SAFETY REPORTING DURING CLINICAL TRIALS IN SOUTH AFRICA

This document has been prepared to serve as a guideline to those reporting adverse events occurring during the use of registered or unregistered medicines in approved clinical trials. It represents the South African Health Products Regulatory Authority's current thinking on the measures to ensure safety, quality and efficacy of medicines. It is not intended as an exclusive approach. The Authority reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of safety data.

Guidelines and application forms are available from the Office of the Chief Executive Officer and the website

First publication released for implementation and comment - Title "Reporting Adverse Drug Reactions in South Africa"	May 2003
Version 2: Fully revised, publication under new title for comment	August 2016
Version 2: Published for implementation	August 2019
Version 3: Change in section 6.1, 6.2, 7.5, 7.6 and administrative changes	November 2019

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1 PREAMBLE

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

2 INTRODUCTION

This guideline is intended to assist applicants/sponsors in the reporting of ADRs and SAEs occurring during clinical trials that may be related to the investigational product (IP) or the conduct of the trial. It is also intended to provide guidance on the responsibilities of the applicant/sponsor and investigator; and provides a framework for the minimum requirements for the information required. The South African Health Products Regulatory Authority (SAHPRA) guideline for reporting adverse reactions for registered medicines (Post Marketing Reporting of Adverse Drug Reaction to Human Medicines in South Africa, 2017) is used for reporting ADRs occurring during use of registered medicines. Both pre and post-marketing guidelines should be followed for reactions or events reported during use of registered medicines in clinical trials.

The reporting of all Adverse Events (AEs) during a clinical trial will be in accordance with the specific trial protocol evaluated by SAHPRA.

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

Where the nature of the Investigational Product (IP) or medical condition requires a deviation from this guideline, the applicant/sponsor should provide clear arguments justifying the request for a waiver.

This guideline has been aligned with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Integrated Addendum to ICH E6(R1): Good Clinical Practice E6(R2) (2016) and the latest South African Good Clinical Practice (SAGCP) Guidelines and taking the circumstances of clinical trials in South Africa into account.

3 LEGAL BASIS

The guideline pertains to Section 21 of the Medicines and Related Substances Act (MRSA) 101 of 1965 (as amended), Section 30 and 40 of the accompanying general regulations of the MRSA, as well as the Section 71 of the National Health Act 61 of 2003.

4 DEFINITIONS

These terms may have other meaning under different context but the meaning that will be used in this guideline will be as defined in this document.

4.1 Adverse Event

"Adverse event/experience" is any untoward medical occurrence in a patient or clinical trial participant administered an IP that may present during treatment with that IP but which does not necessarily have a causal relationship with this treatment.

An adverse event can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicine, whether considered related or not.

4.2 Adverse Drug Reaction (ADR) or Adverse Reaction

"Adverse drug reaction" or "adverse reaction" means a response to a medicine 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.

Response in this context means that a causal relationship between a medicine and an adverse event is at least a reasonable possibility.

An adverse reaction includes adverse clinical consequences associated with the use of a medicine 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).

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.

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.

4.3 Investigational Product (IP)

"Investigational Product (IP)" is defined as any product, used in a clinical trial being standard of care, investigational or concomitant that is not registered in South Africa and/or has not been packaged and labelled for use in South Africa.

4.4 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:

- country of occurrence (if relevant);
- source (e.g. spontaneous, clinical trial, literature, regulatory authority);
- age of participant;
- gender of participant;

- dose(s) of suspected medicine(s);
- dosage form and/or route of administration, batch number when applicable;
- duration of treatment (prior to event) time to onset;
- description of reaction (as reported);
- patient outcome (e.g. fatal, resolved, ongoing etc.); and
- comment (if relevant)

4.5 Participating Investigator(s)

"Participating Investigator(s)" is/are defined as inclusion of all investigators whom the sponsor/applicant is providing IP under any of its clinical trials. This includes, for example, all investigators participating in clinical trials at South African and non-South African sites.

4.6 Serious Adverse Event (SAE)

A serious adverse event is any untoward occurrence that at any dose:

- results in death;
- is life-threatening;
- requires patient hospitalisation or prolongation of existing hospitalisation;
- results in a congenital anomaly/birth defect;
- results in persistent or significant disability/incapacity; or
- 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.

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.

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.

4.7 Unexpected (unlisted) Adverse Drug Reaction

For the purposes of this guideline, 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).

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.

An expected ADR with a fatal outcome should be considered unexpected unless the South African labelling specifically states that the ADR might be associated with a fatal outcome.

