Adverse Events, Protocol Violations, Protocol Deviations and Unanticipated Problems

(To be read together with SOP on Active and Passive Monitoring)

1. Purpose and Scope

1.1 This document describes the process to be followed by the South African National Blood Service (SANBS) Human Research Ethics Committee (HREC) for documenting and reporting adverse events at SANBS HREC-approved sites in order to ensure compliance with the below-mentioned references.

1.2 Adverse event reporting should be in line with and in compliance with the South African Health Products Regulatory Authority (SAHPRA) Reporting Adverse Drug Reactions guidance and section 2 of this document.

2. References

2.1 Constitution of The Republic of South Africa, Act 108 of 1996;
2.2 The National Health Act 61 of 2003 and its regulations;
2.3 Protection of Personal Information Act 4 of 2013 and its regulations;
2.4 Material Transfer of Human Biological Materials (National Health Act 61 of 2003);
2.5 Ethics in health research: principles, processes and structures, third edition, 2024.
2.6 South African Good Clinical Practice: Clinical Trial Guidelines (SA DOH, 3rd edition, 2020);
2.7 National Regulations Relating to Research with Human Participants R719 of 2014, Gazette No 38000, 19 September 2014, Vol 591 No 10268;
2.8 Regulations relating to the import and export of human tissue, blood, blood products, cultured cells, stem cells, embryos, foetal tissue, zygotes and gametes, R181 of 2012, Gazette No 35099, 2 March 2012;
2.9 Ethical principles for medical research involving human subjects: Declaration of Helsinki (WMA, 2024);
2.10 International Ethical Guidelines for Health-related Research Involving Humans, 2016, CIOMS.
2.11 International Conference on Harmonisation Good Clinical Practice Guideline, (10 November 2016);
2.12 International Committee of Medical Journal Editors (ICMJE) guidelines for authorship (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html); and
2.13 Other relevant legislation, company documents and policies.

3. Definitions

3.1 **Adverse Event (AE):** Any untoward medical occurrence that may present during treatment with a medicinal product/intervention/ interaction, but which does not necessarily have a causal relationship with this treatment/ interaction.

3.2 **Serious Adverse Event (SAE) or (Serious Adverse Drug Reaction):** defined as any negative or untoward occurrence, which does not necessarily have a causal relationship with the research and may:

3.2.1 Result in death.
3.2.2 Be life-threatening.
3.2.3 Require participant hospitalisation or prolongation of existing hospitalisation
3.2.4 Result in persistent or significant disability/incapacity (social harm for displacement from the home)
3.2.5 Any other experience that suggests a significant hazard, contraindication, side-effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.

In all instances, the researcher has to indicate whether the SAE is related or unrelated to the study.

3.3 **Adverse Drug Reaction (ADR) or (Adverse Reaction):** A response to a medicine/intervention which is noxious and unintended. The word "response" means that the causal relationship between the medicinal product/intervention and the adverse event is at least a reasonable possibility.

3.4 **Unexpected Adverse Drug Reaction:** One in which the nature, specificity, severity and outcome are not consistent with the applicable product information (i.e. with the approved package inserts for registered products, or the investigator's brochure or other product information for unregistered products).

3.5 **Deviation:** Any alteration or modification to the approved research without prospective HREC Approval. Deviations are categorized into minor and major.

3.5.1 **Minor Deviation:** A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

3.5.2 **Major Deviation:** A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

3.6 **Protocol violations**, include any unapproved changes, deviations or departures from the study design or procedures of a research project that are under the investigator's control and that have not been reviewed and approved by the HREC. The violation is wilful on the part of the investigator(s). It involves serious or continuing non-compliance with HREC and/or NHREC policies.

4. Responsibility

4.1 The secretariat will receive the adverse event, violation, or deviation report from the investigator and will immediately forward it to the HREC Chairperson, who will convene an ad hod AE sub-committee based on the relevant expertise required for the particular event.

4.2 The secretariat acknowledges receipt and processing of the particular report to the Sponsor and Investigators.

5. Procedure

5.1 Other reporting requirements to be provided by the investigator for all SANBS HREC-approved protocols include the following:

5.1.1 **Serious, unexpected, adverse drug reactions occurring at other South African and Foreign sites.**

To be reported with a management plan within 24 hours to the HREC secretariat (hrecadmin@sanbs.org.za). The HREC chairperson must be notified immediately. The HREC chairperson – with assistance from the secretariat – will convene the ad hoc sub-committee, who will meet and respond within 48 hours. In addition, the report will be included as part of the 6-monthly progress report for Clinical Trials, or annually. Other AEs should be reported with a management plan within 7 day and as part of the six-monthly/annual progress report

5.1.2 **New information which may affect the safety of participants or the conduct of a trial.**

Report with a management plan within 7 days of first knowledge. In addition, report as part of the six-monthly/annual progress report.

5.1.3 **Change in the nature, severity or frequency of expected Adverse Drug Reactions.**

Report with a management plan within 7 days of first knowledge and in the 6-monthly/annual progress report.

5.2 **Protocol violations and protocol deviations**

5.2.1 Protocol violations and deviations shall be reported in the same manner as adverse events, and in addition will include a root cause analysis, corrective and preventative actions.

5.2.2 Deviations include deviating from any HREC-approved materials and documents including the detailed protocol, HREC application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

5.2.3 Protocol violations have potential for serious harm to the safety of the research participants, the research itself, and the integrity of SANBS.

6. Suspension or termination of approval

6.1 The HREC may suspend or terminate approval of a study that is not being conducted in accordance with prevailing HREC or South African Department of Health ethical requirements or in the case of certain SAEs, it becomes evident that the harms of the study have started outweighing the benefits.

6.2 The primary justification for suspension or termination of approval should be the safety of participants.

6.3 Such suspension or termination of approval must be authorized by the HREC Chairperson in consultation with the HREC and/or other co-opted party as soon as possible, but not more than seven days after receipt of relevant information by the Chairperson.

6.4 An ad-hoc REC meeting may be convened where required. This will depend on the seriousness of harm to participants.

6.5 All such discussions should be fully minuted.

6.6 All actions must be reported to the HREC at the next quorate meeting.

6.7 Should a research study be prematurely suspended or terminated by the study sponsor, Data Safety Monitoring Board or any other relevant authority outside SANBS HREC, the PI must notify the HREC immediately.

6.8 A summary must be communicated regarding the reasons for the suspension or termination.

Revision Summary

VERSION NUMBER	**REVISION DETAILS**
0	18 February 2025

.

Adverse Event and Protocol Violation/Deviation Reporting		
Study Title		
Ethics Clearance Number		
Participant Identifier		
Date of Report		
Date of Event		
SAE	**YES**	**NO**
Grade		

Related to an investigational product?	**YES**	**NO**
Deviation	**YES**	**NO**
Minor Deviation	**YES**	**NO**
Major Deviation	**YES**	**NO**
Violation	**Yes**	**No**
Description of Event		

Principal Investigator	**Signature**	**Date**
Study Coordinator	**Signature**	**Date**
	Signature	**Date**