STANDARD OPERATING PROCEDURE, JULY 2026, V12

Research Ethics Committee

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Final Version	Reason for Amendment	Effective Date
9	Updated and published for implementation	October 2023
	Administrative changes	March 2024
10	Definition amendment	June 2024
11	NDOH 2024 and ICH GCP Updates	July 2025
12	Annual Fee Increase and Administrative Changes to align with updated NDOH Research Ethics Guidelines 2024 V3.2	July 2026

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

DEFINITIONS AND INTERPRETATIONS

In this document, unless the contents otherwise requires, the following words shall mean:

1. **"Amendments"** refers to changes in the PID and Protocol which are forwarded to the SAMAREC in the most recently approved versions of same. All changes must be indicated with track changes.
2. "**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.
3. **"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.
    - Any reference to the singular includes the plural and vice versa.
    - Any reference to natural persons includes legal persons and vice versa.
    - Any reference to a gender includes the other gender.
    - The clause headings in the Standard Operating Procedures have been inserted for convenience only and shall not be considered in interpreting this SOP.
4. A "**Clinical Trial"** refers to a prospective biomedical or behavioural research study of human participants 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).
5. **"Co-Principal Investigator"** refers to a qualified non-clinician scientist or equivalent qualified and experienced person who can provide trial oversight management, and who is jointly and severally liable for the clinical trial with the Principal Investigator.
6. **"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),
7. **"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.

8. **"Participant(s)"** refers to the person(s) 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(s)" or "participant(s)"** may be used interchangeably, where applicable.
9. A **"Patient"** is defined as a participant with a diagnosed clinical condition.
10. "**Physician**" refers to 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.
11. **"Principal Investigator"** shall refer to a person responsible for the conduct of the clinical trial at a trial site.
12. **"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 "**research"** shall have a corresponding meaning, and the term experiment or clinical trial may be used interchangeably with the word "**research"**, when applicable. Research can be broadly classified as therapeutic and non-therapeutic.
13. **"Researcher"** shall refer to an individual responsible for 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 (research).
14. **"Sub-Investigator"** refers to 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.
15. **"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.
16. **"Study Staff"** collectively refers to the investigators, study coordinators, study nurses, pharmacists, raters, and any other people rendering support to the investigator.
17. **"Study site" refers to** the location(s) where trial-related activities are actually conducted wherein the context of this SOP shall be within the borders of the republic of South Africa.
18. **"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.
19. **"Witness"** refers to someone who witnesses the signing (consent confirmation process) by the participant and confirms same. However, when the participant is illiterate the meaning of '*witness'* changes whereby referring to a person delegated person to accurately explain and confirm that consent was voluntarily given.

INTRODUCING SAMAREC

1. LEGISLATIVE FRAMEWORK AND VALUE STRUCTURE.

1.1 LEGISLATIVE FRAMEWORK

1.1.1 The South African Medical Association Research Ethics Committee (SAMAREC) was established by the South African 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.

1.1.2 SAMAREC recognises that health research includes research on health systems, public health, behavioural, and social determinants of health, provided such research impacts health outcomes, health service delivery, or population health.

1.1.3 The National Health Act (NHA), 61 of 2003, as amended, 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 thus registered on the National Department of Health (NDOH) National Research Ethics Council database.

1.1.2 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 the Republic of South Africa 1996 provides that everyone has the right not to be subjected to medical or scientific experiments/research without their informed consent (See Section 12(2)(C).

1.1.3 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.

1.1.4 In the execution of its responsibilities in evaluating the ethics of research protocols, SAMAREC is guided by the relevant South African law(s), research and ethics guidelines, professional standards, international standards and guidelines including codes of practice that might be relevant to the situation.

1.1.5 The NHA provides that health research ethics committees (HRECs) must be established by every institution, health agency and health establishment at which health research is conducted, alternatively must have access to a HREC, which is registered with the NHREC.

"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 **NHREC**, 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.*

1.1.6 In terms of the NHA the NHREC must: -

(a) determine guidelines for the functioning of health RECs.
(b) register and audit health RECs.
(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 RECs and hear any complaint by a researcher who believes that he or she has been discriminated against by a health REC.
(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."

1.1.7 According to the Guidelines for Ethics in Health Research, published by the National 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.

1.1.8 SAMAREC follows the standards adopted by:

a) the latest version of the American Food & Drug Administration (FDA) where applicable to internationally sponsored research and
b) The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidelines for Good Clinical Practice;
c) World Medical Association, in particular, the latest version of the Declaration of Helsinki (2024),
d) the Belmont Report,
e) the NDOH,
f) the South African Health Products Regulatory Authority (SAHPRA), and
g) other relevant statutory bodies involved in the healthcare sector.

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

a) the scientific relevance of the clinical study;
b) the suitability of the investigator(s) for the proposed study in terms of his/her availability, qualifications, experience, supporting staff, and available facilities;
c) the relevance of the study rationale and the appropriateness of the inclusion / exclusion criteria to the South African context;
d) 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;
e) 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;
f) that the number of participants to be recruited is adequate to demonstrate the predicted effect;
g) 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;

h) if placebos are to be used, whether their use can be justified;

i) that by their participation in a clinical study the participants are not denied timely access to medical personnel, investigations, equipment, or procedures;

j) 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;

k) 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;

l) that the application allows the participants and/or their representatives adequate time to consider the patient information document before informed consent is sought;

m) the content of any advertisements or public notices which will be used to recruit participants to a study;

n) the study protects participants' rights to privacy and confidentiality according to the provisions of the Protection of Personal Information (POPI) Act, Act 4 of 2013;

o) 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;

p) the extent to which investigator(s) and participants are to be compensated for participation in the study;

q) 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;

r) the demographic information available to assess whether the patient population is adequate to support the study;

s) whether there is no cost to the participant, medical schemes, or insurance for trial specific procedures;

t) 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;

u) whether any restrictions will be placed on the publication of results by the investigators after completion of the trial;

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

1.1.10 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.

1.2 REGISTRATIONS OF SAMAREC

1.2.1 SAMAREC has been registered and audited in accordance with the NHA (61 of 2003). Registration number: 280808-016. Valid until 30 November 2027

1.2.2 In March 2002, SAMAREC became a registered REC at the Department of Health and Human Services (DHHS) of the USA (IRB: 0001 1624)

1.2.3 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: 0002 7240).*** Valid until **06 July 2028**.

1.3 SAMAREC's COMMITMENT TO ETHICAL PRINCIPLES

1.3.1 Foundational Ethical Principles in Research

SAMAREC is committed to upholding the highest ethical standards in all research activities involving human participants. These principles guide the conduct, review, and oversight of research and serve to protect the rights, dignity, and welfare of all involved, while promoting high-quality scientific inquiry.

1.3.1.1 Ethical Principles for Research Involving Human Participants:

1.3.1.1.1 *Beneficence and Non-Maleficence*

SAMAREC recognizes the ethical obligation to maximize potential benefits and minimize potential harms in all human research. Research must be scientifically valid, ethically designed, and conducted by competent professionals. No deliberate harm may be inflicted on participants, and risks must be reasonable in relation to anticipated benefits.

The guiding question remains: Does the research aim to enhance human understanding or well-being? If not, the study **may** not meet ethical standards. While curiosity-driven ("blue sky") research is supported, studies lacking foreseeable value or purpose may not be ethically justifiable.

1.3.1.1.2 *Distributive Justice (Equity)*

Research must reflect fair distribution of risks and benefits among all involved – including individual participants, their communities, and broader South African society. No group should bear an undue burden or be unfairly excluded from research benefits. The source population should have a reasonable likelihood of benefiting from the research outcomes, either directly or in the future.

1.3.1.1.3 *Respect for Persons (Dignity and Autonomy)*

All individuals must be treated with dignity, respect, and fairness. Those capable of making informed decisions should be empowered to do so; individuals with diminished capacity must be protected from harm.

Respect for persons includes:

a) Autonomy and informed decision-making,
b) Protection of privacy, confidentiality, and wellbeing,
c) Recognition of cultural, societal, and contextual influences on consent.

These principles are rooted in the SAN Code of Research Ethics (2017) and are consistent with the African philosophy of *Ubuntu*, which emphasizes shared humanity, justice, and reciprocity. The interests of participants must generally outweigh those of science and society, except in exceptional contexts such as public health emergencies where societal interests may be prioritized.

1.3.2 Application of Ethical Principles

These ethical principles serve as the foundation for SAMAREC in reviewing protocols which include:

a) Safeguard participant welfare;
b) Promote integrity in research; and
c) Fostering the development of high-quality, socially beneficial knowledge.

All researchers conducting research are expected to adhere to these principles throughout the research

lifecycle.

1.4 CORE NORMS FOR ETHICAL HUMAN RESEARCH

SAMAREC applies the following operational norms in the review and approval of human research:

1.4.1 *Relevance and Value*

Research must respond to the needs of South Africa's people, contributing to knowledge that can inform meaningful interventions, policies, or practices that promote health and wellbeing.

1.4.2 *Scientific Integrity*

Protocols must reflect sound study design and methodology. Poorly designed studies that expose participants to risk without meaningful outcomes are ethically unacceptable and will be rejected.
Scientific Validity and Prior Review Requirement

All research protocols submitted for review must demonstrate adequate scientific validity prior to or as part of ethics review. We require evidence of independent scientific review (e.g., institutional scientific committee approval, peer review, or sponsor validation) confirming that the study design, methodology, and statistical considerations are sound and capable of answering the research question. In the absence of documented prior scientific review, we will undertake or commission an appropriate scientific assessment before granting approval. In accordance with the principles outlined by the National Health Research Ethics Council, National Department of Health, and South African Good Clinical Practice Guidelines, no study shall be approved unless SAMAREC is satisfied that the research is scientifically valid, as scientifically unsound research is considered unethical.

1.4.3 *Stakeholder Engagement*

Researchers are expected to engage stakeholders early and continuously. This includes co-researchers, communities, and relevant institutions, to promote transparency, trust, and shared ownership of the research process.

For research that is community-embedded, high risk, or involves vulnerable or marginalised populations, investigators must demonstrate appropriate **community engagement mechanisms**, which may include Community Advisory Boards (CABs), stakeholder consultation processes, and structured plans for feedback of study progress and results to participant communities.