5 ROLES AND RESPONSIBILITIES

5.1 Sponsor/Applicant

The sponsor/applicant of a clinical trial is required to notify 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.

Sponsors/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.

The entity responsible for reporting SAEs should be specified in the clinical trial application form.

5.2 Investigators

Investigators should report adverse events to the sponsor/applicant in a manner defined in the protocol.

6 SUBMITTING SAFETY REPORTS

6.1 The sponsor/applicant is required to provide SAHPRA with the following safety reports:

6.1.1 Reports of Serious Suspected Unexpected Adverse Reaction (SUSAR) occurring in the clinical trial (CIOMS format /Annexure B)

6.1.2 Reports of all SUSAR and trends occurring with the IP in South Africa

6.1.3 Six-monthly Progress Report

6.1.4 Annual Development Safety Update Reports (DSUR)

6.1.5 Final Progress Report

6.1.6 Final Study Report

6.2 Reporting Timeframes

The sponsor/applicant is required to notify SAHPRA as follows:

Table:1

Type of Report	**Timeline for reporting (Initial)**	**Timeline for reporting (Follow up)**	**Format**
Preliminary reports: Local Reports: • Fatal or life-threatening related and unexpected	7 calendar days*	Within 8 calendar days	CIOMS format/ SAHPRA SAE form
Foreign Reports: • Fatal or life-threatening related and unexpected (of special concern)	30 calendar days (should be earlier if results in premature study closure, ie. 7 days)	6-monthly as part of progress report* (should be earlier if results in premature study closure, ie. 8 days)	Line listing
Local Reports : Other serious (unexpected, not fatal or life threatening)	15 calendar days	6 monthly	CIOMS format/ SAE form
Line listing of all Local reports: •Serious (unexpected and expected) adverse events And 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 trial	3 calendar days	6-monthly	Detailed report
Other major safety concerns (changes in nature, severity or frequency of risk factors, etc.)	15 calendar days	6-monthly	Detailed report
Progress reports	6-monthly after the initial approval of the clinical trial	30 days of the completion or termination of the clinical trial	Six-Monthly progress report form
Final progress report	30 days of the completion or termination of the clinical trial		Progress report form
Final Study Report	180 days of the completion or termination of the clinical trial.		
Annual Development Safety Update Reports (DSUR)	Annually		

Notes:

*A preliminary report should be provided to SAHPRA within 7 calendar days of first knowledge by the Applicant/Sponsor followed by a follow-up/expedited report within another 8 calendar days.

SAHPRA reserves the right to impose additional reporting timelines on an individual protocol basis. SAHPRA/CTC may require expedited reporting of AEs of special interest, whether serious or not.

Six-Monthly Progress Reports must be submitted to SAHPRA during the entire duration of the clinical trial.

Clinical trial closure occurs when no further data is being collected and not on termination of recruitment.

6.3 Content of 6 Monthly Progress Report

The sponsor/applicant must identify in each progress report all safety reports previously submitted to SAHPRA concerning a similar suspected adverse reaction and must analyse the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The analysis must include similar reports from all reports held by the sponsor and any other relevant information known to the sponsor. Sponsors should evaluate a suspected adverse reaction in the context of other related reports or adverse events, including those that occurred in the placebo or active comparator group.

The analysis should include consideration of data from reports in the scientific literature and reports from foreign commercial marketing experience.

SAHPRA recognises that in investigator-initiated studies, the investigator may not have access to complete safety data maintained by a commercial sponsor or other investigators, but are responsible for evaluating all safety information available to them.

6.3.1 Reporting Safety Study Endpoints

All SAEs occurring during a clinical trial should be reported regardless, whether they are related to any study end points or not.

6.4 Findings from Other Sources

The sponsor/applicant must also report expeditiously any findings from clinical, epidemiological, or pooled analyses of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the IP.

6.4.1 Findings from Other Studies

Findings that suggest a significant risk generally arise from ongoing or completed clinical studies, pooled data from multiple studies, epidemiological studies, and published and unpublished scientific papers.

6.4.2 Findings from Animal or *In-Vitro* Testing

Findings from animal studies, such as carcinogenicity, mutagenicity, teratogenicity, or reports of significant organ toxicity at or near the expected human exposure are examples of the types of findings that could suggest a significant risk.

7 ANY OTHER SAFETY REPORTING REQUIREMENTS

7.1 Investigator Brochure (IB)

The purpose of the investigator brochure (IB) is to provide the investigator with information (clinical and non-clinical) about the IP that is relevant to the study of the IP in human participants. Updated IBs should be submitted to SAHPRA within 30 days of being finalised.

