CHAPTER 6

REVIEW OF SERIOUS ADVERSE EVENT REPORTS

SOP NUMBER: SOP/020/01

INSTITUTIONAL REVIEW BOARD
(IRB)

Khesar Gyalpo University of Medical Sciences of Bhutan

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1. PURPOSE

The purpose of this SOP shall be to provide instructions on the review and follow-up reports of serious adverse experience and unexpected events for any active study approved by the IRB. The SAE shall be reported by the investigators or sponsors within 10 working days after the incident occurred and in the event of deaths it should be reported within 24 hours and unexpected events shall be included in the continuing review report submitted to IRB.

Unanticipated risks are sometimes discovered during the course of studies. Information that may impact on the risk/benefit ratio shall be promptly reported to and reviewed by the IRB to ensure adequate protection of the welfare of the study participants.

The unanticipated risks may as well include any event that in the investigator's opinion, may adversely affect the rights, welfare or safety of subjects in the study.

2. SCOPE

This SOP shall apply to the review of SAE and unexpected events reports submitted by investigators, Data Safety Monitoring Board (DSMB), sponsor, local safety monitor, IRB members or other concerned parties.

3. RESPONSIBILITY

The IRB shall be responsible to review and address SAE and unexpected events involving risks to subjects or others as well as ethics complaints. In addition, the Committee is authorized to offer mediation under appropriate circumstances.

IRB shall also make sure that researchers are made aware of the policies and procedures concerning reporting and continuing review requirements.

The IRB Member Secretary in consultation with the Chairperson shall be responsible for first screening the assessment of the reports and seeing whether they need a review by the Chairperson, other qualified IRB members or full IRB meeting, or external consultants/experts or by the National Health Research Board (NHRB).

4. FLOW CHART

No.	Activity	Responsibility
1	Review and determine the review channel ↓	IRB Member Secretary, Chairperson, members
2	Safety Report Review Process ↓	IRB members and Chairperson
3	Communicate the decision to investigator or clinical trial office. ↓	IRB Secretariat and Chairperson
4.	Storage of the documents	IRB Secretariat and Chairperson

5. DETAILED INSTRUCTIONS

5.1. Review and determine the review channel

5.1.1. IRB Member Secretary or members shall review the safety report and determine whether the report requires review by full Board of IRB or by the Chairperson or other qualified/relevant IRB member(s).

5.1.2. Criteria for the review. The **review criteria** are as follows:

5.1.2.1. Assessment of adverse experience is unknown or unlikely

5.1.2.1.1. Report is forwarded to the Chairperson for review and determination if report shall be reviewed at the convened meeting by full Board of IRB.

5.1.2.2. Assessment of adverse experience is possibly caused by, or probably caused by the investigational product.

5.1.2.2.1. The report is added to the agenda for review at a convened meeting by full Board of IRB.

5.1.2.3. An adverse experience/IND Safety Report has been previously seen by full Board but being resubmitted by another investigator participating in the multi-study site (as part of a multi-centre /site study).

5.1.2.3.1. This notification does not require full Board review.

5.1.2.3.2. To be reviewed by the Chairperson or other qualified IRB members and secretariat

5.1.3. Complete the general information on the Safety Report Review Form

5.2. Safety report review process

5.2.1. Expedited Review process

5.2.1.1. Distribute the review package to the expedited reviewer. The package includes:

5.2.1.1.1. Safety Report

5.2.1.1.2. Safety Report Review Form (AF/03-019/01)

5.2.1.1.3. Protocol, ICF, and related documents

5.2.1.2. The reviewer records the review decision and recommendations on the Safety Report Review From

5.2.1.3. Refer to SOP 008 – Expedited Review

5.2.2. Full Board Review Process

5.2.2.1. After reading and reviewing the report, the Chairperson or designee entertains discussion on the study and similar adverse experiences or advisories.

5.2.2.2. If appropriate to the discussions, the Chairperson or another IRB member may call for a consensus on whether to:

5.2.2.2.1. Request an amendment of the protocol

5.2.2.2.2. Request an amendment of the consent form.

5.2.2.2.3. Request further information.

5.2.2.2.4. Suspend the enrolment

5.2.2.2.5. Terminate the study.

5.2.2.2.6. No action

5.2.2.3. The IRB Secretariat records the decision and recommendations on the Safety Report Review Form.

5.3. Communicate the decision to the investigator and the clinical trial officer

5.3.1. The IRB secretariat drafts a formal letter to the investigators or the clinical trial office to notify them of the IRB decision and recommendations and if any action they shall take accordingly.