1.4.4 *Favourable Risk-Benefit Ratio*

A robust risk-benefit analysis must demonstrate that potential benefits outweigh risks to participants or society. Studies with unjustified risks or those involving vulnerable populations require heightened justification and safeguards.

Social science research risks such as psychological, moral, or social harm must be considered and addressed with equal diligence.

1.4.5 *Fair Selection of Participants*

Recruitment must be based on scientific and ethical rationale, not discriminatory or exploitative criteria. Inclusion and exclusion must not be based on prohibited grounds as defined by the South

African Constitution (see Section 9).

1.4.6 *Informed Consent*

Participation must be voluntary and informed. Researchers are responsible for ensuring a comprehensive consent process prior to and throughout the study. The necessary considerations much be given to vulnerable populations to protect their interests and wellbeing.

1.4.7 *Ongoing Respect for Participants*

Once enrolled, participants' rights, autonomy, and wellbeing must continue to be protected. Participants have the right to withdraw at any time and must be kept informed. Confidentiality must be rigorously maintained throughout the research process.

1.4.8 *Researcher Competence and Expertise*

All researchers must demonstrate appropriate qualifications, training, and experience. Principal Investigators (PIs) or research leaders are responsible for ensuring scientific integrity, ethical conduct, and participant safety. For international multi-site research, at least one (co-)PI must be physically in South Africa.

Researchers must:

a) Hold relevant academic and ethical credentials;

b) Demonstrate recent ethics training (within 3 years);

c) Disseminate findings responsibly and inclusively, including to participant communities where appropriate.

2. COMPOSITION OF SAMAREC

2.1 General

2.1.1 Research Ethics Committees must consist of members who collectively have the necessary qualifications and experience to review and evaluate the science, health legal, and ethical aspects of proposed research. Committees must be independent, multi-disciplinary, multi-sectorial and pluralistic.

2.2 Appointment of Committee Members.

2.2.1 When a specific portfolio on the committee is required or becomes vacant (e.g., legal member), a new member will be recruited by means of advertisements in the applicable field. Prospective members are then requested to present their credentials and once the REC leadership (through consultation of the existing members) become satisfied of such a person meeting the necessary criteria, such a member will then attend a formal meeting (while signing a confidentiality agreement). Should the specific member have the required expertise and have a definite interest in the committee, they are requested to join the committee.

2.2.2 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. Once elected, members will receive formal appointment letters signed by the current Chief Executive Officer of SAMA (on behalf of the Board of Directors of SAMA). The Chairperson and Vice (Deputy)-Chairperson are elected by the current committee members based on their expertise and experience levels. The Vice (Deputy) Chairperson will

assist the Chairperson and will act as Chairperson when necessary and will also assist the Chairperson with responsibilities as required.

2.2.3 The SAMAREC Composition will be updated as and when changes occur. 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. These individuals will also only be approached should they not have a conflict of interest in the study in question and will also be required to sign a confidentiality agreement. These individuals will be approached based on a referral basis and shall be provided to the necessary appointment letter from SAMA which confirms their scope of function. Curricula vitae of the Committee members and external experts (if applicable) are available on request as these are kept by the SAMAREC Officer.

The current composition of SAMAREC is as per Annexure 5

2.3 Training Requirements for SAMAREC Members:

2.3.1 All SAMAREC Committee members and Administrators/Officers will receive internal training which includes a Mentorship 'Program', as well as external training involving Research Ethics and Good Clinical Practice (GCP) training, funded by SAMA in order to remain compliant with the NHREC's training requirements. SAMAREC maintains record of training activities for all Committee members in a training log which is reviewed annually by SAMAREC and NHREC.

a. CONTACT DETAILS

The SAMAREC Officer (currently Lisa Reid) or SAMAREC Administrator (currently Michelle Snijder) collectively referred to as the SAMAREC Secretariat, may be contacted at:

Telephone	:	(012) 481 2082
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

b. PROTOCOL REVIEW FEES

SAMAREC Submission and other relevant Fees for evaluation of protocols appears on Annexure 6 (hereto attached). All submissions must be submitted with the SAMAREC Application form. Once applications are received, SAMA will send through an invoice for payment.

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.

NB: SAMA reserves the right to retain approval letters until payment is received in full.

If a protocol submitted for review is of a unique, complex, or highly specialised nature that requires consultation with external subject-matter experts or specialist reviewers, additional costs may be incurred beyond the

standard protocol review fee. In such instances, the Ethics Committee reserves the right to obtain appropriate expert input to ensure a thorough and competent scientific and ethical review of the study. Any such additional costs will be reasonable and directly related to the specialist consultation required, and the applicant will be informed in advance where applicable.

3. PROCEDURES AND ADMINISTRATIVE GUIDELINES MEETINGS

SAMAREC meets on the second Wednesday of each month unless circumstances require otherwise E.g., loadshedding, no quorum indicated prior to the meeting.

Applications for consideration must be submitted via e-mail to the SAMAREC Secretariat via email samarec@samedical.org, Please request the latest Meeting Dates and Submission details – available in SOP Annexure 1. Kindly contact the SAMAREC Officer if you are unable to meet a submission deadline for alternative arrangements.

4. DECISIONAL ANALYSIS, PROTOCOL, AND INFORMED CONSENT REVIEW PROCESS

- A written response regarding decisions is usually forwarded to applicants within ten working days after the meeting.
- Sixty percent (60%) of the Committee constitutes a quorum. Provided required scientific, ethical, legal and lay representation is present
- Confidentiality of the content of applications, the protocols, and the procedures of SAMAREC, is maintained as far as is reasonably possible.
- SAMAREC Secretariat will prepare the meeting packs as per the submission dates and submit to the Committee at least ten (10) days prior to meeting dates.
- Final decisions are discussed during the SAMAREC Meetings via voting, discussion and noted accordingly in the meeting minutes.
- SAMAREC will always ensure the privacy and confidentiality of patients and participants is the priority of the study.
- Decisions will be finalized by the approval of the entire Committee and feedback will be provided to applicants within ten working days of the SAMAREC Meeting.

(A list of the scheduled meetings for the current year is available in the SAMAREC SOP Annexures)

5. SUBMISSION OF RESEARCH PROTOCOL REVIEWS

All submissions to SAMAREC should be done electronically (via e-mail) to samarec@samedical.org

5.1. New applications

For new applications, the following documents - with dates and version numbers - relevant to the proposed study need to be submitted: -

- SAMAREC Application Form (Refer to Annexure 2);
- Covering letter (for rapid and expedited reviews, covering letter must detail the request. Motivation for rapid review must also clearly indicate the need for urgency). Please provide a numbered list of all documents submitted with the application;
- Protocol summary/synopsis;
- Protocol;
- Patient Information and Informed Consent Document (PID) (*pro forma* attached as Annexure 4). Please note: This document must be submitted in Word format.;
- Investigator's Brochure;
- Material Transfer Agreement (proforma attached as Annexure 12);
- Questionnaires (if any);
- Copy of the Insurance Certificate;
- Data Management Plan (Template attached as Annexure 11);
- South African Health Products Regulatory Authority (SAHPRA) approval or notification letter of submission;
- Proof of South African National Clinical Trial Register (SANCTR) registration;
- Details and breakdown of study budget, 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 7);
- Justification for the use of a placebo (if applicable);
- *Curricula Vitae* of all study personnel according to the SAHPRA format (as a minimum format / requirement - copy of format attached as Annexure 3). Submissions to include outline of additional Research Ethics Training other than Good Clinical Practice Training;
- Declarations by Trialists (Please refer to Annexures 8 and 9 for the declaration template);
- Proof of personal Malpractice Indemnity cover of study doctors, nurses, and pharmacists;
- GCP certificates (SAMAREC recommends that site staff be trained in latest version of both ICH GCP and SA GCP); and
- Dispensing License (if applicable).

Submitted documentation required to include the following information in footers "**Protocol number/ Participant Information and Informed Consent Document, SAMAREC Version XX dated XXX**." Furthermore, no product logos should be displayed on any documentation.

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 / SANCTR 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.

Submission of additional site staff once approval has been obtained should include the following:

- Covering letter listing study staff. (Please note that letter must be presented with an indication of their submitted documents (example attached as Annexure 10), and
- Relevant documentation as mentioned above.

Protocol Criteria:

According to the South African Ethics in Health Research Guidelines, 3rd Edition (NDoH 2024), a clinical trial protocol must include several minimum essential elements to ensure ethical, scientific, and regulatory compliance.

A well-structured protocol should

- clearly define the research question and objectives, enriched by a detailed background and rationale;
- it must describe the trial design (including interventions, control groups, randomization, blinding, inclusion/exclusion criteria, sample size justification, and endpoints), along with a statistical analysis plan;
- It should articulate roles and responsibilities of the investigator(s) and sponsor, including relevant qualification documentation (e.g., CVs, facility approvals);
- stipulate adherence to Good Clinical Practice and national legal frameworks (such as the National Health Act)
- cover safety monitoring, including adverse event reporting procedures, and specify provisions for informed consent, privacy, confidentiality, and protections for vulnerable populations; and lastly
- outline ethical governance structures such as Research Ethics Committee (REC) oversight, Data Safety Monitoring Boards (where applicable), plans for trial registration (e.g., SANCTR/PACTR), and policies for data sharing, post-trial access, and dissemination of results.

For studies involving immunocompromised participants or those receiving biologic or immunosuppressive therapies, SAMAREC recommends that TB and HIV screening be considered and justified within the protocol and submission documents. If TB and HIV screening are not applicable, a clear rationale should be provided.

5.2. Annual Renewal and 6-Monthly Progress Reports

For annual renewals, the following documents - with dates and version numbers - relevant to the proposed study need to be submitted:

a) Covering Letter; and
b) Progress Report.

5.3. Additional Post Approval Notification

Additional post approval notifications may include resignation of site staff, additional site staff, additional translation of patient facing material, Development Safety and Update Report (DSUR), Investigational Medical Product Dossier (IMPD) etc.

