Quality Medicines for Malawi

PHARMACY AND MEDICINES REGULATORY AUTHORITY

Confidential [PMRA ACT [CHAPTER 35:01]

SERIOUS ADVERSE EVENTS (SAEs) REPORTING MANUAL FOR CLINICAL TRIALS IN MALAWI

1. Responsibilities of sponsors, investigators, & clinical sites

The sponsor of a clinical trial and investigators participating in a clinical trial are responsible for proper reporting of Serious Adverse Events (SAEs). The purpose of reporting SAEs is to better understand the toxicity and safety of investigational products. Reporting and monitoring of SAEs is required to alert the PMRA, sponsor and clinical investigators of real and potential volunteer safety issues. The PMRA will carefully review the SAE Report and use this information to monitor the investigational product's toxicity profile and volunteer safety.

Serious adverse events data provide the PMRA and investigators with an early toxicity profile of an investigational product. The toxicity profile is an early warning system of potentially serious events that may occur with the use of an investigational product. This information might also be used during the application for registration of a new medicine review to determine if a product is safe for marketing. If a product is approved, the safety information reported by the clinical sites during the clinical trial phase of product development will have contributed to the "Adverse Reaction" section of the Product Package Insert.

The Serious Adverse Events (SAE) Form must be completed and submitted to PMRA as soon as possible **(within 24-72 hours)** after the site becomes aware of an event. PMRA may need to contact the clinical site for additional information regarding the SAE. PMRA will maintain all SAE reports confidential on file and in a regulatory database.

2. General Information

2.1 Definitions

2.1.1 Adverse Event (AE):

Any adverse event associated with the use of a medicine in humans, whether or not considered medicine related including the following: An adverse event occurring in the course of the use of a medicine product in professional practice; an adverse event occurring from medicine overdose whether accidental or intentional; an adverse event occurring form medicine abuse; an adverse event occurring from medicine withdrawal; and any failure of expected pharmacological action.

2.1.2 Serious Adverse Event (SAE):

A serious adverse event is an adverse experience occurring at any dose that results in the any of the following outcomes: death, a life-threatening adverse medicine

experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or an important medical event that, based upon appropriate medical judgement, may jeopardize the patient or subject and may require intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization.

2.1.3 **Investigational Product**:

All products (medicines, biologics, or other combinations) listed in the clinical trial protocol document.

2.2 Adverse Event grading

The toxicity grades were adopted from the USA Division of Aids (DAIDS) "Table for Grading Severity of adverse events." The Toxicity Table should be used by site clinicians to assign toxicity grades to all Adverse Events. For clinical events or laboratory abnormalities NOT identified in the Toxicity Table, refer to the specific "Guide for Estimating Severity Grade" within the Toxicity Table. There are five toxicity grades that can be assigned to an SAE, which are defined as follows:

1 = Mild
2 = Moderate
3 = Severe
4 = Life - threatening
5 = Death

2.3 Relationship Assessment

Relationship between a Serious Adverse Events and an Investigational Product is determined by the site investigator or sub-investigator physician listed on the clinical trial protocol. In general, relationship is one of the main criteria used to determine the reportability of a Serious Adverse Event to the PMRA. There are four relationship assessment categories:

- Definitely related
- Probably related
- Possibly related
- Not related

In some cases, events assessed by the site investigator as ***Not related*** to the Investigational Product or Study Vaccine are not reported on an SAE Form. However, such events must have an alternative, definitive etiology documented in the volunteer's medical record.

2.4 Follow-up Information

For the circumstances listed below, or as requested by PMPB, clinical sites are required to submit follow-up information as soon as it becomes available. Additional information may include copies of diagnostic test results, laboratory reports, or medical record progress notes. All additional information should be clearly marked as update information and should include the Protocol Number and Volunteer ID Number.

