principal Investigator's Signature

Declaration by Sub- and Co-Investigators and other staff involved in a Clinical Trial.

Name:

Title of Trial:

Protocol:

Site:

Designation:

1. I will carry out my role in the trial as specified in the protocol.
2. I will not commence with my role in the trial before written authorisations from the relevant ethics committee(s) as well as the South African Medicines Control Council (MCC) have been obtained.
3. If applicable to my role, I will ensure that informed consent has been obtained from all participants, or if they are not legally competent, from their legal representatives.
4. I will ensure that every participant (or other involved persons, such as relatives) shall at all times be treated in a dignified manner and with respect.
5. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.
6. *[Conflict of interest exists when an investigator (or the investigator's institution) has financial or personal relationships with other persons or organisations that inappropriately influence (bias) his or her actions.]***Modified from: Davidoff, F. Et al Sponsorship, Authorship and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)
7. *Delete the inapplicable option below:*
   I have not previously been the Principal Investigator at a site which has been closed due to failure to comply with Good Clinical practice.

   OR

   I have previously been the Principal Investigator at a site which has been closed due to failure to comply with Good Clinical practice and attach the relevant explanatory documents to this declaration.
8. I will submit all required reports within the stipulated timeframes.

_____

Printed Name Date Signature

Annexure 9

Example of List of study staff and their submitted documents.

Protocol number:_____

Table indicating the staff members who are requesting approval for participation in the trial and a record of their submitted documents.

Name	Position	CV	Declaration	MPI	GCP	HPCSA or other prof bosy.	Dispensing licence
Dr A	Principal Investigator	✓	✓	✓	✓	✓	n/a
Dr B	Sub-investigator	✓	✓	✓	✓	✓	✓
Ms C	Co-ordinator	✓	✓	n/a	✓	n/a	n/a

Annexure 10

SOUTH AFRICAN MEDICAL ASSOCIATION RESEARCH ETHICS COMMITTEE

MATERIAL TRANSFER AGREEMENT

Entered into between:

[Company name]

[Legal address]

Represented by:

[name of PROVIDER representative]
(hereinafter referred to as “the Provider”)

and

Company name]

[Legal address]

Represented by:

[name of REPCIPIENT representative]
(hereinafter referred to as “the Recipient”)

WHEREAS:

a) the Provider remains custodian of the Materials;

b) the Provider hereby transfers the Materials to the Recipient, and the Recipient accepts the Materials subject to the terms and conditions below; and

c) each Party undertakes to engage with the other in the utmost good faith and to conduct itself in the highest ethical standards and comply with all applicable legislation, including but not limited to the legislative ban on the sale of or trade in tissues, gametes, blood or blood products;

d) the recipient shall use the Materials to conduct non-commercial research in relation to the research project;

e) the Parties agree to conduct themselves hereunder in compliance with the SAMAREC Standard Operating Procedures on research on human biological materials; and

f) understanding, therefore, that no Materials can be transferred for purposes of a research project that has not been approved by the SAMAREC.

THE PARTIES THEREFORE AGREE AS FOLLOWS:

1. DEFINITIONS

1.1 In this agreement the following terms/expressions shall bear the meanings assigned to them below:

"Agreement"	shall mean this agreement and all annexures thereto, which annexures shall also be signed by the parties and shall form an inextricable part of this agreement;
"Benefit"	shall mean the benefit that will be received by the Provider from the use of the Materials by the Recipient. Benefits may include, amongst others, the sharing of information, use of research results, royalties, acknowledgement of the Provider as the source of the Materials, publication rights, transfer of technology or materials, and capacity building;
"Benefit sharing"	shall mean the process or act of sharing in the benefits that derive from the Project in a manner that is fair and equitable;
"Biobank"	shall mean an organised collection of Human Biological Material and associated data from different individuals, which are usually kept for an unlimited period of time, for the purposes of health research;
"Clinical Research Organization"	Shall mean a company or organization contracted by a sponsor to assume various aspects of the human research project.
"Country"	shall mean the Republic of South Africa;
"Custodian"	shall mean a person or entity entrusted by the Donor(s) with safeguarding and protecting the Materials;
"Data"	shall mean any information, including personal information in any form, derived directly or indirectly from Human Biological Materials, which will be used for research purposes;
"Donor"	shall mean a person who has donated Materials to be used for health research purposes;