For additional post approval notifications, the following documents relevant to the proposed study need to be submitted:

a) Covering Letter; and
b) Relevant Report i.e., DSUR report Documentation as per section 3.1

5.4. Retrospective Approvals

Quality assurance and quality improvement studies (audits), programme evaluation activities, performance

reviews and consumer surveys usually do not constitute research and thus usually do not undergo formal ethics review. It should be noted, however, that if publication of such studies is desirable, it is prudent to obtain ethics approval before the study begins. RECs may not grant retrospective ethics approval.

6. COVERING LETTER

The Covering Letter must be dated and contain the following details:

a) A brief summary of the protocol;
b) Confirmation of the study sites;
c) The study doctor's assessment of any potential additional risks or discomforts to the participants;
d) Study staff must be listed with an indication of their submitted documents (example attached as Annexure 10); and
e) Details of documents submitted with dates and version numbers.

7. DECLARATIONS

Declarations by all study staff must reflect:

a) the name of the sponsoring company;
b) Protocol number and title, as well as
c) the study staff's name and designation (*proforma* attached as Annexures 8 and 9).

Please note, declarations must be properly completed and signed.

8. SITE STAFF CURRICULUM VITAE

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

8.1 The approval criteria for Principal Investigators are:

a) must be a suitably qualified health care professional;
b) must have participated in two completed trials as Sub-Investigator;
c) must have proof of valid GCP training in the last 3 years; and
d) trial must be within the Principal Investigator's scope of practice.

8.1.1 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 specialty, confine his or her practice to the specialty or related specialties in which he or she is registered;
(b) in the case of a sub-specialty, confine his or her practice mainly to the sub- specialty in which he or she is registered."

8.2 The approval criteria for Sub-Investigators are:

a) must be suitably qualified health care professional such as a qualified medical doctor;
b) 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).

c) if not previously involved in a trial, they should work under the supervision of the Principal Investigator; and

d) the trial should be within the Sub-Investigator's scope of practice.

8.2.1 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-

(c) (a) in the case of a specialty, confine his or her practice to the specialty or related specialties in which he or she is registered;

(d) (b) in the case of a sub-specialty, confine his or her practice mainly to the sub- specialty in which he or she is registered."

According to the 2024 National Department of Health Research Ethics Guidelines, all research site staff involved in the conduct of health research are required to provide proof of completed research ethics training, in addition to Good Clinical Practice (GCP) certification (All those involved in touching participants clinically and working on study data). This training should specifically address the ethical principles, legal frameworks, and local context relevant to research involving human participants in South Africa. While GCP focuses on the quality and integrity of clinical trial conduct, research ethics training ensures that staff understand the rights, safety, and well-being of participants, ethical decision-making, and compliance with national and institutional ethical standards. Investigators and sponsors must ensure that documented evidence of such training is submitted to Research Ethics Committees (RECs) as part of initial applications or amendment packages and updated as necessary. Further, internal staff training registers should be maintained and kept on record.

9. 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).

Any proposed change to financial arrangements after approval of a study that introduces or modifies payments to investigators or study sites, particularly where such payments are linked to participant recruitment, screening, or enrolment, shall be regarded as a major amendment In line with South African Good Clinical Practice (SA GCP 2020) and the National Department of Health Ethics in Health Research Guidelines (2024), such incentives may create real or perceived conflicts of interest and have the potential to influence recruitment practices, participant selection, and the integrity of the informed consent process. Accordingly, all recruitment-linked or performance-based payments must be fully disclosed to SAMAREC, together with a justification and appropriate safeguards to mitigate the risk of undue influence or compromised scientific and ethical standards. No such changes may be implemented prior to receipt of formal approval. To be compliant, the recruitment-linked payment must be:

- Ethically justified
- Scientifically neutral

- Transparent
- Actively monitored for risk

10. 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).

11. PUBLISHING OF RESULTS

In the interest of transparency, it is preferable that the Principal Investigator may independently publish their results, subject to internationally approved conditions and have undergone peer review. However, where this is not the case, the agreed-upon procedure for publishing the results and including co-authors/co-investigators should be explicitly stated in the application. The sponsor must be identified in all research publications.

Investigators are expected to provide **appropriate feedback of study results to participants and, where applicable, participant communities**, in a format that is understandable and accessible.

12. 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' preferred 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 additionally consent to the presence of the interpreter. Should a translator be present during the consent process, the information provided to the patient should clearly stipulate that the privacy of the consent will be compromised to that extent (DOH 2024), and this should also be stated in the protocol. Translators should not unduly influence the consent process.

Submission Requirements:
A covering Letter and SAMAREC-approved documents translated into other languages must be sent to SAMAREC along with the translation certificates for record purposes.

13. SOUTH AFRICAN HEALTH PRODUCTS

REGULATORY AUTHORITY (SAHPRA) APPROVAL

Where SAHPRA approval for the trial is required, a copy of the approval letter must be submitted. If SAHPRA approval is pending, proof of application to the SAHPRA must be included. Where only SAHPRA notification is required, a copy of the notification must be submitted. Clients are requested to ensure that they abide with SAHPRA regulations, whether their projects need approval or only notification. SAMAREC Approval is subject to that of SAHPRA approval.

14. FIRST IN HUMAN, PHASE 1 CLINICAL TRIALS

SAMAREC shall review and approve all proposed remuneration, reimbursement, compensation, and incentive arrangements for research participants prior to study approval. For Phase 1 clinical trials involving healthy volunteers, remuneration shall be fair, transparent, and commensurate with the time commitment, inconvenience, discomfort, restrictions, and burdens associated with study participation, in accordance with applicable South African Health Products Regulatory Authority (SAHPRA) guidance. Remuneration must not constitute an undue inducement or compromise the voluntariness of informed consent. Informed Consents must ensure that payment structures do not encourage participants to conceal relevant medical information, disregard adverse events, or remain in a study against their interests. Payments should, where appropriate, be prorated to ensure that participants who withdraw or are withdrawn from a study are compensated fairly for completed study procedures. Reimbursement for reasonable out-of-pocket expenses, including travel, meals, accommodation, and other participation-related costs, shall be distinguished from remuneration for time and inconvenience. SAMAREC will assess all participant payment arrangements in accordance with the principles of respect for persons, beneficence, justice, and voluntariness as set out in the National Health Research Ethics Council (NHREC) guidelines and relevant SAHPRA clinical trial compensation guidance. Any deviations from approved remuneration schedules shall require prior review and approval.

To include the following in all Informed Consent Documentation for Phase 1 clinical trials to keep patients aware of the risks of the study:

"This study is a Phase-1 ('first-in-human') study and is the first time this medicine is being tested in people. The aim is to understand this medicine's safety, how the body processes it, and what dose levels can be used safely. It is not expected to provide medical benefit to participants. If you choose to take part, you will attend scheduled visits, take the study medicine as instructed, and undergo safety checks such as blood tests, vital-sign measurements, and monitoring for any side effects. You may need to stay in a hospital or research facility for several days, so the study team can closely monitor your response during and after dosing. Because this is the first use in humans, there may be unknown or unexpected side effects, including serious ones, and the study doctor may pause or stop dosing at any time if needed for your safety."

15. MAJOR AND MINOR AMENDMENTS

Amendments to be submitted to SAMAREC will be ratified by the full Committee at the subsequent meeting. The Amendment's will also be allocated to the original main evaluators of the first submission of protocol as main evaluators wherein additional evaluators may be appointed by the Committee as deemed necessary.

a) ***Major Amendment*** involve Ethical Changes e.g., Protocol or PID, Changes in patient recruitment or reimbursement. Such amendments will receive a Full Review by the Committee which will be tabled at the subsequent meeting.

b) ***Minor Amendment*** involve Sponsor Name Changes, Addresses, Administrative not involving ethical concerns (10 Working Days). Such amendment will be reviewed by the Committee in-between formal meetings, however, should the reviewer be of the opinion that the minor amendment requires formal Committee input, the amendment will be distributed to the entire Committee and added to the next scheduled meeting's agenda for final approval.

Submitted documentation are required to include the following information in footers "*Protocol number/ Participant Information and Informed Consent Document, SAMAREC Version XX dated XXX*".

NB: No product logos should be displayed on any documentation.

Submission Requirements:

Covering letters accompanying amended PIDs must state the date of their original approval. Covering letter should provide a brief paragraph or summary outlining the amendment(s). Amendments must be shown on the latest SAMAREC approved documents containing the changes recommended by SAMAREC, and the changes should be highlighted to facilitate review. A track-changes-copy, and a clean copy of the amended document must be provided in the submission.

NB: All amendments must be submitted electronically.

16. PRESENTATIONS

Presentations at meetings by sponsors and/or researchers who wish to explain and elucidate complicated and/or sensitive trials will be allowed upon written request received at least fifteen (15) days before the scheduled meeting, and shall be at the discretion of SAMAREC. SAMAREC may also request the sponsor to present should they have any concerns regarding the trial.

17. REPORTING OF PROTOCOL DEVIATIONS AND VIOLATIONS

Protocol deviations and violations where the participants or patients health is affected (severely or slightly) must be reported immediately to SAMAREC. The SAMAREC Chairperson will review the deviation within 48 hours should any urgent concerns be addressed. The reports will also be discussed and reviewed by the full Committee at the next meeting wherein same will be included in the meeting pack supplement. Alternatively, the 6 Monthly SAHPRA Report will be accepted.

Submission requirements:

Accompanied by a Covering Letter, a description of the protocol deviation, rectifying action, and preventive action should be described. Further, SAMAREC must be provided with the date of the deviation, study site at which the protocol deviation took place, investigator(s) of the site, study ID of patient(s), and the severity of the deviation(s).

18. REPORTING OF ADVERSE REACTIONS AND EVENTS

SAMAREC holds to the SAHPRA definition of adverse events and reporting timelines.

SAMAREC requests the Council for International Organizations of Medical Sciences (CIOMS) reports for each notification, for our causality assessment, risk-benefit assessment and determination of whether protocol or consent amendments are needed for South African patients.

I. **Adverse Event:** Adverse event is any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment. An adverse event can be any unfavourable and unintended sign, symptom or disease temporarily associated with the use of a medicine, whether considered related to the medicine, or not.

