ADDENDUM

Republic of South Africa

General Comments

The South Africa Addendum to the Evaluation Instrument for Accreditation ("Evaluation Instrument") is intended for use by organizations in South Africa seeking accreditation, by AAHRPP peer reviewers evaluating organizations in South Africa, and by accredited organizations in the US that conduct or oversee research in South Africa. This Addendum includes Standards and Elements where South Africa law, regulations, and guidelines require significant additional protections beyond those defined in the Evaluation Instrument, or are significantly different from requirements in the Evaluation Instrument, and is intended to be used in conjunction with the Evaluation Instrument. The Addendum focuses on the laws most relevant to human research protection programs, including research ethics committees. However, it is not an exhaustive account of all requirements covering research involving human participants in South Africa.

AAHRPP evaluates organizations in South Africa under South Africa law, not US FDA requirements. AAHRPP will not request that organizations in South Africa add US FDA definitions to policies. Organizations that follow ICH-GCP (E6) will be evaluated under that Guideline. Organizations that must follow the US DHHS regulations will be reviewed under those regulations.

The Addendum is based on a review of the South Africa laws, policies, and guidance including but not limited to:

- **National Health Act**, Act 61 (2003)
    - **National Health Amendment Act**, Act No. 12 (2013)
- **National Department of Health/NHREC (National Health Research Ethics Council): South African Ethics in Health Research Guidelines: Principles, Processes and Structures, 3rd ed**. **(NDoH)** (2024)
- **Regulations Relating to Research with Human Participants No. R719 (R719)** (2003)
- **South Africa Good Clinical Practice (SA GCP)** (2020)
- **South African Health Products Regulatory Authority (SAPHRA)**
    - **CT-02: Guideline for Clinical Trial Participant Time, Inconvenience, and Expense Compensation Model** (2022)
    - **CT-05: Liability Insurance for Clinical Trials** (2022)
- **Protection of Personal Information Act (POPIA),** Act 4 (2013)
    - **POPIA Regulations** (2018, Amended April 17, 2025)

The organization must comply with laws, regulations, and guidelines issued under the National Department of Health (NDoH) and its National Health Research Ethics Council (NHREC) per the National Health Act, the South African Health Products Regulatory Authority (SAHPRA) [which replaced the Medicines Control Council (MCC)], the Information Regulator under POPIA;

and, where applicable, adhere to Health Care Professions Council of South Africa (HCPCSA) ethical rules for registered practitioners. Guidance from the South African Medical Research Council (SAMRC) and Human Sciences Research Council (HSRC) applies when they are the funder, host, or reviewing Research Ethics Committees (RECs), but is not generally a regulation for all research.

This Addendum represents AAHRPP's current understanding of additional requirements covering organizations sponsoring, managing, conducting or reviewing research in South Africa.

We appreciate questions, concerns, and suggestions to improve this document. Please email accreditation@aahrpp.org.

Domain I: Organization

Standard I-1: The organization has a systematic and comprehensive Human Research Protection Program that affords protections for all research participants. Individuals within the organization are knowledgeable bout and follow the policies and procedures of the Human Research Protection Program.

Element I.1.A. The Organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.

When following the National Health Act (NHA, 2003), written materials include a description of how health research may be understood to include, but is not limited to, research that contributes to knowledge of:

- biological, clinical, psychological, or social welfare matters including processes in human beings
- improved methods for the provision of health services
- human pathology
- the causes of disease
- the effects of the environment on the human body
- the development of new application of pharmaceuticals, medicines, and related substances
- the development of new applications of health technology

When following NDoH, written materials:

- Define research as a systematic investigation designed to contribute to generalizable knowledge, or equivalent definition based on conventional scientific and ethical standards appropriate for the context. Research includes a range of activities conducted by many

different disciplines that may use different methodologies and explanatory frameworks to extend knowledge through disciplined inquiry or systematic investigation.

- Describe that ethical principles apply to living humans, and also to research involving use of human biological materials and data collected from living or deceased persons, including human embryos, fetuses, fetal tissue, reproductive materials, and stem cells.