"Effective date"	shall mean _____2016 irrespective of the date when the parties have signed the agreement;
"Human Biological Materials"	shall mean material from a human being, including but not limited to Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA), blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, tissues and growth factors and any modifications or derivatives thereof;
"Intellectual Property"	shall mean all patents, trademarks, service marks, designs, copyright (including all copyright in any designs and computer software), including source codes, formats, inventions, trade secrets and all other incorporeal property which may be the subject-matter of a right whether registered or capable of registration or not;
"Informed Consent"	shall mean the continuous information sharing process which allows a Donor(s) to consent to participate and determine whether and how their Materials will be utilised in the Project, as approved by SAMAREC;
"Materials"	shall mean Human Biological Materials and Data;
"Party"	shall mean either of the entities that entered into this Agreement as represented by their duly authorised signatories to this Agreement and **"Parties"** means any of them collectively and shall be deemed to mean and include their respective successors and permitted assigns;
"Patient Information and Informed Consent Document"	shall mean the document signed by the Donor(s), confirming their informed consent to participate in the research study, and "**PID**" shall have the correspondent meaning

"Project"	shall mean the health research project for which the Materials will be used hereunder;
"Research Results"	shall mean all products of the research, whether tangible or intangible;
"SAMAREC"	shall mean the South African Medical Association Research Ethics Committee registered with the National Health Research Ethics Council (NHREC), with the purpose of evaluating the ethics of research protocols developed for clinical trials to be conducted in the private healthcare sector;
"Secondary Use"	shall mean the use of the Materials for health research purposes other than the uses determined in the approved protocol. Secondary uses must be approved by SAMAREC;
"Sponsor"	An individual, company, institution or organization which takes responsibility for the initiation, management and /or financing of a health research project.
"Termination Report"	shall mean a report prepared by the Recipient and submitted to the Provider on termination of the Project. The Termination Report will include, inter alia, the reason for termination, status of Project at termination and current state of Materials.

2. OBLIGATIONS OF THE PROVIDER

2.1. The Provider agrees to transfer to the Recipient the Materials more fully described in **Annexure A**, and in the quantity, packaging and by mode of transport as more fully described in **Annexure A**.

2.2. Should the Provider be informed that the Materials have become identifiable for any reason whatsoever, the Provider is responsible for informing SAMAREC and the relevant Donor(s) of same and for obtaining approval from SAMAREC and consent from the Donor(s), where reasonably possible, for any further uses of the Material.

2.3. This Agreement is subject to the suspensive condition that SAMAREC has approved the study of which this Agreement forms part of, and is of no force or effect unless and until such approval has been granted.

3. ACKNOWLEDGMENTS BY AND OBLIGATIONS OF THE RECIPIENT

3.1. The Recipient acknowledges that the Materials have been obtained and/or developed by the Provider.

3.2. The Recipient acknowledges that the Materials are of health research value.

3.3. The Recipient may only carry out research according to the protocol approved by SAMAREC.

3.4. The Recipient will be responsible for obtaining the necessary permits and authorisations, and for arranging and bearing the costs of the appropriate transport for the Material to be transferred to the Recipient.

3.5. The Recipient acknowledges that the Materials may contain sensitive and confidential information, which information the Recipient undertakes to protect and keep confidential.

3.6. Other than those parties stipulated in **Annexure A**, the Provider may not transfer or otherwise provide the Material to any party without approval of SAMAREC. Such

approval will be on such written conditions as the Provider may deem fit in its sole discretion and will be agreed by the Recipient in writing.

3.7. Should the Materials become identifiable for any reason whatsoever, the Recipient must inform the Provider and SAMAREC without delay.