2.4.1 Changes to Relationship Assessment

The clinical site obtains new information which changes the site investigator's assessment of the relationship between the event an Investigational Product

2.4.2 Updated Death Information

The clinical site obtains new information from the Death Certificate or autopsy results after an SAE Form is submitted. This pertains to deaths initially reported with limited or preliminary information.

2.4.3 **HIV Disease Progression**

The clinical site should only submit an Update SAE Form for HIV disease progression as follow-up to a previously reported HIV infection. This would include changes in immunologic status, new onset of opportunistic infection (OI) or progression of HIV infection to a severe or life-threatening status.

2.5 Recurrent Events

Serious Adverse Event (SAEs) recurring in the same volunteer on a particular protocol are only reportable to PMRA under the following circumstances:

2.5.1 Recurrent episode is attributed to a NEW ETIOLOGY, or

2.5.2 Recurrent episode has progressed to a higher reportable toxicity grade level.

2.6 Means of Reporting Serious Adverse Event (SAEs)

Serious Adverse Events (SAEs) that meet reporting requirements must be reported on the completed SAE forms and submitted to the PMRA by:

PMRA office email or hand delivered to the offices on the following address:

The Director General,
Pharmacy and Medicines Regulatory Authority,
P.O. Box 30241,
Lilongwe 3,
Malawi
Tel: 265-1755166/165 Email: info@pmra.mw, registration@pmra.mw

REPORTABLE SERIOUS ADVERSE EXPERIENCES

A. OCCURRING DURING INVESTIGATIONAL PRODUCT ADMINISTRATION OR UP THROUGH 12 WEEKS AFTER THE LAST DOSE OF INVESTIGATIONAL PRODUCT

A-1. Reportable regardless of Relationship to Investigational Product

Death

Includes neonatal deaths, regardless of whether the neonate was being followed as part of the protocol.

Cancer

Includes new onset and recurrent malignancies.

Congenital Anomaly/Birth Defect or Spontaneous Abortion

Includes Congenital anomaly/birth defect occurring in a neonate/infant born to a mother who has received

Investigational Product or Spontaneous abortion occurring in a mother who has received Investigational Product

Permanent Disability/Incapacity

A permanent disability/incapacity is defined as a substantial disruption of a person's ability to conduct normal life functions.

Immune Dysfunction

Includes autoimmune and immune deficiency diseases.

Reporting timeframe

Submit SAE Form to PMRA within 3 working days of site awareness.

DEATHS assessed as definitely, probably, or possibly related: Notify PMRA within 24 hours of site awareness and SAE Form within 3 working days of site awareness.

A-2. Reportable if relationship to Investigational Product is assessed as definitely, probably or possibly related:

Grade 3 or 4 event

Not previously reported for this volunteer on this protocol

Grade 1 or 2 event considered unusual by the site investigator

Not previously reported for this volunteer on this protocol AND considered unusual by the site Investigator.

Reporting Timeframe

Submit SAE Form to PMRA within 3 working days of site awareness.

B. OCCURRING AFTER 12 WEEKS OF INVESTIGATIONAL PRODUCT

B-1: Reportable regardless of relationship to Investigational Product

Immune Dysfunction

Includes autoimmune and immune deficiency diseases

Reporting Timeframe

Submit SAE Form to PMRA within 3 working days of site awareness

B-2: Reportable if relationship to Investigational Product is assessed as definitely, probably, or possibly related:

Death
Includes neonatal deaths, regardless of whether the neonate was being followed as part of the Protocol.

Cancer

Includes new onset and recurrent malignancies.

Congenital Anomaly/Birth Defect or Spontaneous Abortion

Includes Congenital anomaly/birth defect occurring in a neonate/infant born to a mother who has received Investigational Product or Spontaneous abortion occurring in a mother who has received Investigational Product.

Permanent Disability/Incapacity

A permanent disability/incapacity is defined as a substantial disruption of a person's ability to conduct normal life functions.

Reporting Timeframe

Submit SAE Form to PMRA within 3 working days of site awareness