When following SA GCP, written materials describe that a clinical trial (or clinical study) refers to any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Regulatory and guidance references

- **National Health Act, 2003**. Chapter 12: Definitions
- **NDoH, 2024:**
    - 1.1. Introduction
    - 3.3 Scope of SOPs
    - Appendix 1: Glossary
    - 6.3 Research Ethics Committees
    - 6.4.2. Registration
- **SA GCP, 2020**. Glossary

Standard I-3 The organization's transnational research activities are consistent with the ethical principles set forth in its Human Research Protection Program and meet equivalent levels of participant protection as research conducted in the organization's principal location while complying with local laws and taking into account cultural context.

When following NDoH, written materials describe that, for reciprocal recognition of Research Ethics Committee (REC) review for international multi-site research, at least one (co- principal investigator) must be physically in South Africa.

Regulatory and guidance references

- **NDoH, 2024:**
    - 2.3.8 Researcher competence and expertise
    - 5.5 Standard Operating Procedures

Standard I-4 The organization responds to the concerns of research participants.

Element I.4.C. The Organization promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results.

When following SA GCP, written materials require:

- the sponsor must ensure that trial results and outcomes are reported to the researchers and South African Health Products Regulatory Authority (SAHPRA) as well as to the Department of Health via the South African Clinical Trials Register (SANCTR).
- the sponsor and the principal investigator are responsible for appropriate dissemination of the trial findings.
- results should be disclosed within one year of completion of the analysis of the trial results.

Regulatory and guidance references

- **SA GCP, 2020**:
    - 4.4 South African National Clinical Trials Register (SANCTR)
    - 6.15 Reporting and Release of Trials Results

Standard I-6 The organization has and follows written policies and procedures to ensure that research is conducted so that financial conflicts of interest are identified, managed, and minimized or eliminated.

Element I.6.B. The organization has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of Researchers and research staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. The organization works with the Institutional Review Board or Ethics Committee in ensuring that financial conflicts of interest are managed and minimized or eliminated, when appropriate.

Regulations and laws of South Africa require that an organization must maintain a written conflict of interest policy that specifies the procedures for disclosure including, if someone is uncertain that a conflict of interest exists, then they must make enquiries to the appropriate person per the policy. (e.g., the Research Ethics Council (REC) Chair, Institutional COI Officer, or Principal Investigator).

When following SA GCP, written materials describe that:

- the range of potential conflict of interest (COI) includes direct benefits, such as sponsorship of the investigation; indirect benefits, such as

provision of material or facilities; and individual support, such as provision for travel or accommodation expenses to attend conferences.
- a COI exists whenever such interests may, or may be perceived to, affect decisions.

Regulatory and guidance references

- **SA GCP, 2020**. 10.1 Conflict of Interest

Standard I-7 The organization has and follows written policies and procedures to ensure that the use of any investigational or unlicensed test article complies with all applicable legal and regulatory requirements.

Element I.7.A When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions.

When following SA GCP, written materials describe:

- Research involving the use of unregistered medicinal substances and new indications of registered substances must obtain or verify approval from South African Health Products Regulatory Authority (SAHPRA).
- The process for ensuring all relevant regulatory and ethical permission is in place to conduct the research prior to initiating the clinical trial.

When following SA GCP, written materials describe that essential documents must be retained for at least 10 years by the sponsor after final closure of clinical trial, or for at least two years after formal discontinuation of clinical development of the Investigational Product.

Regulatory and guidance references

- **SA GCP, 2020**. 2.3.1.3: Clinical trials involving unregistered medicines or new indications of registered medicines
- **SA GCP, 2020**. 5.10 Records and Reports

Element I.7.B. The organization has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.

When following SA GCP, written materials for control of investigational drugs and devices describe processes for:

- manufacturing, handling, and storage in accordance with applicable good manufacturing practice.
- where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial site to an

appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.
- the investigator, pharmacist, or other designated individual maintaining records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products.
- investigators maintaining records that document adequately that the participants are provided with the doses specified by the protocol and reconcile all investigational products received from the sponsor.
- storing the investigational product as specified by the sponsor, and in line with Good Pharmacy Practice (GPP) and Good Manufacturing Practice (GMP) in South Africa, SAHPRA regulations and conditions.
- disposing of all unused investigational product of a trial in line with the protocol approved by SAHPRA.