II. **Adverse Reaction:** An adverse reaction refers to an adverse event which is assessed, by the Sponsor or Investigator, to have a causal relationship with the treatment.

III. **Serious Adverse Event**: Refers to any untoward medical occurrence that, whether drug related or not:

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

Reports of serious adverse events must be reported to SAMAREC immediately and should include recommendation(s) by the Principal Investigator regarding the continuance of the study trial, a brief motivation on whether, in his/her opinion the SAE is trial related or not motivated by reasons thereto of the aforementioned opinion.

IV. **Unexpected Adverse Drug Reaction:** Refers to an adverse reaction in which the nature, specificity, severity, and outcome is not consistent with domestic labelling or holder of registration of certificate or expected from the characteristics of the medicine (i.e., the investigator brochure or product package insert).

V. **Unexpected Serious Adverse Event**: Refers to an event in which the specificity or severity is not consistent with the current investigator brochure (i.e., investigational drug or device). Serious Unexpected 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. Additionally, 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.

VI. **Suspected Unexpected Serious Adverse Reaction**: is the term used to refer to an adverse event that occurs in a clinical trial participant or patient, which is assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the study drug.

The timeframes and format for reporting serious adverse events, adverse events and drug reactions are described

in the SAHPRA guidelines and should be strictly adhered to.

All adverse reaction reports will be reviewed by the Chairperson of SAMAREC as well as by the SAE Dedicated Clinical SAMAREC Member as received. Should the Committee members aforementioned be of the opinion that a specific reaction warrants discussion in detail by the full Committee, detail of the specific reaction will be distributed to the entire Committee and the item will be added to the formal Minutes of the next scheduled Committee meeting.

Submission requirements:
A Covering Letter accompanied by a safety report (refer to *SAMAREC Report Form SAE*) should be submitted to SAMAREC. SAMAREC also requests that the CIOMS reports be included for our causality assessment, risk-benefit assessment and determination of whether protocol or consent amendments are needed for South African patients

19. REPORTS, POST-APPROVAL, AUDITING, SUSPENSION, NON-COMPLIANCE, PASSIVE AND ACTIVE MONITORING

Passive Monitoring:

- Following approval of a protocol, six-monthly (bi-annual) reports on the trial must be submitted to SAMAREC. Failure to forward these reports **will** result in suspension or termination of approval for the protocol, without any prior notification by SAMAREC. Any decisions taken by SAMAREC after the review of the 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 SAHPRA reports will suffice otherwise, *SAMAREC Passive Audit Report* may be submitted.

- 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 (3) years after the completion of a trial.

Patients Lost to Follow Up or Withdrawal of Consent:

When a patient explicitly withdraws consent, they have the right to indicate what aspects of their participation should stop. There are two main scenarios:

I. Withdraw from all participation, including follow-up:
   - The site must stop collecting any new data, including from public records.
   - You cannot access survival status through any means, including public databases.

II. Withdraw from study treatment only, but allow follow-up:
   - If the patient agrees to continued follow-up, survival status data may be collected, including from public sources—but only if that was included in the informed consent.

Patient Incarceration:

Should a patient be incarcerated, the Committee is to be notified timeously specifically indicating that the patient was on the trial prior to being incarcerated along with all details related to treatment and follow-up needed whilst incarcerated

Active Monitoring/Auditing:

SAMAREC, in accordance with the NDoH Guidelines, must conduct active auditing and monitoring of sites. Audits **may** be conducted randomly or when there might be causes of concern to patients and participants.

Audit frequency and intensity will be guided by a risk-based approach, taking into account study risk level, vulnerability of participants, and compliance history.

The SAMAREC Secretariat will notify the Sites and/or Sponsors of the audit. The Audit will be conducted by at least two members of the SAMAREC and may or may not include the SAMAREC Secretariat. The findings and feedback will be deliberated with the SAMAREC Chairperson. Feedback will be provided to the Site or Sponsor within 10 days of the physical audit (unless circumstances prevent).

The following is to be noted regarding the monitoring of sites:

- SAMAREC may be entitled to carry out audits, without prior notification to the principal investigators (Declaration of Helsinki 2024).
- SAMAREC may recommend and adopt any appropriate mechanisms for monitoring, including random inspection of research sites, welfare monitoring sheets, data and signed consent forms, and records of interviews.
- SAMAREC may request regular reports from principal investigators pertaining to progress to date, or outcome in the case of completed research, and/or current enrolment status.
- SAMAREC is entitled to request the following information:
    - whether participant follow-up is still active or completed;
    - information concerning maintenance and security of records;
    - evidence of compliance with the approved protocol;
    - evidence of compliance with any conditions of approval;
    - negative reports from monitors or GCP inspectors;
    - list all adverse events in the past twelve (12) months;
    - list all amendments made in the past twelve (12) months.
- SAMAREC should inform principal investigators in writing of concerns arising from such monitoring activities.
- The audits will be conducted in accordance with the applicable laws, regulations, and ethical guidelines.
- The audit will be conducted by independent auditors – SAMAREC members - who are free from any conflicts of interest. The auditors will maintain objectivity and impartiality throughout the auditing process.
- A comprehensive audit plan that outlines the audit objectives, procedures, and timelines shall be made available, which shallspecify key areas of focus, such as ethical review processes, decision-making, and adherence to regulatory requirements (refer to *SAMAREC Active Audit Form* for insight on some key areas of focus).
- SAMAREC must conduct frequent reviews of its documentation practices and record-keeping systems to ensure accurate and complete documentation. SAMAREC must assess the adequacy of records in terms of ethical reviews, decisions, and communications.
- SAMAREC must conduct a compliance assessment, which requires evaluating the committee's compliance with relevant laws, regulations, and ethical guidelines governing research activities. In addition, a review to the committee; ‘adherence to its own policies, procedures, and a Code of Conduct must be undertaken.
- SAMAREC must assess the effectiveness of its ethical review processes, including the evaluation of research proposals, protocols, and amendments. This includes, but is not limited to, evaluating the consistency and transparency of decision-making in granting approvals, providing feedback, and ensuring participant protection.
- A review of SAMAREC's procedures for identifying, assessing, and managing conflicts of interest among members must be conducted. This serves to evaluate the effectiveness of conflict-of-interest disclosure processes and SAMAREC's actions in mitigating conflicts.
- An assessment of SAMAREC’s efforts in providing training and educational resources to members

regarding research ethics, regulations, and emerging ethical issues must be undertaken. Reviewing the member's ongoing professional development initiatives to enhance members' knowledge and expertise is vital.

- A review of the SAMAREC's mechanisms for monitoring approved research projects must be done to ensure ongoing compliance and research participant welfare. This includes assessing the adequacy and effectiveness of SAMAREC's reporting mechanisms, including reporting to regulatory bodies (NHREC) and relevant stakeholders.
- SAMAREC must identify any areas of non-compliance or deficiencies in the protocol and provide recommendations for improvement. It must monitor the implementation of corrective actions and follow- up on the progress made in addressing identified issues.
- SAMAREC must maintain proper documentation of audit activities, findings, and conclusions, and collect sufficient and appropriate audit evidence to support conclusions.
- SAMAREC must prepare clear, accurate, and concise audit reports that highlight findings, recommendations, and action plans, as well as communicate audit results to relevant stakeholders in a timely manner.
- SAMAREC must strive for continuous improvement within the auditing function. This requires regular reviews and enhancement of audit methodologies and processes to align with best practices.
- For more information on SAMAREC's auditing process, refer to the *SAMAREC Auditing Guidelines.*

20. ANNUAL, CONTINUING REVIEW AND RECERTIFICATION RENEWAL

- 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 or Applicant to submit to SAMAREC an Application for Annual Renewal supported by the latest study progress report. The SAMAREC Application for Annual Renewal 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 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 document. The Application for Annual Renewal must also be submitted to SAMAREC for approval via the SAMAREC Application form.

- Annual Renewal applications must be accompanied by progress reports / reference to already submitted progress reports (within the last 6 months).

- 19.4 For more information on the requirements and review process, refer to the *SAMAREC Continuing Review Annual Renewal Recertification*.

21. REPORTING PROPOSED CHANGES IN A RESEARCH PROTOCOL

21.1 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 by way of an expedited review procedure.

21.2 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. See Major and Minor Amendment Process.

22. EXPEDITED REVIEW PROCESS

22.1 Expedited Review Process (Sub-committee review of minor ethical issues). SAMAREC has established procedures for expedited review of research when this is in the public interest. Expedited review will entail review of the lower risk studies (minimal risk). In general, research with potential to cause physical or psychological harm would not be considered for expedited review. This includes drug trials of new investigational products, research involving non-interventional research procedures and research involving sensitive personal or cultural issues. Expedited review applications must be accompanied by a covering letter detailing the request for expedited review. Should the evaluators feel that the study poses more than minimal harm or risk to the patients, the study will be referred to the entire committee for a full review during a formal meeting. Turnaround time for an expedited review is three working days. Please ensure "Expedited Review Process" is requested in the covering letter.
SAMAREC applies a **proportionate approach to ethics review**, whereby the level of scrutiny and review pathway is determined by the nature, complexity, and level of risk associated with the research.

22.2 Risk Definitions:

a) **Lower Risk Studies**: where the only foreseeable risk is one of discomfort.

b) **High/Medium Risk Studies**: where probability and magnitude of possible harms implied by participation are no greater than those posed by daily life in a stable society or routine medical, dental, educational, or psychological tests or examinations.

c) **High Risk Studies**: research involving highly sensitive topics and/or the participation of very vulnerable and marginalised individuals/groups/ research involving procedures that may cause harm.

23. RAPID REVIEW PROCESS

23.1 SAMAREC has established procedures for rapid review of research when this is in the public interest e.g., urgency of disease and value of research to society. Rapid review is done for research protocols where there is more than minimal risk to the subjects e.g., vaccine study of new investigational product. Studies posing a higher risk must be reviewed by the whole Committee which can take place between meetings by way of "round robin" assessment and collation of inputs by the SAMAREC officer for final approval by ways of electronic approval. Rapid review and approval may be considered for research where participants have a disease that may be rapidly fatal.

