# HUMAN RESEARCH ETHICS COMMITTEE: (MEDICAL)

## STANDARD OPERATING PROCEDURE

## SAFETY REPORTING

**SOP-HREC – 005** *(VERSION 1)* **REVISED AND UPDATED:** JANUARY 2025

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| **SUBJECT:** | **Procedure for Safety Reporting in studies approved by the University of the Witwatersrand, Human Research Ethics Committee: (Medical)** |
| **DIVISION / SCOPE:** | **University of the Witwatersrand, Human Research Ethics Committee: (Medical)** |
| **AUTHOR:**<br>**REVISION:** | Ethics Secretariat |
| **PURPOSE:** | This procedure describes the process to be followed by the Wits HREC (Medical) with regards to the reporting of Adverse Events (AEs), Adverse Drug Reactions (ADRs) and Serious Adverse Events (SAEs) occurring during clinical studies conducted at Wits HREC (Medical) approved sites, to ensure compliance with the following guidelines:<br>• South African Good Clinical Practice: Clinical Trial Guidelines. Third Edition (SA GCP 2020)<br>• ICH Harmonised Guideline – Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH – E6(R2) – Current Step 4 version dated 9 November 2016<br>• FDA requirements for Institutional Review Boards (21 CFR Part 56)<br>• SAHPRA Guideline for Safety Reporting During Clinical Trials in South Africa (SAHPGL-CEM-CT-10_v5) dated October 2022 |
| **PREVIOUS VERSIONS /** ***(REASON FOR REVISION)*** | SOP-IEC-005v9<br>Revised |
| **CONTENTS:** | **1. Abbreviations and Definitions**<br>**2. Purpose**<br>**3. Roles and Responsibilities**<br>**4. Procedure for reporting at Wits HREC (Medical) approved sites including timeline**<br>**5. Any Other Safety Reporting Requirements** |
| | **Signature of Chair / Co-Chair of Wits HREC (Medical)**<br>Paul Ruff<br>**Date:** 2025/01/13 |

### 1. ABBREVIATIONS AND DEFINITIONS

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| **HP** | **Health Product** | **A health product is any product used in the management of human illness/disease and includes medicines, medical devices and *in-vitro* devices (IVDs)** |
| **SAHPRA** | **South African Health Products Regulatory Authority** | **Statutory body regulating the use of all health products in South Africa, both registered and unregistered.** |
| **AE** | **Adverse Event** | **"Adverse event/experience (AE)"** is any untoward medical occurrence in clinical study participant that would not have occurred if the participant was not in a clinical study. An AE may be as a result of the administration of an IP but does not necessarily have a causal relationship with the IP.<br><br>An adverse event can be any unfavourable and unintended sign, symptom or event temporally associated with the use of an IP, any comparator or concomitant Health Product, whether considered related or not. |
| **ADR** | **Adverse Drug Reaction or Adverse Reaction** | **"Adverse drug reaction"** or **"adverse reaction"** means a **response** to a medicine/intervention/device in humans which is noxious and unintended, and which occurs at any dose and which can also result from overdose, misuse or abuse of a medicine.<br><br>An **adverse reaction** includes adverse clinical consequences associated with the use of a health product either within or outside the terms of the approved professional information (package insert), applicable product information or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).<br><br>An **adverse drug reaction**, contrary to an adverse event, is characterised by the occurrence of a **suspected causal relationship** between the medicine and the reaction, as determined by the reporter or a reviewing healthcare professional. The fact that the healthcare provider / professional is making a report to a holder of a certificate of registration, serves as an indication that the observed event may be caused by the medicine. All spontaneous reports are, therefore, suspected adverse drug reactions.<br><br>In the case of pre- and post-marketing studies, adverse "events" are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, it is better to treat the event as a reaction. For the purpose of post-marketing clinical trials, an adverse drug reaction includes any adverse event where the contribution of the study medication, concomitant medication or other medicinal intervention of the clinical trial, cannot be ruled out. |