Regulatory and guidance references

- **SA GCP, 2020**. 5.7: Investigational Products

Standard I-8 The organization works with public, industry, and private sponsors to apply the requirements of the Human Research Protection Program to all participants.

Element I.8.A. The organization has a written agreement with the sponsor that addresses medical care for research participants with a research-related injury, when appropriate.

When following R.719, regulations and laws of South Africa indicate that no-fault compensation via comprehensive trial insurance is expected for interventional trials. Sponsors must indemnify sites/investigators and insurance information must be included in consent for greater than minimal risk research.

When following SAHPRA CT-05, written materials describe:

- sponsor responsibility for the provision of insurance in an application for the conduct of a clinical trial.
- Evidence of comprehensive no fault insurance for serious injury and harm and/or death should be provided by the sponsor and/or applicant.
- sponsor/applicant should take responsibility of ensuring that participants are fully compensated.
- provision is made for comprehensive insurance against medical treatment required for trial-related bodily injury.

Regulatory and guidance references

- **R. 719, 2014.** 2.i. Principles guiding research with human participants

- **SAHPRA CT-05. 2022.** 3.1. Responsibility of provision of insurance in an application for the conduct of a clinical trial. 5.1. Insurance against trial-related injury

Element I.8.D. Before initiating research, the organization has a written agreement with the sponsor about plans for disseminating findings from the research and the roles that researchers and sponsors will play in the publication or disclosure of results.

When following SA GCP, written materials describe:

- in addition to the reporting requirements that should be captured in written agreements between organizations and sponsors, sponsors must report trial results to the South African Health Products Regulatory Authority (SAHPRA) as well as to the Department of Health via the South African Clinical Trials Register (SANCTR).
- the sponsor must ensure that trial results and outcomes are reported to investigators.
- the sponsor and the PI are responsible for appropriate dissemination of the trial findings within one year of completion of analysis of the trial results.

Regulatory and guidance references

- **SA GCP, 2020.** 6.15 Reporting and release of trial results

Standard I-9: The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization the rights and welfare of research participants are protected.

Regulations and laws of South Africa indicate reciprocal recognition of review is defined as two or more registered Research Ethics Committees (RECs), recognizing the review and approval of a research protocol granted by another registered South African REC.

When following NDoH guidance, in addition to requirements specified under AAHRPP Standard I-9, written materials describe reciprocal recognition of REC review which includes:

- that the RECs should establish and specify documentation to be filed at each REC.
- that any decision to rely on another REC's approval must be presented at the next REC meeting for noting or endorsement, and the action and decision documented in the minutes.
- documentation of processes, roles, and accountability concerning protocol amendments, site specific versus requiring broader review, and identifying how adverse events and unanticipated problems

including serious adverse events are to be reported among the RECs and to regulatory authorities (e.g., SAHPRA).

Regulatory and guidance references

- **NDoH, 2024:**
    - 5.5.14 Reciprocal recognition of review decisions

Domain II: Institutional Review Board or Ethics Committee

Standard II-1: The structure and composition of the IRB or EC are appropriate to the amount and nature of the research reviewed and in accordance with requirements of applicable laws, regulations, codes, and guidance.

Element II.1.A. The IRB or EC membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB or EC roster. The IRB or EC has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB or EC regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.

When following NDoH, written materials describe that REC membership include, in addition to AAHRPP Essential Requirements:

- members who represent more than a single profession and as many disciplines, sectors, and professions as possible, appropriate to the research under review.
- members from diverse age groups.
- ethnically and culturally diverse members.
- at least one member with knowledge of and current experience in the professional care, counselling or health-related treatment of people (e.g. medical practitioner, psychologist, social worker, nurse).
- at least one member with professional training and experience in qualitative research methodologies.
- members with expertise in biostatistics.
- a member with expertise in research ethics.
- at least one member who is legally qualified and has extensive knowledge of family law, health law, and research ethics.
- at least one member who represents the perspective of research participants and are representative of the communities they serve and reflect the demographic profile of the population of South Africa.
- at least on an ad hoc basis, a member with experience and knowledge of working with inmates when deliberating on the protocol, if the organization conducts or reviews research involving inmates.

