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| **TGHN-256x151px**  **Standard Operating Procedure** | | | **SOP No:**  **Version: 1**  **Effective Date:** | |
| **Title: Safety Assessment and Reporting** | | | | |
|  | NAME | **SIGNATURE** | | **DATE** |
| **PREPARED BY** |  |  | |  |
| **REVIEWED BY** |  |  | |  |
| **QA UNIT**  **AUTHORITY** |  |  | |  |
| **APPROVAL**  **AUTHORITY** |  |  | |  |

1. **Purpose/scope**

To describe the procedure for eliciting, recording, assessing, managing and reporting adverse events/adverse drug reactions in clinical trials conducted by the [institution/group]. NB All clinical research conducted at [institution/group] must comply with the Human Research Ethics Committee (HREC) SOPs regarding unanticipated problems involving risks to research participants and others, including adverse events.

1. **Templates/forms**

CL05.1 Serious adverse event (SAE) form

CL05.2 Safety assessment and reporting guideline

1. **Glossary/definitions**

See also: South African Good Clinical Practice (SAGCP) Guideline; ICH Guideline for Good Clinical Practice E6; ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A; the South African Medicines Control Council (MCC) Guidelines for Reporting AE/Drug Reactions.

**Adverse event (AE)**

Any untoward or unfavourable medical or psychological occurrence in a participant, including any abnormal laboratory finding, symptom or disease. An AE does not necessarily have a causal relationship with the research or any risk associated with the research.

**Adverse Drug Reaction (ADR)**

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

**Essential Documents**

Documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced (See South African Good Clinical Practice Guideline, Second Edition. 2006. Appendix C).

**Investigator’s Brochure**

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

**Investigator Site File (ISF)**

Files of Essential Documents held by the Investigator. NB on occasion the MCRG may also hold the Sponsor's Essential Documents in a Trial Master File, where the Principal Investigator (PI) assumes a Sponsor-investigator role.

**Serious Adverse Event (SAE) or Serious Adverse Drug Reaction**

Any untoward medical occurrence that at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

**Unanticipated problems (as per UCT HREC)**

An ‘unanticipated’ problem is any incident, experience or outcome that meets all the following three criteria:

* Unexpected in terms of its nature, severity or frequency, or the research population being studied; or if anticipated it is not fully addressed or specified in information provided to the HREC or to participants such as in initial protocol applications, any amendments, investigator brochures, scientific literature, product labelling, package inserts and HREC-approved informed consent documents or any existing documentation regarding the research conducted to date under the protocol;
* Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research);
* Suggests that the research places participants or others at a greater risk of physical, psychological, economic or social harm than was previously known or recognised.

In summary, an unanticipated problem is:

**Unexpected** – not in the consent form, investigator’s brochure, protocol package insert or label; or unexpected in its frequency, severity or specificity;

**Related** to the research – caused by, or probably caused by, or associated with a device;

**Harmful** – caused harm to participants or others, or placed them at increased risk of physical, psychological, economic or social harm.

Examples of unanticipated problems include:

* Loss of a laptop computer containing confidential information about participants or others.
* A spouse physically abused by his or her partner for taking part in the study.
* Publication in the literature or a Data and Safety Monitoring Report that indicates an unexpected change in the balance of risks and benefits in the study.
* Finding that laboratory reports on blood or other samples were in error.

**Unexpected Adverse Drug Reaction**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

1. **Responsibilities and procedure**
   1. Safety monitoring of participants in clinical research, including clinical trials, is an ethical requirement. This involves appropriate prevention, monitoring, prompt reporting and management of adverse events (AEs).
   2. The sponsor is responsible for the ongoing safety evaluation of an investigational medicinal product (IMP) and should promptly notify in writing all relevant investigators, the MCC and HREC of any findings that could affect adversely the safety of participants, the trial conduct, or alter an approval/favourable opinion to continue the trial. Participants should also be informed. Accountability for any specific function involved may, however, be delegated in writing to the Principal Investigator (PI).
   3. Depending on the level of risk, the sponsor may appoint a medical monitor, trial safety group or independent data safety monitoring committee to periodically assess safety data and advise on whether a trial should be amended, suspended or terminated.
   4. The PI takes responsibility for safety assessments and reporting at the site but may delegate aspects of the role to suitably qualified and experienced members of his/her team. Such delegation should be documented in a staff delegation and signature sheet (see SOP AD04).
   5. By the time of trial start all staff that may play a part in the process of assessing and/or reporting harms data should receive adequate training according to their role. This may include administrative staff who could be contacted by trial participants in the first instance, through to clinical personnel undertaking protocol-related assessments.
   6. Safety assessments and reporting will be performed according to the approved protocol and current regulatory requirements. If necessary, guidelines documenting trial-specific processes and roles should be developed to clarify issues including:
      * Which staff elicit AEs and how, how AEs are graded and assessed in terms of relationship with the investigational product and their severity, and how AEs should be followed up. In the absence of protocol- or sponsor-specific criteria, assessment of intensity will be:

* Mild: The AE is transient, easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
* Moderate: The AE is sufficiently discomforting to interfere with normal everyday activities.
* Severe: The AE prevents normal everyday activities; the participant may experience intolerable discomfort or pain.
  + - How staff responds to AE reports in terms of the medical care of participants and reporting to the next tier within the site team and/or with the Sponsor.
    - Who takes responsibility for, and the process of, reporting to the regulatory authority/ies, HREC and (if relevant) a data safety monitoring committee.
    - Contact details (phone/fax/email etc.) of all involved.
    - Reference to medical evacuation procedures.
  1. Appropriate template documentation is developed that complies with regulatory and Sponsor requirements. In the absence of these, serious adverse event (SAE) form CL05.1 and guideline CL05.2 may be used or adapted. [Institution/group] HREC’s own reporting form for unanticipated problems (including AEs) must also be used, where relevant [add link if appropriate].
  2. Should the investigator decide that there are safety concerns that require an immediate amendment to the protocol or conduct of the research he/she should communicate this to site(s) staff without delay. Then, as soon as possible, he/she will inform the sponsor, MCC, HREC(s) and any other relevant parties as to what the safety concern was, what measures were taken and what the next steps will be (e.g. to submit a protocol amendment or notice of trial suspension, termination).
  3. Essential Documents relating to safety assessment and reporting should be maintained in the Investigator Site File.

1. **Document history:**

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| **Version No.** | **Date** | **Reviewer** | **Details of changes** |
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