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| | | **Note that all ADRs are AEs but not all AEs are ADRs.** |
| **SAE** | **Serious Adverse Event** | A serious adverse event is any untoward health-related occurrence that at any dose:<br>• results in death;<br>• is life-threatening;<br>• requires patient hospitalisation or prolongation of existing hospitalisation;<br>• results in a congenital anomaly/birth defect;<br>• results in persistent or significant disability/incapacity; or<br>• is a medically significant / important event or reaction. |
| | | The term **"life-threatening"** in the definition of **"serious"** refers to a reaction/event in which the patient was at risk of death at the time of the reaction/event. It does not refer to an event which, hypothetically, might have caused death if it were more severe.<br>Medical and scientific judgement should be exercised when deciding whether other situations are serious or not. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation, or development of drug dependency or drug abuse.<br>The term **"severe"** is often used to describe the intensity (severity) of a specific event. This is not the same as "serious', which is based on patient/event outcome or action criteria. |
| | **Unexpected Adverse Drug Reaction** | An **"unexpected"** adverse reaction is one in which the nature, specificity, severity and outcome is not consistent with the applicable product information (i.e. with the approved professional information or the investigator's brochure).<br>An unexpected reaction includes class-related reactions which are mentioned in the applicable medicine information but which are not specifically described as occurring with a medicine. When the outcome of the adverse reaction is not consistent with the applicable medicine information, the adverse reaction should be considered as unexpected.<br>An expected ADR with a fatal outcome should be considered unexpected unless the SAHPRA-approved labelling specifically states that the ADR might be associated with a fatal outcome. |
| **IP** | **Investigational Product** | **Investigational Product** is defined as any health product, used in a clinical study being standard of care, investigational, comparator or concomitant that is either registered or not registered in South |

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| | | Africa and/or has or has not been packaged and labelled for use in South Africa. |
| **Line Listing** | | A line listing provides key information but not necessarily all the details customarily collected on individual cases. Reactions are classified by body system for the most serious-presenting sign or symptom. The headings usually included are:<br>• country of occurrence (if relevant);<br>• source (e.g. spontaneous, clinical trial, literature, regulatory authority);<br>• age of participant;<br>• gender of participant;<br>• dose(s) of suspected medicine(s);<br>• dosage form and/or route of administration,<br>• batch number (when applicable);<br>• duration of treatment (prior to event) time to onset;<br>• description of reaction (as reported);<br>• patient outcome (e.g. fatal, resolved, ongoing etc.); and<br>• comment (if relevant) |

## 2. PURPOSE

This guideline is intended to assist Sponsors/Applicants in the reporting of AEs, ADRs and SAEs occurring during studies that may be related to the investigational product (IP), comparator or concomitant health products or the conduct of the study. It is also intended to provide guidance on the responsibilities of the Sponsors/Applicants and Investigator(s); and provides a framework for the minimum requirements for the information required.

The reporting of all AEs during a study will be in accordance with the specific study protocol evaluated by the Wits HREC (Medical) and SAHPRA.

The adverse event reporting commitment of a protocol need to be aligned with the minimum requirements set out below but certain studies may require special and exceptional adverse event monitoring and reporting that will be specified by the Wits HREC (Medical) on a protocol-specific basis.

This guideline also applies to the reporting of adverse drug reactions (ADRs) and Serious Adverse Events (SAEs) occurring during studies.

## 3. ROLES AND RESPONSIILITIES

### 3.1. Sponsor/Applicant

The Sponsor/ Applicant of a study is required to notify the Wits HREC (Medical) and SAHPRA and all participating investigators, of any adverse experience associated with the use of the IP that was

both serious and unexpected, and any finding from tests in laboratory animals that suggested a significant risk for human participants.

Sponsor/ Applicant should conduct ongoing safety evaluations including periodic review and analyses of their entire safety database, not only for safety reporting purposes, but also to update investigator brochures, protocols and consent forms with new safety information.