5.3.2. Get the Chairperson to approve, sign and date the letter.

5.3.3. Send the letter to the investigator or the clinical trial office within 5 working days.

5.4. Store the document

5.4.1. Keep the letter in the “Correspondence File”

5.4.2. Keep the SAE reports, review forms along with the related review minutes in the protocol file.

6. GLOSSARY

Adverse Event	Any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. The adverse event can therefore be any unfavourable or unintended sign or experience associated with the use of the investigational product, whether or not related to the product.
Adverse Drug Reaction	In the pre-clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established all noxious or unintended responses to the product related to any dose shall be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between the product and the adverse event is at least a reasonable possibility, i.e., the relationship can not be ruled out. Regarding marketed products, a response to a product 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.
IND	Investigational New Drugs means substances with potential therapeutic actions during the process of scientific studies in human in order to verify their potential effects and safety for human use and to get approval for marketing.
SAE	The adverse event is SERIOUS and shall be reported when the patient outcome is: **Death** - Report if the patient's death is suspected as being a direct outcome of the adverse event. **Life-Threatening** - Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. *Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive drug dosing.* **Hospitalization** (initial or prolonged) - Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event. *Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalization.* **Disability** - Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life. *Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy.* **Congenital Anomaly** - Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child. *Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.* **Requires Intervention to Prevent Permanent Impairment or Damage** – Report if suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent

	impairment or damage to a patient. *Examples: Acetaminophen(paracetamol) overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent mal-union of a fractured long bone.*
Unexpected ADR	Unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the informed consent / information sheets or the applicable product information (e.g., investigator's brochure for the unapproved investigational product or package insert / summary of product characteristics for an approved product.
NHRB DSMB	Highest decision making body in Bhutan in terms of health research.

7. REFERENCES

7.1. World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000.

7.2. International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 2016.

8. ANNEX

ANNEX 1	AF/01-020/01	Serious Adverse Event Report
ANNEX 2	AF/02-020/01	Unexpected Adverse Drug Reaction Report
ANNEX 3	AF/03-020/01	Safety Report Review Form

ANNEX 1
AF/01-020/01

Serious Adverse Event Report

Principal Investigator: …….. Study Site:

Protocol Title: …… Protocol No.:

Sponsor (if applicable)……

Name of the study drug / medical device:

Report Type
☐ Initial ☐ follow-up
☐ Final

Report Source:
☐ Investigator ☐ Sponsor
☐ DSMB ☐ IRB member
☐ Others, specify:

Subject's initial/number:	Age:	☐ Male ☐ Female

Describe Reactions (onset date, signs, symptoms, including relevant tests/ lab data)
Medical treatment
Progression of the SAE

Seriousness:	Relation to ○ Drug ○ Device ○ study
☐ Death	☐ Not related
☐ Life Threatening	☐ Possibly
☐ Hospitalization –○ initial ○ prolong	☐ Probably
☐ Disability / Incapacity	☐ Definitely related
☐ Congenital Anomaly	☐ Unknown
☐ Other……	

Changes to the protocol recommended?	☐ No ☐ Yes , attach proposal
Changes to the informed consent form recommended?	☐ No ☐ Yes , attach proposal

Reported by: ……

Report Date:

ANNEX 2
AF/02-020/01

Unexpected Adverse Event Summary Report

Principal Investigator: ……

Study Title: ……... **Protocol No.:**

Name of the studied medicine/device……..…….. **This report covers the period :**

Sponsor: ……... **From……To…….**

#	Description of Unexpected Adverse Events	Date of Event (D/M/Y)	Date start and end of Tx (D/M/Y)	F or M	Age (Y)	SERIOUS Yes No	RELATED TO STUDY Yes No	Concomitant medication	Intervention
						☐ ☐	☐ ☐		
						☐ ☐	☐ ☐		
						☐ ☐	☐ ☐		
						☐ ☐	☐ ☐		

Comment:

Reviewed by: …… **Date** (D/M/Y): ……

ANNEX 3
AF/03-020/01

Safety Report Review Form

General Information	
Protocol Title:	
Protocol No.:	**Report received date:**
Review Channel:	
☐ Full Board Review Review Date:	☐ Expedited Review Reviewer Name:
Completed by: (Signature) Date:	
Review Decision:	
☐ Terminate the study	☐ Suspend the enrolment
☐ Request protocol amendment	☐ Request ICF amendment
☐ Request further information	☐ No Action
Recommendation:	
Reviewer Signature: (For Expedited Review) Date:	IRB Secretariat Signature: (For Full Board Review) Date:
IRB Chairperson Sign: Date:	