23.2 Rapid review applications must be accompanied by a covering letter detailing the request and motivation for rapid review clearly indicating the need for urgency. Should the evaluators feel that the study poses

significant risk more than minimal harm or risk to the patients or participants, then the study will be referred to the entire committee as per usual process for a full review during a formal meeting. Turnaround time for rapid reviews is ten (10) working days. Please ensure "Rapid Review Process" is requested in the covering letter.

For more information on the rapid review process, refer to the *SAMAREC Rapid Review Guidelines.*

24. SITE/STUDY CLOSURE PROCESS

24.1 Upon completion of the trial, the Principal Investigator must inform SAMAREC and provide a summary of the trial outcome. When a study is closed, cancelled for any reason, or is prematurely completed, a *Study Closure Report* must complete. The Study Closure Form is intended to accompany the final summary of study results and should be submitted once the study has been completed and final results are available for reporting to SAMAREC. This serves as notification to SAMAREC that continuing review of the study is no longer required.

24.2 Where a site close-out visit (COV) has been conducted but final study results are not yet available, you should proceed with submitting the COV notification to SAMAREC at this stage. The Study Closure Form should then be submitted separately once the study has been formally completed and the results are available.

24.3 A Notification Letter and Site Closure Report must be submitted. All Site/Study Closure Reports will be reviewed by all SAMAREC Members and noted formally in the SAMAREC Supplement to the Minutes Report.

Closure Reports should include the following:

- participant numbers
- safety summary
- protocol deviations
- IP accountability
- PI sign-off
- Participant follow-up 18-month report and contact information of responsible persons where applicable

The Committee shall ensure that appropriate **post-study obligations** are met, including continued access to beneficial interventions where applicable, referral for ongoing care, and the communication of study results to participants and relevant communities in an accessible and appropriate manner.

25. REPORTING OF ALLEGATIONS OF MISCONDUCT/NON-COMPLIANT AND COMPLAINT PROCEDURES

25.1 Complaints may be lodged by researchers, or any other persons involved in the research being conducted. Complaints relating to administrative conduct or REC processes are distinct from formal appeals against ethics decisions, which are governed by Section 28
Complaints should be directed to the Committee first. Should the matter not be resolved, the complaint

may be escalated to the NHREC.

25.2 Complaints may be lodged, in writing, with the SAMAREC Secretariat who will submit such complaints to the Chairperson or relevant officer(s)/bodies as soon as possible for investigation.

25.3 Formal written feedback will be provided to the complainant once the investigation has been concluded from the Chairperson.

25.4 Complaints against SAMAREC members can be lodged with the SAMA Governance Department at governance@samedical.org,. The complaints will be handled by the SAMA Board or necessary authorities depending on the nature of the complaint.

26. WHISTLE BLOWERS

A SAMAREC Whistle-blower feedback form is available for all study staff, patients or participants at the following link https://samedical.org/samarec/. The complaints will be handled by SAMAREC or necessary authorities depending on the nature of the complaint.

For further information on the whistleblower process refer to *SAMAREC Whistle Blower* guidelines.

27. BLANKET APPROVAL

A blanket approval of ethics documentation is strictly prohibited, as each application must undergo a thorough and independent review by the designated ethics committee responsible for the project.

Ethics approval cannot be transferred from or granted by another REC, as doing so undermines the integrity of the review process and fails to ensure that the specific risks, context, and safeguards relevant to the study have been fully evaluated. Bypassing the required Committee's review processes is considered unethical and compromises participant safety, potentially exposing patients to avoidable harm. All submissions must therefore be assessed directly by the appropriate REC to ensure compliance with regulatory standards and the highest level of protection for participants.

28. ETHICS VIOLATIONS

Ethical violations in research may include, but are not limited to:

a) failure to adhere to the guidance or conditions set by the ethics committee,
b) proceeding with a study or study amendment without prior ethics approval,
c) deviating from the approved protocol without notification or approval,
d) inadequate or misleading informed consent processes,
e) breaches of participant confidentiality or data protection requirements, and
f) failure to report serious adverse events or protocol deviations.

Such violations may compromise participant safety, scientific integrity, and regulatory compliance, and may result in corrective actions, suspension of the study, or notification to relevant regulatory authorities, depending on the severity of the breach.

Below are five categories of possible ethical violations, aligned with the structure and intent of the NDoH 2024

Ethics in Health Research Guidelines, presented in order of seriousness (from most serious to least serious). These are framed in a practical REC-appropriate format:

1. **Critical / Major Ethical Violations (Serious Misconduct)**
These include conducting research involving human participants without prior REC approval, continuing a study after approval has expired or been suspended, deliberate falsification or fabrication of data, intentional non-disclosure of serious risks, or exploitation of vulnerable populations. Such violations are considered serious breaches of the National Health Act and may trigger regulatory, institutional, or professional disciplinary action.

2. **Serious Protocol and Participant Protection Breaches**
This category includes major protocol deviations that compromise participant safety or rights, inadequate or misleading informed consent, failure to report serious adverse events, breaches of confidentiality or data protection, or failure to provide required insurance or compensation for research-related injury.

3. **Non-Compliance with REC Conditions and Governance Requirements**
Examples include failure to comply with REC-imposed conditions, failure to submit required progress reports, amendments implemented without approval, failure to adhere to recruitment limits or competitive recruitment guidance, or non-compliance with national ethical norms and standards.

4. **Administrative and Procedural Non-Compliance**
These include late submissions of reports, incomplete documentation, failure to maintain essential study records, or minor deviations from SOPs that do not directly impact participant safety or scientific integrity.

5. **Minor or Technical Deviations**
This category includes clerical errors, minor documentation inconsistencies, or administrative oversights that do not affect participant welfare, data integrity, or regulatory compliance but still require corrective action and documentation.

Research misconduct, including fabrication, falsification, or plagiarism, shall be distinguished from protocol non-compliance and may be managed in accordance with applicable institutional and regulatory processes, including referral to relevant authorities.

SAMAREC will apply proportionate corrective or enforcement actions based on the severity classification of the violation, ranging from corrective action requests and increased monitoring to suspension, termination, or regulatory escalation

29. APPEALS AGAINST DECISIONS

29.1 Appeals against decisions should be lodged in writing to the SAMAREC Chairperson (samarec@samedical.org who will then investigate the appeal and endeavour to deal with it to the satisfaction of the complainant.

Appeals must be submitted within a defined timeframe (typically 10–20 working days from receipt of the decision) and must include a written motivation with supporting documentation specifying the grounds for reconsideration, including new information, material factual error, or procedural concern.

All appeals will be reviewed in a confidential manner by the SAMAREC Chairperson

If a party wishes to appeal or query a decision of SAMAREC, please refer to the *SAMAREC APPEALS SOP*

30. SAMAREC AND RESEARCHER TRAINING

Research Ethics Committees and research staff must ensure continued education in research ethics**,** GCP training as well as to ensure they are kept aware of current issues and developments in the broad area of research ethics and science.

New Committee members go through a 'Mentorship Program' which is open to all Committee members to attend. 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.

31. MATERIAL TRANSFER AGREEMENT (MTA)

31.1 An executed Material Transfer Agreement (MTA) must be submitted for review and approval prior to any transfer, sharing, export, import, storage, or secondary use of Human Biological Material (HBM) related to research or clinical trials. The MTA must comply with the National Department of Health (NDoH) Ethics in Health Research Guidelines (2024), the South African Good Clinical Practice (SA GCP) Guidelines (2020), applicable SAHPRA requirements, the National Health Act, and POPIA.

31.2 The MTA must clearly define:

- the purpose and scope of the transfer;
- the roles and responsibilities of the Provider and Recipient institutions;
- conditions of use, storage, retention, destruction, and future use of the HBM;
- restrictions on further third-party transfer;
- participant confidentiality and data protection measures;
- intellectual property and publication arrangements;
- benefit-sharing provisions where applicable;
- indemnity and liability clauses; and
- arrangements for return or disposal of materials at study completion.

Where associated data are shared, a separate Data Transfer or Data Sharing Agreement (DTA/DSA) should be in place where appropriate.

Ensure that the proposed transfer is scientifically and ethically justified, aligns with the participant informed consent and protocol approvals, and that all necessary institutional, regulatory, import/export, and SAHPRA approvals are obtained prior to transfer of materials, including for cross-border shipment of HBM. The SAMAREC MTA *pro-forma* must be used by all clients and sent through for approval. See Annexure 12 for template.

All SAMA branding to be removed as this is a template.

32. LABORATORY ASSAY VALIDATIONS AND

VERIFICATIONS

When establishing a laboratory, assay validations and verifications are required. In the case where participants would not be identified in any validation and verification results, there is no ethical approval required. Genetic assays inherently generate identifiable information; therefore, ethical approval is required prior to their validation or verification.

33. BIOLOGICAL MATERIAL

Informed Consent to use biological materials in research must be obtained from the tissue donor. Human biological materials and their products may not be used for commercial purposes without the consent of the tissue donor. All information on biological material must be included in the applications and submissions.

For further considerations on using biological materials in research, refer to the *SAMAREC Biological Materials, Databases, Registries and Repositories SOP.*

34. DATA, REGISTRIES AND REPOSITORIES

34.1 The Informed Consent Documents should clearly explain the purposes and nature of Databases, Registries and Repositories.

- The purpose, nature, and specifics for which consent is being sought, how and what types of research it supports must be included.

- Further considerations on using databases, registries and repositories in research reference to the *SAMAREC Biological Materials, Databases, Registries and Repositories SOP* is recommended.

- **Data Handling**: In ensuring data security of all trial related documentation, inclusion to fit for purpose data tools and validity must be considered. Source records are needed to allow the applicable evaluation of the trial conduct.

- An SOP should be available for the maintenance of equipment in order to maintain the integrity of the data. Computer systems must be fit for purpose and electronic records securely maintained.

- **Essential Records**: Documents, data and meta data should be able to determine the reliability of trial results produced. Investigator Site File should be controlled by the Principal Investigator. Some records may be retained by the Sponsor or Investigator as per the essential list record documents.