7.2 Development Safety Update Reports (DSURs)

The sponsor/applicant of a clinical trial 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.

7.3 Ongoing Reports

7.3.1 Six-Monthly Progress Report

SAHPRA requires that any trial of more than 6 months duration must submit regular progress reports, starting from 6 months after the trial approval and six monthly thereafter until the final report that details the progress of the trial, which must include *inter alia*:

a) SAHPRA study tracking number and Protocol number

b) Study title

c) The investigational product (IP)

d) Details of sponsor and applicant

e) Trial information

f) Participant enrolment

g) Line listing of local serious adverse events and suspected unexpected serious adverse reactions (SUSARS), including deaths

h) And any other item specified during the SAHPRA approval of the protocol application

i) Any safety issue of special concern outside South Africa

j) Line listing of all critical and major protocol violation at the site

k) Signatures of national PI and representative of Applicant/Sponsor

7.3.2 Other Ongoing Reports

This includes, for example Independent Data Monitoring Committee (IDMC) and other interim reports. The interim report timeframe depends on trial-specific factors as per approved protocol.

7.4 Unblinding

SAHPRA will assess safety reports and consider appropriate actions to be taken. SAHPRA may request unblinding in cases of significant safety concerns on the part of itself or investigators. If a sponsor has

concerns that unblinding of adverse events will compromise the integrity of the study, the sponsor can propose an alternative reporting format to maintain the blind that must be agreed to by SAHPRA.

7.5 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 6.2 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.

7.6 Overdose

Reports of overdoses should be submitted when the overdose was associated with a Serious Adverse Event according to section 6.2. Overdoses should be reported regardless of whether they were intentional or accidental which must be specified.

7.7 Duration of Safety Reporting

The duration of safety reporting for a clinical trial should be defined in the protocol and the clinical trial application form and approved by SAHPRA. If a delayed SAE is identified that would affect participants who received the IP, SAHPRA should be notified so that participants can be followed up.

8 SUBMITTING ADR AND SAE REPORTS

8.1 Safety Reporting Requirements

Adverse Drug Reactions occurring during post-marketing studies (Phase 4 and observational studies) should be reported to the Vigilance Unit of SAHPRA.

Adverse Drug Reactions occurring during the use of concomitant and/or comparator medicine in a clinical trial should be reported to the Clinical Trials Unit of SAHPRA.

Where to Submit a Report

Reportable Safety Information under clinical trials must be sent to:

Chief Executive Officer

SAHPRA

CSIR Campus

Brummeria

Pretoria

Tel: 012 842 7602/7606

E-mail: ctcsaes@sahpra.org.za

Reportable Safety Information for post-marketing studies must be sent to:

Chief Executive Officer

SAHPRA

CSIR Campus

Brummeria

Pretoria

Tel: 012 842 7609/7610

E-mail: adr@sahpra.org.za

Reporting of SAEs for medicines used under Section 21:

Chief Executive Officer

CSIR Campus

Brummeria

Pretoria

Tel: 012 842 7600

E-mail: section21@sahpra.org.za

9 REFERENCES

General regulations made in terms of the medicines and related substances act, 1965 (act no. 101 of 1965), as amended.

International Council for Harmonisation (ICH) Topic E2A. 1995. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Step 5 – (CPMP/ICH/377/95). June.

International Council for Harmonisation (ICH) Topic E2B (M). 2000. Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports, Step 5 – (CPMP/ICH/287/95) November.

International Council for Harmonisation (ICH) Topic E2F: 2010. Note for guidance on development safety update reports. EMEA/CHMP/ICH/309348/2008).

International Council on Harmonisation, harmonised tripartite guideline on Clinical safety data management: Definitions and standards for Expedited reporting E2A. II D. Managing Blinded Therapy Cases.

National Department of Health. 2006. South African Good Clinical Practice Guideline. 2nd ed. South Africa.

National Department of Health. Medicines and Related Substances Act, 1965 (Act 101 of 1965).

National Department of Health, National Health Act, 2003 (Act 61 of 2003).

United States Food and Drug Administration. 2012. Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies.