**3.2. Investigators**

Investigators should report serious adverse events to the Sponsor/Applicant within 24 hours of becoming aware of the event(s).

## 4. PROCEDURE FOR REPORTING AT WITS HREC (MEDICAL) APPROVED SITES

**Reporting Timeframes**

The sponsor/applicant is required to notify Wits HREC (Medical) as follows:

| Type of Report | Timeline for reporting (Initial) | Timeline for reporting (Follow up) | Format |
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| Preliminary reports:<br><br>Reports:<br>• Fatal or life-threatening related and unexpected | 7 calendar days * | Within 8 calendar days | CIOMS format/ SAHPRA SAE form |
| Foreign Reports:<br>• Fatal or life-threatening related and unexpected (of special concern) ** | 30 calendar days (should be earlier if results in premature study closure, i.e.. 7 days) | 6-monthly as part of progress report*<br>(should be earlier if results in premature study closure, i.e.. 8 days) | Line listing |
| Other serious adverse reaction (unexpected, not fatal or life threatening) | 15 calendar days | 6 monthly | 1. CIOMS format/ SAE form<br>2. Line Listing (follow up) |
| Line listing:<br>• All Serious (unexpected and expected) adverse events<br>• Any other issues of special concern outside South Africa** | 6-monthly as part of the progress report | | Line listing |
| New information impacting on risk-benefit profile of product or conduct of study | 3 calendar days | 6-monthly | Detailed report |

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| Other major safety concerns (changes in nature, severity or frequency of risk factors, etc.) | 15 calendar days | 6-monthly | Detailed report |

**Notes:**
*A preliminary report should be provided to Wits HREC (Medical) within 7 calendar days of first knowledge by the Sponsor/Applicant followed by a follow-up/expedited report within another 8 calendar days.

**Significant safety issue defined for each study that require urgent attention of the Wits HREC (Medical). Adverse Reactions of special concern from foreign jurisdiction should be based on appropriate Regulatory Authority's decision.

A safety issue leading to international regulatory action is considered to be significant at all times and hence reportable.

Wits HREC (Medical) reserves the right to impose additional reporting timelines on an individual protocol basis. Wits HREC (Medical) may require expedited reporting of AEs of special interest, whether serious or not.

## 5. ANY OTHER SAFETY REPORTING REQUIREMENTS

### 5.1. Development Safety Update Reports (DSURs)

The Sponsor/Applicant of a study in South Africa is responsible for the submission of an annual Development Safety Update Report [ICH E2F] that includes information gathered from all clinical experience with the IP, whether in SA or elsewhere. Development Safety Update Report (DSUR) should be submitted within one year from approval of the study and annually thereafter.

**Guidance for Industry E2F Development Safety Update Report E:Recipients of the DSUR (1.5)**
The DSUR is intended to serve as an annual report to regulatory authorities. Where national or regional laws or regulations require submission of an annual safety report on an investigational drug to ethics committees/institutional review boards, the DSUR Executive Summary might be appropriate, supplemented with line listings of serious adverse reactions (SARs) as warranted.

### 5.2. Reports Relating to Pregnancy and Breast-Feeding

The Sponsor/Applicant must report suspected adverse drug reactions related to pregnancy or breast-feeding as specified in section 4 above, regardless of whether the drug is contra-indicated in pregnancy and/or lactation. Reports on pregnancy should not be forwarded before the outcome is known, unless unintended pregnancy is suspected as an adverse drug reaction. Reports on pregnancy should not be submitted if there is no adverse effect to the foetus/infant.

### 5.3. Overdose

Reports of overdoses should be submitted whether or not the overdose was associated with a Serious Adverse Event according to section 4. Overdoses should be reported regardless of whether they were intentional or accidental, which must be specified. An overdose is considered to be any dose of >10% above the intended dose.