Regulatory and guidance references

- **NDoH, 2024:**
    - 5.3.1. REC Membership Composition
    - 3.2.9. Inmates

ELEMENT II.1.D.: The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.

When following NDoH, written materials specify:

- REC members should disclose information that may lead to potential, actual as well as perceptions of conflict of interest.
- REC members and ad hoc reviewers must not use the ethics review process to impose personal biases, professional jealousy or territorial protection conduct about an applicant's protocol, including research methods or the topic.
- Applicants who pay fees to benefit from the ethics review service must not be allowed to negatively affect the rigor of reviews, the integrity of the process, or the capacity to monitor the research that the REC approves. The attraction of earning fees must never outweigh the capacity of the REC to perform its work as expected.

Regulatory and guidance references

- **NDOH, 2024:**
    - 4.4.1 Conflict of Interest
    - 4.42. Fees and Independence

Standard II-2: The IRB or EC systematically evaluates each research protocol or plan to ensure the protection of participants.

Element II.2.A. The IRB or EC has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB or EC. Such policies and procedures indicate that exemption determinations are not to be made by researchers or others who might have a conflict of interest regarding the studies.

Regulations and laws of South Africa do not define categories of research that are exempt from applicable laws and regulations.

Written materials describe the process when ethics review is not required:

- research that relies exclusively on information that is publicly available and does not require gatekeeping, site or platform permission, or accessible in terms of legislation or regulation

    - This research may need to undergo formal ethics review, depending on ethical considerations relevant to the research.
- research involving observation of people in public spaces (including virtual public spaces), and natural environments, usually need not undergo formal ethics review, provided that: the researcher does not interact directly with individuals or groups, the researcher does not stage an intervention, or the groups do not have a reasonable expectation of privacy, or dissemination of research findings does not identify individuals or groups.

Regulatory and guidance references

- **NDoH, 2024**. 1.1. Introduction

Element II.2.E. The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or EC.
1. Element II.2.E.1. – Initial review
2. Element II.2.E.2. – Continuing review
3. Element II.2.E.3. – Review of proposed modifications to previously approved research

Regulations and laws of South Africa recognize a specific process for circumstances of urgency, such as a major incident or localized emergency), referred to as “rapid review”. It is triggered by circumstances of urgency, where higher-risk or time-sensitive research may be moved through the ethics system at an accelerated timeline, but still under ethical safeguards. Rapid review is not synonymous with expedited review.

When following NDoH requirements, written materials:

- Establish standard operating procedures for the REC rapid review process for applicable research that describe:
    - The definition of rapid review
    - The process for triage and assessment of whether a protocol is eligible for a rapid review process
    - The process for selection of a 3 to 5 person reviewer group with appropriate expertise to conduct the rapid review
    - Reporting of REC deliberations and outcomes of the rapid review process to the full REC at its next meeting
    - How equivalent protections are ensured when the rapid review process is used

Regulatory and guidance references

- **NDoH, 2024**. 5.5.1.6. Rapid Review

Element II.2.F. The IRB or EC has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used.

Element II.2.F.1. – Initial review
Element II.2.F.2. – Continuing review
Element II.2.F.3. – Review of proposed modifications to previously approved research

When following NDoH, written materials:

- Specify that expedited review:
  - Applies to research that poses no more than minimal risk of harm
  - Means that no fewer than two REC members review the protocol
- Describe that deliberation in the full committee meeting is unnecessary, unless the reviewers believe there are issues that the REC should discuss
- Describe the kinds of research that may be expedited

Regulatory and guidance references

- **NDoH, 2024**. 5.5.1.5. Expedited review

Standard II-3: The IRB or EC approves each research protocol or plan according to criteria based on applicable laws, regulations, codes, and guidance.

Element II.3.A. The IRB or EC has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.

When following NDoH, written materials describe how the REC does not classify risk, but completes an analysis that must conclude that the anticipated risks are minimized to the extent possible and are justified by the potential benefits, either to participants directly or to society. This includes confirming there is an adequate monitoring of risks, and that sponsors provide insurance/indemnity for potential harm.