10 UPDATE HISTORY

Date	Reason for Update	Version & Publication
May 2003	First publication released for implementation and comment - Title "Reporting Adverse IMP Reactions in South Africa"	v1 May 2003
Oct 2010	Formatted, contact details updated	v1.1 Oct 2010
Dec 2012	Exclusion of reporting of post-marketing ADRs and reference to new guideline	v1.2 Dec 2012
September 2017	Fully revised document, publication under new title for comment	v2 Aug 2016
September 2017	Approved for Implementation	v2 October 2017
July 2019	Published for implementation	v2 August 2019
November 2019	Section 6.1, 6.2, 7.5, 7.6 including administrative changes	V3 November 2019

ANNEXURE A: REQUIRED INFORMATION

Outline of the required information

1. Initial Expedited SUSAR reports

Within 7 or 15 days a complete report inclusive of the required administrative and clinical data must be submitted to SAHPRA, refer to section 6.2:

a) SAHPRA study reference number and Protocol number

b) The suspected investigational product

c) An identifiable participant (e.g. study participant code number)

d) An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship

e) An identifiable primary reporting source

f) Identity of the sender of the report to SAHPRA

g) Other comment or background information

2. Follow-up/Final Expedited Report

Eight days after the initial safety reporting, complete report inclusive of the required administrative and clinical data.

Contents of the Follow-up/Final Expedited Report:

a) Copy/Information of the Initial Expedited report

b) Administrative and Identification Information

   i. Identification of the case safety report

   ii. Primary source(s) of information

   iii. Information on sender and receiver of case safety report

c) Information **on the Case**:

   i. Patient characteristics

   ii. Reaction(s)/event(s) - time to reaction (immediate, latent, etc.)

   iii. Results of tests and procedures relevant to the investigation of the patient

   iv. IP(s) information

   v. Narrative case summary and further information

ANNEXURE B: SAE REPORTING FORM

This form should preferably be typed

PART 1: ADMINISTRATIVE DETAILS	
1.1 Study Title or abbreviated title	
1.2 Protocol Number	
1.3 SAHPRA reference number	

PART 2: SITE INFORMATION	
2.1 Name and address of site	
2.2 Name of Principal Investigator	

PART 3: PARTICIPANT INFORMATION	
3.1 Participant trial ID	
3.2 Age	
3.3 Gender	
3.4 Relevant pre-medical history summary	

PART 4: SAE INFORMATION **(where possible, tick (√) the appropriate box)**	
4.1 Type of report	☐ Initial ☐ Follow-up ☐ Final
4.2 Reaction onset date	YYYY/MM/DD
4.3 Reaction stop date	YYYY/MM/DD
4.4 Outcome of adverse event	☐ Participant died ☐ Hospitalisation or prolongation ☐ Life threatening ☐ Congenital abnormality/ Birth defects ☐ Persistent or significant disability/incapacity ☐ Other (list)_____
4.5 Description of event summary	
4.6 Relationship of event to study product (causality)	☐ Definitely ☐ Probably related ☐ Possibly related

	☐ Unrelated
4.7 Was study product discontinued due to event?	☐ Yes ☐ No ☐ N/A
4.8 Describe steps taken to manage SAE (narrative)	
4.9 Did adverse event abate after withdrawal of study product?	☐ Yes ☐ No ☐ N/A
4.10 Did adverse event reappear after re-initiation of product?	☐ Yes ☐ No ☐ N/A
4.11 Crucial additional information	

PART 5: SUSPECTED MEDICINE (S) INFORMATION	
5.1a List suspected product(s) including Investigational Product (IP)	
5.1b List suspected concomitant or comparator medicine(s)	
5.2 Route(s) of administration	☐ Intravenous injection/Intravenous infusion (IV/IVI) ☐ Intramuscular ☐ Sub-cutaneous ☐ Topical ☐ Oral ☐ Sub-lingual ☐ Rectal ☐ Vaginal ☐ Other (list)_____
5.3 Dose(s)	
5.4a Indication(s) for use of IP	
5.4b Indication for concomitant medicines	
5.5a Date of initiation of treatment of IP	YYYYY/MM/DD
5.5b Date of initiation of treatment of comparator or concomitant	YYYYY/MM/DD
5.6 Therapy duration (prior to	

onset of SAE)	

PART 6: FINAL OUTCOME	
6.1 What was the final outcome of the SAE?	☐ Ongoing ☐ Recovered completely ☐ Recovered with sequelae ☐ Permanent ☐ Died
	Date related to above:

PART 7: CONTACT DETAILS	
7.1 Name of applicant	
7.2 Contact details	
7.3 Signature and date	

PART 8: PERSON COMPLETING THE FORM	
8.1 Name and designation of person completing this form	
8.2 Signature and date	

E-mail to: ctcsaes@sahpra.org.za