



Standard Operating Procedures
Research Ethics Committee (Human) (REC-H)

- **Unanticipated problems reporting**

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1 UNANTICIPATED PROBLEMS REPORTING

Nelson Mandela University researchers (staff and/or students) of currently active studies making use of human participants who experience an unanticipated or adverse event during the data collection activity are required to immediately suspend data collection activities and to please alert Imtiaz.Khan@mandela.ac.za for advice on the required procedure to follow.

1.1 POLICY

1. In line with local and international ethical and regulatory requirements, the RECH must have written procedures to ensure timely reporting to the committee, sponsors and appropriate regulatory agencies unanticipated problems, including serious adverse events, which might place human research participants at a greater risk of physical, psychological, economic or social harm.

1.2 PURPOSE

2. The purpose of this policy is to outline requirements and timelines for reporting and reacting to internal and external reports of unanticipated problems, including adverse events in research with human participants.

1.3 DEFINITIONS

1. Unanticipated problems
 - a. An 'unanticipated' problem is any **internal** incident, experience or outcome that meets all the following three criteria:
 - i. 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 Human Research Ethics Committee or to participants such as in initial protocol applications, any amendments, investigator brochures, scientific literature, product labelling, package inserts and Human Research Ethics Committee-approved informed consent documents or any existing documentation regarding the research conducted to date under the protocol;
 - ii. 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);
 - iii. 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.
 - b. In summary, an unanticipated problem is:
 - i. **Unexpected** – not in the consent form, investigator's brochure, protocol package insert or label; or unexpected in its frequency, severity or specificity;
 - ii. **Related to the research** – caused by, or probably caused by, or associated with a device;
 - iii. **Harmful** – caused harm to participants or others, or placed them at increased risk of physical, psychological, economic or social harm.
 - c. Examples of unanticipated problems include:
 - i. Loss of a laptop computer containing confidential information about participants or others.
 - ii. A spouse physically abused by his or her partner for taking part in the study.
 - iii. 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.
 - iv. Finding that laboratory reports on blood or other samples were in error.
2. Adverse Events

- a. An adverse event is defined as any untoward or unfavourable medical or psychological occurrence in a participant, including any abnormal laboratory finding, symptom or disease. An adverse event does not necessarily have a causal relationship with the research, or any risk associated with the research.
- b. **Unexpected adverse events.** Unexpected adverse events are those in which any of the following applies:
 - i. The specificity or severity is not consistent with the current Investigator's Brochure.
 - ii. The event is inconsistent with the risk information in the current protocol application.
 - iii. The event is occurring more frequently than anticipated.
 - iv. For example, liver failure due to diffuse hepatic necrosis in a participant without any underlying liver disease if the protocol did not identify liver disease as a potential adverse event. In contrast, prolonged neutropenia and opportunistic infections in participants given an experimental chemotherapy regimen as part of an oncology trial would be examples of expected adverse events if the protocol described prolonged severe neutropenia and opportunistic infections as common risks for all participants.
- c. **Internal Adverse Event**
 - i. Internal adverse events are those experienced by participants enrolled at a site under the jurisdiction of the Nelson Mandela University.
- d. **External Adverse Event**
 - i. External adverse events are those experienced by participants enrolled at other institutions or in a study for which Mandela University is not the coordinating centre.
- e. **Serious Adverse Event (SAE)**
 - i. A serious adverse event is any adverse event in research that results in any of the following:
 - a. Death.
 - b. A life-threatening incident (places the participant at immediate risk of death from the event as it occurred).
 - c. Hospitalisation (initial or prolonged).
 - d. Disability.
 - e. Congenital abnormality.
 - f. Requires medical or surgical intervention to prevent permanent impairment or damage (e.g., allergic bronchospasm requiring intensive treatment in the emergency room or at home).
 - g. Inadvertent disclosure of confidential information if this presents an immediate risk to a participant such as from spousal or child abuse.

1.4 TIMELINES FOR REPORTING

1. Reporting Unanticipated Internal Problems or Adverse Events
2. Unanticipated Problems
 - a. Principal investigators must report to the Human Research Ethics Committee within seven calendar days after the investigator first learns of their occurrence all unanticipated problems that increase the risk of harm to participants or others.
3. Fatal and Life-threatening, Unexpected Adverse Drug Reactions
 - a. Principal investigators must report to the Human Research Ethics Committee as soon as possible but not later than seven calendar days after the investigator first learns of their occurrence all fatal and life-threatening adverse drug reactions in clinical trials.
4. Serious and Unexpected Non-fatal Adverse Drug Reactions