When following SA GCP, written materials describe how the REC should consider:

- That the risk-benefit analysis takes full cognizance of benefits and harms beyond the life of the study itself, particularly in relation to chronic life-threatening conditions.
- Making specific recommendations regarding the continuation of treatments beyond the life of the study, or mechanisms to ensure that participants are fairly protected.
- If placebos are to be used, whether their use can be scientifically justified.

Regulatory and guidance references

- **NDoH, 2024.** 1.6 Ethical research review
- **SA GCP, 2020:**
    - 2.3 Risk, Burdens, and Benefits
    - 7.5.4. Trial Design

Element II.3.F. The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the researcher appropriately document the consent process.

Health RECs are specifically provided under the National Health Act and must follow Department of Health guidelines. Non-health RECs are not created by the National Health Act and are typically established by universities or research institutions and governed by institutional policies.

When following SA GCP, written materials describe the consent process, which encompasses the discussion and documentation, include the following in addition to AAHRPP Essential Requirements:

- Information about the sponsor;
- Any potential conflict of interests;
- Information about approval from a health REC or SAHPRA, where relevant;
- Insurance/indemnity in the event of research-related injury, for more than minimal risk research; and
- The availability of beneficial products or interventions after completion of the research.
- The alternative procedures or treatment that might be available to the participant, and their important potential benefits and risks.
- That the monitor, the auditor, the REC, and the regulatory authority will be granted direct access to the participant's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant's legally acceptable representative is authorizing such access.

Regulatory and guidance references

- **SA GCP, 2020.** 5.9. Informed Consent for Clinical Trial Participants

Element II.3.G. The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.

Deferred Consent

Deferred (or delayed) consent is a type of consent used when a participant has a temporary loss of decision-making capacity and there is a reasonably held prognosis that they will regain capacity within a predictable period (e.g., an unconscious Emergency Unit patient expected to awaken within hours). It alters the requirement for prospective consent; however, it is not a waiver. Once capacity returns, the participant must be told they were enrolled in a study and consent must then be obtained; if they object, this is a refusal and their data should be withdrawn.

When following NDoH requirements, written materials describe that:

- Deferred consent is permissible when it is impracticable to obtain consent, because neither the prospective participant nor the participant's legally acceptable representative is able to give consent in advance.
- A REC may approve a research project without prior consent if it is satisfied that:
    - the proposed research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care, and
    - participation is not contrary to the medical interests of the patient, and
    - when the patient regains capacity to make decisions, they must be informed that they have been enrolled in a research study, and
    - a clear and full justification for the proposed use of deferred consent is provided.

- When the deferred consent process is used and decision-making capacity is regained:
    - If the participant objects to having been enrolled in the study, this counts as a refusal to participate.
    - The participant should be asked whether their data already collected must be withdrawn.
    - If death of the participant occurs before deferred consent can be obtained, it should not be assumed that continued use of the data and/or samples is ethical. The deceased's wishes or those of their proxy or mandate holder should be ascertained.

Regulatory and guidance references

- **NDoH, 2024.** 3.1.10.2.c. Formats of consent: Deferred consent

Standard II-4: The IRB or EC provides additional protections for individuals who are vulnerable to coercion or undue influence and participate in research.

Element II.4.A. The IRB or EC has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.

When following R719, written materials:

- define "vulnerable persons" as persons at increased risk of research-related harm, or who are limited in their freedom to make choices, or relatively incapable of protecting their own interests.
- The REC must determine the research:
    - May involve vulnerable persons only when non-vulnerable persons are not appropriate for inclusion;
    - Does not systematically avoid inclusion of vulnerable participants because to do so is unfairly discriminatory and vulnerable persons are potential beneficiaries of relevant research;
    - Is responsive to the health needs and the priorities of vulnerable persons; and
    - Receives special attention in ethical review to ensure that research-related risks are assessed and minimized and that appropriate consent procedures are followed.

Minors (children and adolescents)

When following NDoH, written materials describe:

- the legal status of minority protects young people under 18 years of age, from their own emotional, cognitive, and physical immaturity and limited life experience.
- the circumstances when it may be ethically justifiable for children and adolescents to choose independently without parental assistance to participate in research.