3.8. The Recipient agrees to deliver feedback to the Provider on the development and progress made with regard to the Project by supplying the Provider with updated information, where relevant, and in terms of applicable ethical and legal requirements.

4. USE AND PURPOSE OF MATERIAL

4.1. The Recipient warrants that the Materials will be used only for the purposes of the Project, as set out in **Annexure A**, attached hereto.

4.2. The Recipient agrees that the Material will be stored at, including any Biobank, the following address:

_____

_____

_____

4.3. The Recipient shall not, use the Materials for any purpose other than that permitted in terms of this Agreement.

5. BENEFIT SHARING

The sharing of benefits should be discussed and negotiated between the Provider, Recipient, the sponsor and/or the clinical research organization before Materials are transferred to the Recipient. The Parties agree to Benefit Sharing as detailed in **Annexure B**, attached hereto.

6. TERM AND TERMINATION

This Agreement will commence on the effective date and shall continue until the termination date.

7. TERMINATION OF PROJECT

7.1. In the event that the Project terminates, for any reason whatsoever, the Recipient will provide the Provider and SAMAREC with a Termination Report.

7.2. Termination of the Project will occur under one or more of the following circumstances:

7.2.1. the Project reaches completion;

7.2.2. the Project cannot be carried out by the Recipient for any reason whatsoever, including but not limited to the following:

a) the Donor(s) withdraw consent for use as contemplated hereunder, and in such that the numbers render continuation of the Project impracticable or impossible;

b) the Recipient entity dissolves, winds-up or ceases to continue operating;

c) SAMAREC withdraws approval for the Project in its entirety;

d) either Party terminates the Agreement on reasonable notice; or

e) a force majeure makes continuance of the Project impracticable or impossible.

7.3. On termination, the Recipient will immediately discontinue using the Material for any purpose whatsoever, and destroy the Material.

7.4. Destruction, return to the Provider or transfer of Materials will be undertaken, or any other arrangements made, with the express approval of SAMAREC.

8. INFORMED CONSENT

8.1. The Provider has to obtain informed consent from the Donor(s), on the SAMAREC approved PID, to provide Materials to the Recipient to undertake the Project as contemplated. In the event of Secondary Use of the Materials, the Donor(s) must consent thereto, insofar as the Secondary Uses have been approved by SAMAREC.

8.2. The Donor(s) must be informed that, where reasonably possible, the Provider will inform them of developments or progress made by the Recipient in the Project and which is relevant to the Donor(s)' Informed Consent.

8.3. The Donor(s) must be informed and accept that on termination of this Agreement, the Material will be returned to the Provider or destroyed, or any other arrangements made, as determined by the Provider under clause 7.

8.4. The Donor(s) must be made aware that all Materials and associated data are de-identified.

8.5. In the event that the Recipient wishes to conduct studies or use the Material for any other purpose either than that approved by SAMAREC, the Provider must be notified in writing and SAMAREC approval must be obtained prior to any other studies or uses.

9. DISPUTE RESOLUTION – NEGOTIATION, MEDIATION AND ARBITRATION

9.1. If any dispute arises out of or in connection with this Agreement, or related thereto, whether directly or indirectly, the Parties must refer the dispute for resolution, firstly

by way of negotiation and in the event of that failing, by way of mediation and in the event of that failing, by way of Arbitration. The reference to negotiation and mediation is a precondition to the Parties having the dispute resolved by arbitration.

9.2. A dispute within the meaning of this clause exists once one Party notifies the other in writing of the nature of the dispute and requires the resolution of the dispute in terms of this clause.

9.3. Within 10 (ten) business days following such notification, the Parties shall seek an amicable resolution to such dispute, by referring such dispute to designated representatives of each of the Parties for their negotiation and resolution of the dispute. The representatives shall be authorised to resolve the dispute.