34.2 A Data Management Plan should be included with all new clinical trial submissions. Any **secondary or future use** of data or biological material beyond the scope of the original approval must be reviewed and approved by SAMAREC, unless explicitly covered by prior participant consent and REC approval.
Researchers must clearly specify data sharing, reuse, storage duration, and governance mechanisms at the time of initial submission.

35. NON-COMPLIANCE CONSEQUENCES, SUSPENDED OR TERMINATED PROJECTS

35.1 SAMAREC may withdraw approval of a study should the study be non-compliant with the approved protocol. A due process must be followed for withdrawal of approval.

35.2 Once SAMAREC becomes aware of an indication that warrants non-compliance with the approved protocol, the situation will be investigated, and all parties involved (Sponsor/CRA/Principal Investigator/ Researcher) will be expected to be transparent regarding their practices.

35.3 Findings from monitoring, audits, or reported violations will be assessed in accordance with SAMAREC's non-compliance framework and may result in corrective actions, additional oversight, suspension, termination of approval, or escalation where warranted.

Findings during the investigation may warrant the study be suspended or discontinued. The applicant and parties involved will be requested to comply with certain recommendations and provide evidence that same have been implemented before the study is reviewed and approved to resume again.

36. THE SAMAREC REVIEW PROCESS

36.1 INTRODUCTION

Ethical oversight by SAMAREC extends across the **full lifecycle of research**, including protocol review, approval, implementation, monitoring, reporting, and study closure. 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. For further insight into the principles, processes, and considerations of the review process, refer to *SAMAREC Decisional Analysis Guidelines*. To approve a research project involving participants, SAMAREC must assure itself of the following:

36.2 STUDY DESIGN

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

36.3 VOLUNTEER PARTICIPATION

a) The recruitment of participants is free of coercion;

b) The method used to obtain informed consent is ethically and legally acceptable;
c) The necessary consideration has been given to protect vulnerable populations/groups;
d) The degree to which confidentiality is maintained is acceptable;
e) Compensation must be provided in accordance with applicable no-fault clinical trial injury compensation principles acceptable to SAHPRA and SAMAREC, SAHPRA and NDOH increasingly expect:

- no-fault compensation principles,
- sponsor insurance clarity,
- and local applicability.

f) Any other factors deemed appropriate.

37. 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 carefully examine 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, frail and terminally ill persons, and persons of low socio- economic status must be clearly justified.
Research involving vulnerable populations shall be subject to **enhanced ethical scrutiny**, including additional safeguards, justification of inclusion, and, where appropriate, increased monitoring or oversight by SAMAREC.

38. 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 7).

39. REVIEW OF EXPERIMENTAL DESIGN

39.1 SAMAREC will review the experimental design in order to be assured that it is scientifically and socially sound and that the potential risks to the participants are minimised and the potential benefits maximised by using procedures consistent with acceptable research design.
39.2 SAMAREC shall assess whether the research demonstrates **clear social or scientific value**, including relevance to South African health priorities, and whether the study avoids unnecessary duplication or research waste.
39.3 The research design should be described in a clear and detailed protocol. Where applicable an investigational brochure detailing all relevant preclinical and clinical data to support the research should be

made available.

39.4 The use of socially constructed categories (race, gender, religion etc.) in the research need to be justified, with the onus lying on the researcher to explicitly clarify the role of these categories in the research and risks and benefits associated with their description.

40. SEX AND GENDER EQUITY IN RESEARCH (SAGER) COMPLIANCE

40.1 SAMAREC requires that all research protocols align with the principles of the latest Sex and Gender Equity in Research (SAGER) guidelines where relevant to ensure appropriate consideration of sex and gender throughout the research process. Investigators must clearly indicate whether sex (biological attributes) and gender (socially constructed roles and identities) are relevant to the study objectives, design, data collection, analysis, and interpretation of findings.

40.2 Where applicable, protocols should include a justification for the inclusion or exclusion of specific sexes or genders, describe recruitment strategies that promote equitable representation, and outline plans for sex- and gender-disaggregated data analysis.

40.3 Study reports and publications must present results disaggregated by sex and/or gender where scientifically appropriate and discuss any observed differences. Failure to adequately address sex and gender considerations must be scientifically justified.

41. REVIEW OF THE POTENTIAL RISKS

41.1 A **risk** is a potential harm (injury) associated with the research that a reasonable person would be likely to consider significant in deciding whether to participate in the research or not. The concept of risk includes discomfort, burden, or inconvenience that a participant may experience as a result of the research procedures. Underlying the consideration of risk is the implicit moral guideline that all investigators/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: -

a) **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 maximum exercise testing);
b) **Psychological risk** (e.g., depression and confusion as a result of administration of drugs, emotional upset precipitated by a sensitive survey);
c) **Social risk** (e.g., invasion of privacy, loss of community standing, stigmatization);
d) **Legal risk** (e.g., compromising medical scheme benefits); and
e) **Economic risk** (e.g., loss of employment, loss of potential monetary gain, cost to state or patient or medical scheme). Financial reimbursement of the research site or study doctor must not be excessive to result in a conflict of interest.

41.2 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.

41.3 Examples of ***"minimal risk***" procedures include collection of urine, collection of sweat, 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 without stress.

41.4 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.

41.5 Examples of ***"significant risk"*** procedures include chemotherapy, radiation therapy and major surgery.

41.6 For further considerations on SAMARECs review of risks and a risk assessment tool, refer to the *SAMAREC Risk Assessment* SOP.

42. REVIEW OF POTENTIAL BENEFITS

42.1 A **benefit** in research ethics, refers to the positive outcomes or advantages that may arise from a research study, both for participants and for society as a whole. It encompasses the potential for improved health, well-being, or knowledge generation.

42.2 A key aspect of research ethics is ensuring that the potential benefits of a study outweigh any associated risks to participants. Benefits associated with participation in research can be classified as those that accrue to the participant directly (e.g., improvement of the participant's health status; acquisition of knowledge considered of value by the participant) 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 to individual and societal benefits, SAMAREC shall consider whether research provides **fair and equitable benefit to participant communities**, including appropriate benefit-sharing mechanisms where relevant, particularly for community-based, genomic, or publicly funded research

42.3 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 as an underlying value construct.

42.4 Financial and other forms of reimbursement are not considered a benefit to be derived from research participation. Although the patient may consider financial reimbursement a desirable outcome, this fact will not be used in the risk- benefit analysis and should not be mentioned. For example, the fact that patients may receive a certain sum of money per visit to defray travel expenses cannot be reflected as a benefit (see SAHPRA Guidelines). Please note that it must be stated in the protocol document that the participant would receive an exact amount for travel and / or other associated costs. This includes a breakdown of any amounts to be received by the participant including any formulas that were considered in determining the amount.

43. RISK-BENEFIT ANALYSIS

Once the potential risks and benefits are identified, an ethical 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 the research is therapeutic in nature:

a) 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.

b) 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.

c) 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 considering 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.

44. REVIEW OF PARTICIPANT COMPENSATION AND ASSESSMENT OF FINANCIAL ARRANGMENTS/REIMBURSEMENTS

44.1 SAMAREC shall review all proposed participant compensation, reimbursements, incentives, and financial arrangements to ensure compliance with the latest South African Health Products Regulatory Authority (SAHPRA) Time, Inconvenience and Expense (TIE) Compensation Model, the National Department of Health Ethics in Health Research Guidelines (2024), and South African Good Clinical Practice (SA GCP) Guidelines.

44.2 SAMAREC shall ensure that compensation is fair, reasonable, transparent, and proportionate to the participant's time, inconvenience, travel, meals, and study-related expenses, without constituting undue inducement, coercion, or improper influence on participation or continued participation in the research study.

44.3 Assessing whether the proposed reimbursement methodology, payment schedule, and amounts are adequately justified within the protocol, informed consent process, and participant-facing documents.

44.3.1 Special consideration shall be given to vulnerable populations, high-burden procedures, overnight stays, invasive sampling, and Phase I studies where additional remuneration may be applicable in accordance with current SAHPRA guidance.

44.3.2 Any amendments to participant compensation or reimbursement arrangements during the course of the study shall require SAMAREC review and approval before implementation, unless necessary to eliminate immediate hazards to participants. Please submit Study Budgets in excel format in order to view the calculations.

44.4 It is required that all amounts payable to any participants shall be expressed reflecting the relevant formula taken into account to ensure that no undue benefit is attributable to participants.

45. REVIEW OF MEASURES TO PROTECT PERSONAL INFORMATION

45.1 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 thereto.

45.2 SAMAREC will also consider whether appropriate consent has been sought for the retention and use of the confidential personal information in line with the requirements of the POPI Act, 2013 as well as other laws applicable for the protection of such confidential information.

45.3 For AI-enabled, digital health, or data-intensive research, SAMAREC shall consider risks related to **algorithmic bias, automated decision-making, re-identification, and secondary data use**, and require appropriate safeguards and transparency in participant information materials.

46. REVIEW OF THE PATIENT/PARTICIPANT INFORMATION AND INFORMED CONSENT

46.1 Participant Reimbursement

All informed consent documents (Participant Information and Informed Consent Documents – PIDs) submitted for review must clearly describe all participant reimbursement arrangements in accordance with the latest SAHPRA Trial Information Exchange (TIE) guidance, the National Department of Health (NDoH) *Ethics in Health Research Guidelines* (2024), and South African Good Clinical Practice (SA-GCP) Guidelines (2020). Reimbursement must be limited to compensation for reasonable time, inconvenience, and actual out-of-pocket expenses incurred as a result of study participation, including but not limited to transport, toll fees, meals, accommodation (where applicable), childcare, and cellular data costs directly related to study participation.

The reimbursement schedule, method of calculation, frequency of payment, and payment mechanism must be clearly described in the PID and protocol. Reimbursement must not constitute undue inducement, coercion, or exploitation, particularly in vulnerable populations. Reimbursement must be equitable, fair, and proportionate to study-related burden and inconvenience, and should not be structured in a manner that encourages participants

to remain in a study against their best interests. Participants who withdraw early from a study must be reimbursed proportionately for study procedures already completed and expenses incurred, irrespective of study completion or outcome.

a) SAMAREC will review all monetary and non-monetary reimbursement arrangements to ensure alignment with SAHPRA TIE principles and approved reimbursement schedules. Reimbursement may not be used as a recruitment incentive or benefit that could impair voluntary informed consent.