When following SA GCP, written materials describe:

- Research with minors should only take place when:
    - Their participation is indispensable to the research, i.e. the research cannot deliver the desired outcomes if adult participants were to be used instead.
    - Ministerial consent has been provided for non-therapeutic research and the REC included appropriate pediatric research expertise, reviewed the research as 'non-therapeutic' in terms of the legal framework, and ensured its deliberations on the specified requirements for inclusion of minors as participants are properly recorded.
        - 'Non-therapeutic research' means research that includes interventions that will not hold out the prospect of direct health related benefit for the participant but may produce results that contribute to generalizable knowledge.

Adults unable to consent

When following R719, written materials describe research with adults unable to consent is appropriate when:

- The research cannot be conducted with adults who have decision-making capacity;
- The research poses no more than a minimal risk; or
- The research poses more than a minimal risk, but holds out the prospect of direct benefit to the participant; or
- The research poses a minor increase over minimal risk, and holds out no prospect of direct benefit but is anticipated to yield generalizable knowledge about the condition under study.

When following SA GCP, written materials describe reviewing clinical trials involving adults unable to consent, the REC determines:

- A non-therapeutic clinical trial (i.e., a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent and who sign and date the written consent document.
- Non-therapeutic clinical trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:
    - The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally.
    - The foreseeable risks to the participants are low.
    - The negative impact on the participant's wellbeing is minimized and low.
    - The clinical trial is not prohibited by law.
    - The opinion of the REC is expressly sought on the inclusion of such participants, and the written opinion covers this aspect.
    - Unless an exception is justified, the clinical trial is conducted in participants having a disease or condition for which the investigational product is intended.
    - Participants are particularly closely monitored and withdrawn if they appear to be unduly distressed.

Incarcerated Individuals

When following R719, written materials describe how research with incarcerated individuals is appropriate when:

- The risk of harm posed by the research is commensurate with risks that would be accepted by non-incarcerated individual volunteers;
- The rights of incarcerated individuals, including but not limited to the rights to dignity, privacy, bodily integrity and equality, will be protected; and
- The procedures and guidelines issued by the Department of Correctional Services will be followed.

Dependent or hierarchical relationships

When following R719, written materials describe research with persons in dependent or hierarchical relationships:

- Includes but is not limited to research with users and their health-care workers; persons with life-threatening diseases and their caregivers, wards of the state and their guardians or caregivers, employees and their employers, prisoners and the relevant prison authorities and members of the national defense force and their superiors; and
- Is appropriate when research-related risks of harm are minimized, and appropriate consent procedures have been followed.

Pregnant women

When following NDoH requirements, written materials describe:

- how researchers and RECs should exercise extra caution when women participants are or may become pregnant. Exclusion of women from research may be justifiable:
  - to protect the health of the embryo, fetus or infant and
  - if exclusion is scientifically supportable.
- Research involving pregnant women is permitted when:
  - the purpose of the proposed research is to meet the health needs of the mother of the embryos, fetuses or infants
  - appropriate studies on animals and non-pregnant women have been completed
  - the risk of harm to the embryo, fetus or infant is minimal, when procedures or interventions have no potential individual benefit for the women or embryo, fetus or infant,
  - the risk of harm is outweighed by the prospect of potential individual benefit, when procedures or interventions have potential individual benefit for the women or embryo, fetus or infant, and
  - in all cases, inclusion poses the least risk of harm possible for achieving the objectives of the research.

Regulatory and guidance references

- **R719, 2003.** 4. Research with vulnerable persons
- **NDoH, 2024:**
  - 3.2.2 Minors (children and adolescents)
  - 3.2.3 Women
- **SA GCP, 2020.** 2.3 Risk burdens and benefits

Standard II-5: The organization measures and improves, when necessary, compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The organization also measures and improves, when necessary, the quality, effectiveness, and efficiency of the Human Research Protection Program.

Element II.5.A. The IRB or EC maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, sponsor requirements, and organizational policies and procedures.

When following SA GCP, written materials describe how the REC will retain all relevant records (e.g. written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings and correspondence) for a period of at least three years or as per institutional requirement, whichever period is longer, after completion of the trial and make them available upon request from the applicable regulatory authority.