- a. Principal investigators must report to the Human Research Ethics Committee as soon as possible but not later than fifteen calendar days after first learning of their occurrence all serious unexpected drug reactions that are not fatal or life-threatening.
5. Expected Adverse Drug Reactions
 - a. Principal investigators must notify the Human Research Ethics Committee within fifteen calendar days after the investigator first learns of their occurrence all adverse drug reactions that are expected but are judged to be occurring at a significantly higher frequency or severity than expected. The basis for these assessments must be included in the investigator's report.
6. Serious and Unanticipated Adverse Device Effects
 - a. Principal investigators must **report** to the Human Research Ethics Committee and to the sponsor (if applicable) as soon as possible but not later than seven calendar days after first learning about their occurrence all unanticipated adverse device effects. The sponsor shall immediately conduct an evaluation of the unanticipated adverse device effect.
7. New Information that might Impact the Conduct of a Clinical Trial
 - a. Principal investigators must report to the Human Research Ethics Committee within three calendar days of first learning about their occurrence other unexpected adverse events, regardless of severity, that may alter the balance of risks and benefits in a study and as a result warrant consideration of substantive changes in the overall conduct of a clinical trial. The report could include individual case reports or a major safety finding from other sources.
8. Reporting External Serious Unexpected Adverse Drug Reactions
 - a. Principal investigators must report to the Human Research Ethics Committee as part of the six-monthly progress report in a line listing format all serious unexpected adverse drug reactions originating from other South African or international sites.

1.5 HOW ARE INTERNAL REPORTS SUBMITTED?

1. Investigators typically learn about internal adverse events from participants, another collaborating investigator or the participant's health care provider. If the investigator judges that the event represents an unanticipated problem or adverse event that requires timely reporting as described above, the principal investigator shall use the standard SAE reporting form to notify the Human Research Ethics Committee and the sponsor as required under a monitoring plan described in the Committee-approved protocol. The standard internal reporting form must be completed regardless of whether other forms (e.g., sponsor, CIOMS, Medwatch) have already been completed. Information such as a summary of the event, or drug company reports may be attached and submitted with the form.
2. Reports of unanticipated problems, including serious adverse events, submitted to the Human Research Ethics Committee must include the following:
 - a. Appropriate identifying information for the research protocol, such as title, investigator's name, and Human Research Ethics Committee reference number.
 - b. A detailed description of the adverse event, incident, experience or outcome.
 - c. An explanation of the basis for determining that the adverse event, incident, experience or outcome represents an unanticipated problem.
 - d. A description of any changes to the protocol or other corrective actions taken or proposed in response to the unanticipated problem.
3. The investigator must independently determine and comment on whether the event was thought to be related, possibly related, unrelated or the relationship is unknown. The Human Research Ethics Committee therefore relies on the principal investigator's expertise to assess the causality of the problem or event, its seriousness and whether it was expected. Investigators must also recommend whether a change in the protocol is needed to minimise risks to participants, whether the consent form should be revised to reflect this risk and whether participants in the study should be re-consented in light of this risk.

4. All adverse event reports are acknowledged with an official Human Research Ethics Committee stamp and returned to the principal investigator. A copy of the stamped original is placed in the protocol file.

1.6 INVESTIGATION AND EVALUATION OF THE REPORTS

1. The Human Research Ethics Committee Chair or a designee is responsible for reviewing adverse events.
2. If there are immediate risks to participants, the Chair or designee may take one or more of the following actions:
 - a. Suspend Human Research Ethics Committee approval to ensure the ongoing safety of participants.
 - b. Call an emergency Human Research Ethics Committee meeting to act on the report.
 - c. Request additional information from the principal investigator or others.
3. If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring body subsequently determines that the event does represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring body should report this finding to the investigator and such reports must be promptly submitted to the Committee.
4. Reportable events that are not serious and do not require immediate action are reviewed by the Human Research Ethics Committee Chair or designee using an expedited procedure. At the Chair's discretion, reports will be reviewed at convened Human Research Ethics Committee meetings. The Chair or full committee may request further information or require the following remedial actions:
 - a. Revise the protocol.
 - b. Modify inclusion or exclusion criteria to mitigate the newly identified risks.
 - c. Suspend enrolment of new participants.
 - d. Suspend procedures in currently enrolled participants.
 - e. Modify informed consent documents to include a description of newly identified risks.
 - f. Provide additional information about newly recognised risks to previously enrolled participants.
 - g. Suspend approval.
 - h. Terminate approval.
5. Any proposed changes to a research study in response to an unanticipated problem, including serious adverse events, must be submitted as amendments, and approved by the Human Research Ethics Committee before being implemented, except when necessary to eliminate apparent immediate hazards to participants.
6. At the time of continuing review, principal investigators must submit a summary of serious problems and serious adverse events that occurred at the investigator's site (i.e. internal), are study-related and that have occurred since the last continuing (or initial) review of the study.
7. In most cases, an appropriate summary would be a statement that there have been no unanticipated problems and that serious adverse events have occurred at the expected frequency and level of severity as documented in the protocol, the informed consent form and the investigator's brochure, where applicable. The principal investigator must also summarise in the continuing review report all internal non-serious adverse events that have occurred since the last continuing (or initial) review of the study. For multi-centre studies, the principal investigator shall include the following documents with the continuing report:
 - a. Most recent copy of the sponsor's analysis of adverse event reports, if applicable.
 - b. Most recent copy of the DSMB report, if applicable.
 - c. Summary of all external serious adverse events presented in the context of the entire multi-centre study, if possible.