46.2 Financial Arrangements and Participant Liability

a) All financial arrangements involving participants, investigators, sponsors, or study-related medical care form part of the review process. The PID must clearly distinguish between research-related procedures and standard-of-care treatment, including which costs will be covered by the sponsor and which costs, if any, may remain the responsibility of the participant or their medical scheme. Any potential participant liability for routine care or non-study-related treatment costs must be transparently explained in plain language, including a clear cost breakdown where applicable, either within the PID or as an annexure.

Participants may not be charged for investigational products, protocol-required procedures, or management of trial-related injuries where such costs are required to be covered by the sponsor in accordance with SAHPRA and SA-GCP requirements.

46.3 Professional and Dispensing Fees

Fees charged for the dispensing of medicines or professional services must comply with all applicable South African legislation, regulations, and ethical rules governing healthcare practitioners. Professional fees may only be charged by appropriately registered healthcare professionals rendering the service. Any study-related billing arrangements must be transparent, justifiable, and compliant with SAHPRA, HPCSA, and other applicable regulatory requirements.

46.4 Changes to Approved Reimbursement

Any proposed changes to participant reimbursement after SAMAREC approval, including amendments to reimbursement amounts, payment schedules, payment methods, or categories of reimbursable expenses, must be submitted to SAMAREC for prior review and approval together with appropriate justification. Where reimbursement changes are implemented in response to updated SAHPRA TIE guidance, inflationary adjustments, or sponsor-wide policy updates, supporting documentation must accompany the submission. Participants should be informed of approved reimbursement changes where relevant to their continued participation.

46.5 Reimbursement Deviations

The management of reimbursement-related protocol deviations must be proportionate to the nature, impact, and potential ethical implications of the deviation. Reimbursement deviations that do not affect participant rights, safety, welfare, voluntary participation, or the integrity of the informed consent process may generally be managed through site-level corrective and preventive action (CAPA) processes and included in periodic protocol deviation reporting.

46.5.1 Minor Administrative Reimbursement Deviations

Minor reimbursement deviations may include:

- Incorrect reimbursement calculations;

- Delayed reimbursement payments;
- Administrative processing errors;
- Incorrect transport or travel reimbursement calculations; or
- Isolated payment discrepancies that do not affect participant welfare or voluntariness.

Such deviations should generally be:

- Corrected promptly at site level;
- Documented in the protocol deviation log;
- Addressed through appropriate CAPA measures; and
- Included in the periodic protocol deviation line listing submitted to SAMAREC.

Immediate separate reporting is generally not required unless the deviation meets criteria for significant non-compliance or impacts participant rights or welfare.

46.5.2 Reimbursement Deviations Requiring Separate Reporting

Separate and prompt notification to SAMAREC is required where reimbursement issues:

- Result in undue inducement or overpayment outside the REC-approved reimbursement schedule;
- Result in systematic underpayment or financial prejudice to participants;
- Suggest coercion, exploitation, or inequitable treatment;
- Reflect systemic site failures or repeated non-compliance;
- May influence participant's willingness to remain in the study;
- Represent deviations from the REC-approved reimbursement model; or
- Potentially compromise the voluntariness of informed consent.

In such cases, SAMAREC may require:

- Immediate deviation notification;
- A formal CAPA plan;
- Evidence that affected participants were appropriately compensated or reimbursed; and/or
- Additional monitoring or compliance oversight measures.

46.5.3 Best Practice Management of Reimbursement Deviations

The following best practice approach should be implemented for reimbursement deviations:

1. Correct the reimbursement issue without delay, including payment of any outstanding amounts where applicable;
2. Conduct a root-cause assessment and implement CAPA measures;
3. Document the deviation in the site deviation log;
4. Include the deviation in the periodic protocol deviation line listing with an appropriate CAPA summary.

For transparency, deviation reporting should include:

- A description of the reimbursement error;
- Number of participants affected;
- Nature and value of the discrepancy;
- Corrective action implemented; and
- Preventive measures introduced to avoid recurrence.

47. DOCUMENT (PID) PROCESS INCLUDING MINORS AND VULNERABLE PATIENTS/ PARTICIPANTS

47.1 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 research study. The principal reason for informing participants about the research study is founded by their right to know what would be done to them and what risk such participation entails before they grant consent thereto. 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 and such should privilege should be protected and respected at all times. 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.

47.2 SAMAREC takes the view that clinical trials compare to medical procedures, 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 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 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, an 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**.**

47.3 In order for consent to be ethically and legally valid it must meet the requirements stated in the historic 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*." Helsinki 2024 and NDOH Research Ethics 2024 Guidelines remain the primary consent authorities.

47.4 The PID and informed consent documents are legal documents proving that informed consent was indeed 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 has 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 and that consent has been obtained appropriately. (The requirement for a witness for a literate patient will be determined by the Committee on a case-to-case basis). 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 for SAMAREC's preferred standard wording).**

47.5 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(s). The study doctor as an instrument to guide the negotiations with the prospective patient, therefore, should use the PID for this purpose. SAMAREC contact details must be provided on the PID. A paragraph informing the patient that the study received ethics approval should be included **(See Annexure 4 for SAMAREC's preferred standard wording)**. 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.

47.6 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.

47.7 For further considerations and SAMAREC guidelines, refer to *SAMAREC Informed Consent* SOP.

47.8 Phase I Informed Consent Documentation should contain the following paragraph: "This study is a Phase-1 ('first-in-human') study and is the first time this medicine is being tested in people. The aim is to understand this medicine's safety, how the body processes it, and what dose levels can be used safely. It is not expected to provide medical benefit to participants. If you choose to take part, you will attend scheduled visits, take the study medicine as instructed, and undergo safety checks such as blood tests, vital-sign measurements, and monitoring for any side effects. You may need to stay in a hospital or research facility for several days, so the study team can closely monitor your response during and after dosing. Because this is the first use in humans, there may be unknown or unexpected side effects, including serious ones, and the study doctor may pause or stop dosing at any time if needed for your safety."

48. RECONSENT

Reconsent of participants shall be conducted whenever an amended Informed Consent Form (ICF) has been approved by SAMAREC and the changes are deemed to be material to participant decision-making, including but not limited to new safety information, changes in risk, study procedures, or participant burden. Where amendments are non-material and do not affect participant rights, safety, or willingness to continue participation, reconsent may be obtained at the participant's next scheduled study visit, provided that no study-related procedures requiring updated consent are performed prior to reconsent. The timing and method of reconsent must comply with SAMAREC approval conditions and be in accordance with latest South African Good Clinical Practice (SA GCP) and the National Department of Health Ethics in Health Research Guidelines. The Principal Investigator shall ensure that the rationale for the timing of reconsent is documented, and that all reconsent activities are

appropriately recorded in the study files.

49. PRIVACY AND CONFIDENTIALITY REGARDING PARTICIPANTS AND THEIR HEALTH CARE INFORMATION FOR APPLICANTS

- Privacy and confidentiality regarding participants and their healthcare information are of utmost importance in healthcare settings and research. Protecting the privacy and confidentiality of individuals and their health information is not only a legal and ethical requirement but also essential for maintaining trust and ensuring the success of healthcare services and research studies.

- Legal Framework: Healthcare providers and researchers must adhere to relevant laws and regulations. Such as the POPI act.

- Informed Consent: Participants in healthcare research must provide informed consent, understanding how their information will be used and its potential risks and benefits. It is also important that such information is translated to the participant's primary language in cases whereby they do not understand English. It has to be standard practice to have trained interpreters on site who facilitates real-time communication between individuals who speak different languages or are hard of hearing.

- Data Security: Implement robust data security measures to protect electronic health records, research data, and other sensitive information. This includes encryption, access controls, and secure storage.

- De-identification: When sharing or using data for research, it is required that appropriate steps are taken to remove or encrypt personally identifiable information (PII) to protect the privacy of participants.

- Data Minimization: Refers to the consideration of collecting and storing data that is only necessary for the intended purpose. Minimizing data reduces the risk of breaches and potential misuse.

- Access Control: Limitation of access to healthcare information to authorized personnel only and establishing protocols for granting and revoking access. A material transfer agreement should always be attached stating exactly what type of information will be shared, how it will be shred and protected, who it will be shared with etc.

- Audit Trails: Maintaining records of who accesses healthcare information and when such access is utilised, which can be helpful in identifying unauthorized access.

- Secure Communication: The use of secure channels for communicating healthcare information, whether in electronic form or in conversations.

- Training and Awareness: Ensure that all staff and researchers are trained in privacy and confidentiality policies and procedures. This includes regular updates to account for changing regulations and best practices.

- Data Retention and Disposal: Establishing guidelines for retaining healthcare data and securely disposing of such data when it is no longer needed.

- Breach Response Plan: Development of a plan for responding to data breaches, including notification of affected individuals and appropriate authorities as required by law.

- Third-Party Vendors: If using third-party vendors for data processing, ensure they also meet the necessary privacy and security standards remains a key consideration by SAMREC.

- Ethical Considerations: Beyond legal requirements, considering the ethical implications of using healthcare data remains paramount in the approval process by SAMAREC. Ensure that research is conducted with respect for participants and their rights can never be overlooked.

- Patient Portals: Encouragement of the use of secure patient portals for accessing health information which allows individuals to have control over their own data.

- Regular Audits and Assessments: Periodical assessment of the privacy and security measures in place to identify potential vulnerabilities and areas for improvement.

- Maintaining privacy and confidentiality in healthcare is an ongoing commitment by SAMAREC, and requires a multi-faceted approach involving technology, policies, training, and ethical considerations. The goal is to ensure that individuals can trust that their personal health information is being handled with the utmost care and respect for their privacy.