Regulatory and guidance references

- **SA GCP, 2020.** 4.3 Research Ethics Committees (RECs)

Domain III: Researcher and Research Staff

South African regulations interchangeably use “researcher”, “Investigator”, and “PI”.

Standard III-1: The IRB or EC provides additional protections for individuals who are vulnerable to coercion or undue influence and participate in research.

Element III.1.B. Researchers and research staff identify and disclose financial interests according to organizational policies and regulatory requirements and, with the organization, manage, minimize, or eliminate financial conflicts of interest.

When following SA GCP, written materials describe that:

- all individuals involved in conducting, managing, or reviewing research are required to identify, disclose, and manage any real or perceived COI.
- each individual is responsible for recognizing situations in which they may have or may be perceived to have a COI or might reasonably be seen by others to have a conflict, and for disclosing this to the appropriate person or entity as established by an organization’s policy.

Regulatory and guidance references

- **SA GCP, 2020**. 10.1 Conflict of Interest

Element III.1.C. Researchers employ sound study design in accordance with the standards of their discipline. Researchers design studies in a manner that minimizes risks to participants.

When following SA GCP, written materials describe how the investigator follows the clinical trial's randomization procedures, if any.

- In blinded studies, the protocol must specify the circumstances under which the code is broken, and the procedure for unblinding.
- If the clinical trial is blinded, the researcher promptly documents and explains to the sponsor any premature unblinding.

When following SA GCP, written materials require:

- The investigator describes how they will evaluate whether protocols for clinical trials to be conducted in community settings are customized appropriately for the local setting to ensure that local realities are considered and integrated into the design. Sponsors are responsible for ensuring such customization during protocol development, and the investigator for advising on and implementing it in practice.

Regulatory and guidance references

- **SA GCP, 2020:**
    - 5.4. Medical care of trial participants
    - 5.8 Randomization procedures and unblinding
    - 7.12 Ethical considerations

Element III.1.D. Researchers determine that the resources necessary to protect participants are present before conducting each research study.

When following R719, written materials describe that researchers are responsible for:

- submitting the research proposal for ethics review and approval to a registered health research ethics committee and, where applicable, to the SAHPRA or any other body required by law, before commencing with the research;
- consulting with representatives from the participating community or other relevant research stakeholders, where appropriate;
- consulting with and notify the affected institutional or governmental authorities where necessary;
- assessing the ongoing welfare of participants and take appropriate steps in the event that participants experience harms;

- disseminating research results, whether negative or positive, to research stakeholders, in a timely and competent manner including to participants and participating communities as far as possible; and
- registering the research in the South African National Clinical Trials Register, if classified as a clinical trial.

Regulatory and guidance references

- **R719, 2014. 3.** Obligations of researcher who conduct research with human participants

Element III.1.E. Researchers and Research Staff recruit participants in a fair and equitable manner.

When following SA GCP, written materials describe:

- The investigator informs the participant's primary physician about the participant's participation in the clinical trial if the participant:
  - has a primary physician, and
  - agrees to the primary physician being informed.
- A participant is not obligated to provide reasons for withdrawing from research prematurely.
  - The investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant's right to decline to disclose.

Regulatory and guidance references

- **SA GCP, 2020.** 5.4 Medical care of trial participants

Element III.1.F. Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.

When following SA GCP, written materials describe:

- The investigator informs participants when medical care is needed for any intercurrent conditions of which the researchers become aware.
  - Intercurrent conditions are new medical conditions or illnesses that develop after a participant's enrollment in research and are not necessarily related to the research (e.g., influenza, pregnancy, newly diagnosed hypertension).

Regulatory and guidance references

- **SA GCP, 2020.** 5.4 Medical care of trial participants

Standard III-2: Researchers and Research Staff meet requirements for conducting research with participants and comply with all applicable laws, regulations, codes, and guidance; the organization's policies and procedures for protecting research participants; and the IRB's or EC's determinations.

Element III.2.A. Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the organization's policies and procedures regarding the protection of research participants.