9.4. In the event of the negotiation between the designated representatives not resulting in an agreement signed by the Parties resolving the dispute within 15 (fifteen) business days thereafter, the Parties must refer the dispute for resolution by way of mediation, in accordance with the then current rules of the Arbitration Foundation of Southern Africa ("AFSA").

9.5. In the event of the mediation envisaged in 9.4 failing in terms of the rules of AFSA, the matter must, within 15 (fifteen) business days thereafter, be referred to arbitration as envisaged in the clauses below.

9.6. The periods for negotiation or mediation may be shortened or lengthened by written agreement between the parties.

9.7. Each Party agrees that the Arbitration will be held as an expedited arbitration in _____ (insert city), in accordance with the then current rules for expedited arbitration of AFSA, by 1 (one) arbitrator appointed by agreement between the Parties, including any appeal against the arbitrator's decision. If the Parties cannot agree on the arbitrator or appeal arbitrators within a period of 10 (ten) business days after

the referral of the dispute to arbitration, the arbitrator and appeal arbitrators shall be appointed by the Secretariat of AFSA, who shall administer and manage the arbitration proceedings.

9.8. The provisions of this clause 9 shall not preclude any Party from access to an appropriate court of law for interim relief in respect of urgent matters, by way of an interdict or mandamus, pending finalisation of this dispute resolution process for which purpose the Parties irrevocably submit to the jurisdiction of a division of the High Court of the Republic of South Africa.

9.9. The references to AFSA shall include its successor or body nominated in writing by it in its stead.

9.10. This clause 9 is a separate, divisible agreement from the rest of this Agreement and shall remain in effect even if the Agreement terminates, is nullified or cancelled for whatsoever reason or cause.

10. INTELLECTUAL PROPERTY

Intellectual property will be dealt with through the relevant laws related to the applicable protocol for the project and underlying third party agreements in so far as they are applicable.

11. CONFIDENTIALITY

The Recipient agrees to keep the Materials secure and confidential at all times. Confidentiality includes, but is not limited to: the properties, characteristics, content, composition, potential secondary uses and methods of use of the Material. All information relating to the nature and processes of the research in whatever form, should be treated as confidential. The personal information, including the identity of

the Donor(s), must be protected and kept confidential at all times. Any publications, newsletters or oral presentations must not divulge any details of the Donor(s), unless consent has been obtained for such use from the Donor(s).

12. PUBLICATIONS AND PUBLICITY

12.1. Publications of any health research results must be in accordance with the updated guidelines laid down by the World Medical Association, in particular, the Declaration of Helsinki (2013), and authorship of the publication emanating from the use of the Materials hereunder must be in keeping with the International Committee of Medical Journal Editors Authorship Guidelines (http://www.icmje.org/icmje-recommendations.pdf) as amended from time to time.

12.2. Where the Recipient wishes to publish any information concerning the Project (in either oral or written form), the Provider must be notified and provided with a copy of the publication, at least ten (10) days prior to submission of the proposed publication. The Provider must inform the Recipient whether any information related to the publication must be removed or included and provide reasons to substantiate the removal or addition of such information.

12.3. The Provider must be supplied with a final copy of the publication before the publication is released by the Recipient. The Recipient must acknowledge the Provider's contribution of the Material, unless otherwise requested by the Provider.

12.4. Neither Party shall use the name of the other Party or its employees in any advertisement, press release or other publicity without prior written approval of the other Party.

12.5. Notwithstanding the above, and where relevant, publications must be subjected to the applicable protocol and relevant third party agreements.

13. LIMITED LIABILITY

13.1. The Provider gives no warranty that the Materials are fit for the use and purpose for which they are transferred hereunder, or that they have any particular qualities or characteristics.

13.2. In no event shall either party be liable to the other or any third party in contract, delict or otherwise for incidental or consequential damages of any kind, including, without limitation, punitive or economic damages or lost profits, regardless of whether either party shall be advised, shall have other reason to know or in fact shall know of the possibility.

13.3. The Provider will not be liable to the Recipient for any claims or damages arising from the Recipient's use of the Material.