50. E-CONSENT

50.1 SAMAREC accepts Advanced Electronic Signatures (AES), in the place of wet signatures.

50.2 Section 1 of the *Electronic Communications and Transactions* Act No. 25 of 2002 defines AESs as:

> "*An electronic signature which results from a process which has been accredited by the Authority as provided for in section 37*". This form of E-Consent is also permitted through clause 10.9 of the *South African Good Clinical Practice: Clinical Trial Guidelines (2020)*, which states that "*An electronic signature is a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.*

In general, a signature may not be denied legal effect or validity solely because it is in electronic format, and a contract or other record relating to a transaction may not be denied legal effect, validity, or enforceability solely because an electronic signature or electronic record was used in its formation. To be considered equivalent to full handwritten signatures, electronic signatures must comply with all applicable requirements under 21 CFR part 117. Electronic records that are electronically signed must contain information associated with the signing that clearly indicates the printed name of the signer, the date and time when the signature was executed, and the meaning associated with the signature. In addition, electronic signatures and handwritten signatures executed to electronic records must be linked to the respective electronic records to ensure that the signatures cannot be excised, copied or otherwise transferred to falsify an electronic record by ordinary means."

51. TELEPHONIC CONSENT

51.1 From an NDoH ethics perspective, particularly aligned with the 2024 NDOH Ethics in Health Research Guidelines, telephonic consent is permissible under certain conditions, especially in low-risk research or in circumstances where in-person contact is impractical or may pose a risk (e.g., during public health emergencies or in geographically remote areas).

51.2 Key Considerations for Telephonic Consent:

1. Justification Must Be Clearly Provided

You must justify:

a) Why telephonic consent is necessary (e.g., geographical limitations, time sensitivity, safety considerations).

b) Why written consent is not feasible, and how the telephonic process will maintain ethical and legal standards.

2. Participant Information and Understanding

Even though consent is not written:

a) A Participants' Information and Informed Consent Document should still be developed.

b) The contents must be read out or explained in full to the participant in a language they understand.

c) Allow the participant time to ask questions and ensure their comprehension.

3. Voluntariness and Documentation

Participation must be voluntary, and this must be clearly affirmed by the participant.

It is required that study doctors must document the consent process, including:

- Time and date of the call;
- Name of the participant;
- Name of the staff member obtaining consent;
- Confirmation that the participant understood and agreed;
- Confirmation that the participant has been informed that they may withdraw their consent at any time.
- Confirmation that the research study has been explained including associated risks and benefits; and
- Confirmation of the original method used (audio recording or written field notes) to obtain consent.
- Age at consent.

51.3 If the interview is being audio recorded, it is required that the participants' consent to the recording before the recording begins.

Your protocol must include:

- A full script of the telephonic consent process (i.e., what will be said to participants).
- Explanation of how confidentiality and data protection will be maintained during and after the call.
- Steps for documenting and storing consent.
- If participants are vulnerable persons, additional ethical safeguards may be required.
- If research involves any health intervention or collection of sensitive data, further justification for not using written consent may be required.

52. REVIEW OF INVESTIGATORS

SAMAREC will review investigators and must be assured that they:

a) Have the appropriate qualifications;
b) 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;
c) Maintain adequate malpractice insurance cover;
d) Carry out procedures involved in the clinical trial within their specialty/sub-specialty, if they are registered in that specialty or sub-specialty; and
e) Have adequate facilities and equipment to conduct research with an acceptable degree of risk.

53. SITE STAFF DELEGATION

53.1 When a study is conducted at a site, the responsibility for ethical and competent conduct must be clearly assigned, typically the principal investigator (PI) or co-investigators have overall accountability for participant safety, scientific integrity, and compliance with ethics standards. However, the PI may delegate certain study-related tasks to suitably qualified and trained site staff (e.g. sub-investigators, coordinators, nurses), provided that delegation is documented and those staff have the appropriate expertise, training (including research ethics and Good Clinical Practice where applicable), and clarity about their delegated roles.

53.2 A site should maintain a "site delegation log" to record which staff member is responsible for which tasks — ensuring traceability, role clarity and accountability. Delegation must never obscure overall accountability: the PI remains ultimately responsible for ensuring that all delegated tasks are carried out ethically, competently, and in compliance with the approved protocol and national guidelines. SAMAREC Site Staff Delegation Template available on request.

54. REVIEW OF MONITORING REQUIREMENTS

54.1 The SAMAREC will determine whether 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.

54.2 Studies with a high degree of risk or harm may be requested to provide more frequent status updates. This might include:

a) Progress Reports;
b) Enrolment status (including number of patients still actively participating in the study or who have completed the study;
c) Maintaining security of records;
d) Supplying the Committee with evidence should there be any conditional approvals for the study;
e) Any audit report results;
f) Adverse events lists;
g) List of any amendments.

55. REVIEW OF INJURY COMPENSATION

55.1 Compensation for trial related injuries must be covered and set out in the PID. Compensation must be provided in accordance with applicable no-fault clinical trial injury compensation principles acceptable to SAHPRA SAMAREC, and NDOH increasingly expect:

- no-fault compensation principles,
- sponsor insurance clarity,
- and local applicability.

Or approved no-fault compensation framework.

55.2 Broadly speaking, these guidelines recommend that the sponsor, without legal commitment, should compensate the participant without 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.

55.3 The sponsor will not compensate where such an injury results from any procedure carried out that is not in accordance with the protocol for the study. The participant's legal right to claim compensation for injury where the participant's negligence can be proven and is not affected.

55.4 The following should be present on the insurance certificate:

a) Name and address of the insurance company;
b) Name and address of the company who took out the insurance;
c) Study title and protocol number of the insured study;
d) Date of commencement and termination of coverage;
e) Liability limit – per person and total;
f) Insurance policy number;
g) Number of participants covered by the policy;
h) Countries for which the policy provides cover(particularly important for international research studies);

Please note: Any changes to the insurance policy submitted after initial approval should include a covering letter outlining the updates or changes made.

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

56. CONFLICT OF INTEREST

56.1 All Committee members are required to sign a *Conflict of Interest and Confidentiality form* annually to declare any conflict of interest up front. Furthermore, SAMAREC ensures that no member of the Committee adjudicates a clinical trial in which that member has any conflict of interest in relation to the research project under consideration.

56.2 Members are required to declare before each Committee Meeting of 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 member in question may remain in the meeting for the discussion of the protocol

(should the Chairperson feel that this is appropriate), however, the member may not be allowed to participate in the final decision-making of the specific protocol (NDoH 2024 Guidelines).

56.3 Where the Chairperson is conflicted, the Chairperson will excuse themselves from the meeting and the Vice-Chairperson will take over the proceedings of the meeting.

56.4 Should a SAMAREC Member be an employee or Director of the Institute, they must declare any possible conflicts and recuse themselves from voting should the need arise.

57. ACCESS TO AND PROTECTION OF INFORMATION/MAINTENANCE OF RECORDS

57.1 Protocol, 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 NDOH, 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 made in terms of the Promotion of Access to Information Act 2 of 2000. All personal information is treated as confidential and shall be processed in accordance with the Protection of Personal Information Act, 2013 (POPIA).

57.2 All documents are stored electronically for record keeping and are accessible only to current SAMAREC members. These records are available for audit, conflict, and query purposes. Records will be kept of the following:

a) Main protocol and all supporting documents (study staff documentation etc.);
b) Date of provisional approval and/or final approval;
c) If applicable – special conditions of approval;
d) Adverse events (with de-identified patient information);
e) Additional sites and study staff applications;
f) Administrative, Minor and Major Amendments;
g) General Notifications;
h) Translation with translation certificates;
i) Annual renewal;
j) SAHPRA Approvals;
k) NHREC Approvals;
l) Protocol Deviations.

The maintenance of records will be held in accordance with the latest NDOH guidelines.

58. RECIPROCAL REVIEW PROCESS

SAMAREC ***may***, at their own discretion, recognize prior review and approval of a research proposal by another registered REC to avoid duplication of effort.

i. **Reciprocal recognition** means that two or more registered RECs decide to recognize each other's prior review.

ii. RECs that recognize prior review in this manner must determine the nature of the documents to be filed locally, which must, at minimum, include a copy of the approval letter from the other REC.

The SAMAREC Chairperson will consider the application and the relevant reciprocal review documentation and decide on the most appropriate way forward. This may include:

a. SAMAREC full committee review depending on amongst other factors, the risk level of the project, impact on the local community etc. or
b. An expedited or rapid review (for example, in the time of Research in Emergencies) or
c. The outcome of the review will be communicated to the local.

The Chairperson of the relevant REC will report to the full REC meeting the process and outcome of the reciprocal review for ratification.

59. SAMAREC RESOLUTION (OUTCOMES)

After noting and considering the submission, the Committee will resolve as follows:

a) **Approved:** The Committee accepts the concept of the Study and has granted ethics approval. No further changes are required, and the Study may commence.
b) **Provisionally Approved:** The Committee accepts the concept of the Study; however, corrections must be made before final approval will be granted. The Study may not commence until approval status is obtained.
c) **Not Approved:** The Committee does not accept the concept of the Study. There are major scientific or ethical concerns. The Protocol should subsequently be revised whereby the Study may not commence.

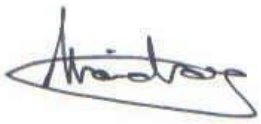
60. DEVELOPMENT AND MANAGEMENT (REVIEW, MONITOR AND APPROVAL) OF SAMAREC SOP

The SAMAREC SOP will be updated as necessary when regulatory or legislative changes are required.

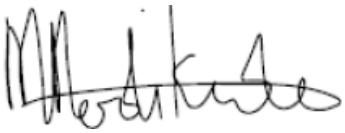
61. ANNEXURES

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

Annexure 1: SAMAREC Meeting Dates
Annexure 2: SAMAREC Application Form
Annexure 3: SAHPRA Format of Curriculum Vitae of Trialists
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)
Annexure 5: Members of SAMAREC
Annexure 6: SAMAREC Fees
Annexure 7: SAMAREC Guidelines for Clinical Study Advertisements
Annexure 8: Declaration by Investigators
Annexure 9: List of Study Staff and their submitted documents.
Annexure 10: Material Transfer Agreement



Name Of SAMAREC Chairperson: Nasheen Naidoo
Date Signed: 14/06/2026



Name of SAMA CEO: Dr Mzulungile Nodikida
Date Signed: 26 June 2026