When following SA GCP, written materials specify qualifications of researchers:

- to serve as a principal investigator, the researcher must be a South Africa-based clinician and must have actively participated in at least two clinical trials as a sub-investigator. The local PI has sole or joint responsibility for the conduct of the trial and delegation of trial responsibilities. Clinical trials must be conducted by a local, South African-based scientist.
- for multi-center studies in South Africa, a National Principal Investigator (NPI), with expertise and experience in the relevant field, may be appointed to take overall responsibility for the conduct of a trial.
- have read, understood and agreed to work according to the protocol, the Declaration of Helsinki, ICH Guideline for Good Clinical Practice, these Guidelines and other relevant legislation; undertake to use the investigational and comparator product(s) only for the purposes of the study as described in the protocol.
- ensure that they have the responsibility to make trial results (both positive and negative) publicly available within a reasonable timeframe.
- have the responsibility to share possible benefits of research results with participants.
- a qualified clinician, who may be the PI, Co-PI, or if appropriate Sub-I, must be responsible for all clinical trial-related medical (or dental) decisions.
- a qualified physician (or dentist, when appropriate), who is a researcher or a co-researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions (not applicable to independent RECs).
- the researcher provides evidence of their qualifications and experience through a current curriculum vitae or other relevant documentation requested by the sponsor, the REC/EC, or the regulatory authority.
- evidence of current (i.e. within three years) GCP training as well as general research ethics training.

When following NDoH, researchers conducting research involving inmates must ensure that their protocols comply with the requirements of the Department of Correctional Services.

Regulatory and guidance references

- **SA GCP, 2020:**
    - 4.3.3 REC documentation requirements for review
    - 5.2. Investigator qualifications
    - 5.4 Medical care of trial participants
- **NDoH, 2024.** 3.2.9. Inmates

Element III.2.D. Researchers and Research Staff follow reporting requirements in accordance with applicable laws, regulations, codes, and guidance; the organization's policies and procedures; and the IRB's or EC's requirements.

When following SA GCP, written materials describe:

- The sponsor is the entity responsible for the trial, while the Applicant is the party that submits and maintains the South African Health Products Regulatory Authority (SAHPRA) application (which may be the sponsor, its local representative/Clinical Research Organization (CRO), or Investigator Initiated Trials).
- Regulatory duties and responsibilities (e.g. safety reporting, SANCTR registration) are assigned to the entity who filed and holds the approval.
- When the investigator and sponsor/applicant responsibilities for reporting information, including:
    - New information that might affect adversely the safety of the participants or the conduct of the clinical trial and any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
        - The investigator must promptly communicate all new safety information, protocol deviations, or increased risks to the sponsor/applicant.
        - The sponsor/applicant is ultimately responsible for ongoing safety evaluation and regulatory reporting.
    - Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations.
        - The investigator should be reported to the sponsor/applicant in accordance with the reporting requirement and within the time periods specified in the protocol.
    - The sponsor/applicant must adhere to the time-periods and format specified in the protocol, conduct ongoing safety

evaluation, and communicate significant findings to the investigator and regulators.

- Participant deaths.
  - The investigator initiates the death report and provides detailed follow-up information to the sponsor/applicant and REC.
  - The sponsor/applicant may submit a formal report or follow-up to SAHPRA if the death reported to them meets criteria for a Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR).
- Initial and follow up reports must identify the affected participants by the participant identification code.
  - The investigator must ensure coding is used consistently in all safety communications.
  - Sponsors/Applicants must ensure coding is used consistently in all safety communications.
- Serious adverse event (SAE) reports.
  - The investigator must document SAEs using a sponsor's report form or the current SAHPRA SAE reporting template and any relevant follow-up information must be sent to the sponsor/applicant.
  - The sponsor/applicant is responsible for forwarding relevant information to SAHPRA.

When following SAHPRA CT-02, written materials describe:

- Investigators must promptly report all SAEs to the Sponsor/Applicant.
- The sponsor/applicant is responsible for submitting all serious unexpected suspected adverse reactions (SUSARs) to SAHPRA in accordance with the requirements with this guideline.

Regulatory and guidance references

- **SA GCP, 2020.** 5.12 Safety reporting
- **SAHPRA CT-02**, 2022. Guideline for Safety Reporting During Clinical Trials in South Africa