13.4. Should either Party breach the terms of this Agreement, notwithstanding 7 (seven) days written notice to rectify the breach, this Agreement may be terminated by the aggrieved Party on written notice.

14. ENTIRE AGREEMENT

This Agreement sets forth and constitutes the entire agreement and understanding of the parties with respect to the subject-matter hereof. This agreement supersedes any and all prior agreements, negotiations, correspondence, undertakings, promises, covenants, arrangements, communications, representations and warranties, whether oral or written, of any party to this Agreement. This Agreement is null and void and of no force and effect unless and until SAMAREC has approved the research of which the Agreement forms a part.

15. CONFLICTS

The terms of this Agreement, including the Annexures forming part hereof, shall take precedence over any conflicting terms in any referenced agreement or document.

16. VARIATIONS

No variation or consensual cancellation of this Agreement will be of any effect unless reduced to writing and signed by the parties.

17. NON-WAIVER

The failure or delay of either party to exercise any of its rights or remedies under this Agreement for a breach thereof shall not be deemed to be a waiver of such rights or remedies, and no waiver by either party, whether written or oral, express or implied, or any rights or remedies under or arising from this Agreement shall be binding on any subsequent occasion, and no concession by either party shall be treated as an implied modification of this Agreement, unless specifically agreed in writing, duly executed by authorised representatives of the parties. Similarly, the rights and remedies of parties arising in common law shall not be capable of being waived or varied otherwise than by an express waiver or variation in writing duly executed by authorised representatives of the parties.

18. CESSION AND ASSIGNMENT

No rights, duties or liabilities under this Agreement may be ceded, assigned, transferred, conveyed or otherwise disposed of by either party without the prior written consent of the other party and the approval form SAMAREC, which consent shall not be unreasonably withheld.

19. SEVERABILITY

The terms of this Agreement are severable – if any term or provision of this Agreements is declared to be illegal, void or unenforceable by a court of competent jurisdiction, the remainder of the provisions shall continue to be void and enforceable.

20. SIGNATURE AUTHORITY

The individual signing below hereby represents and warrants that he/she is duly authorised to execute and deliver this Agreement on behalf of the party whose name appears beneath his/her signature and that this Agreement is binding upon such party.

Thus done and signed on this the _____ day of _____ 2016.

On behalf of the Provider:

_____

(duly authorised thereto)

As witnesses: The Provider:

1. _____

Signature:

Name:

2. _____

Signature:

Name:

Thus done and signed on this the _____ day of _____ 2016.

On behalf of the Recipient:

_____

Name:

Designation:

Developer:

(duly authorised thereto)

As witnesses: the Recipient:

1._____

Signature:

Name:

2. _____

Signature:

Name:

Annexure A

To be completed by the Parties

The details of the entity which will obtain the necessary permits and authorisations and arrange appropriate transport for the Material to be transferred is:

_____

Description of health research project under which the Materials will be used on transfer:

_____

_____

_____

Details of the Sponsor funding the health research project:

_____

_____

_____

Details of the Clinical Research Organization conducting the health research project on behalf of the sponsor (if applicable):

_____

_____

_____

The nature of the Materials Requested:

_____

_____

_____

_____

_____

Specific experimental tests that the Materials will be subjected to on transfer:

_____

_____

_____

_____

_____

_____

Parties (except the sponsor and the clinical research organization) other than the Recipient to whom the Materials might be transferred as required by the Project:

_____

_____

_____

_____

Quantity of Materials required to be transferred:

_____

_____

_____

_____

Preferred method of transfer of Materials:

_____

_____

_____

_____

Period within which Materials will be transferred:

_____

_____

_____

_____

How will confidentiality be maintained should Materials be released into the public domain?

_____

_____

_____

_____

_____

_____

Annexure B

Benefit Sharing Arrangement between the Recipient and Provider



ACKNOWLEDGEMENTS

This MTA is an adaptation of the University of the Witwatersrand MTA template Version 3 dated 02 Dec 2016