MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

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 Medicines Control Council's current thinking on the measures to ensure safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council 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 Registrar of Medicines and the website

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REGISTRAR OF MEDICINES

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1 INTRODUCTION

This guideline is intended to assist applicants in the reporting of adverse reactions/events occurring during a clinical trial that may be related to the medicine or the conduct of the trial.

The Medicines Control Council (MCC) Guideline for reporting adverse events for registered medicines [ADR reporting guideline 2016] is used for reporting these events occurring during use of registered medicines. Adverse events occurring during clinical trials have additional MCC reporting requirements. This guideline is intended to provide guidance on the responsibilities of the investigator and the sponsor in reporting adverse and unexpected adverse events to MCC, and provides a framework for the minimum requirements for the information required.

The reporting of all adverse events during a clinical trial will be in accordance with the specific trial protocol evaluated by the Clinical Trials Committee (CTC) and approved by the MCC.

The design of the adverse event reporting aspects 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 the MCC on a protocol-specific basis.

Where the nature of the investigational product (IP) or condition requires a deviation from this guideline, the applicant should provide clear arguments justifying the request for a waiver.

This guideline has been aligned to the International Conference of Harmonisation (ICH) E6 and the South African Good Clinical Practice guideline (SAGCP) of 2006 and taking the circumstances of clinical trials in South Africa into account.

1.1 Legal Basis

The guideline pertains to Regulations 34 and 37 of the Medicines and Related Substances Act 101 of 1965 (as amended), and the National Health Act 61 of 2003.

A Safety Reporting Requirements

Sponsors investigating a drug are required to notify MCC and all participating investigators, of any adverse experience associated with the use of the drug that was both serious and unexpected, and any finding from tests in laboratory animals that suggested a significant risk for human subjects. The phrase associated with the use of the drug was defined as “there is a reasonable possibility that the experience may have been caused by the drug”.

Because the regulations require reporting certain adverse events in the aggregate rather than as individual cases, it is important for sponsors to collect and evaluate safety data systematically during product development, including accumulating safety data.

B Safety Reporting Requirements for Bioavailability (BA) and Bioequivalence (BE) Studies

Safety information from these studies that provided important information about drugs under investigation. These requirements will help monitor the safety of these drugs and better protect human subjects enrolled in BA or BE studies.

2 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.

The safety reporting rule introduces terms and definitions that are meant to be clear and consistent.

A Adverse Event

Adverse events means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An adverse event (also referred to as an adverse experience) can be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drugs) and with any route of administration, formulation, or dose, including an overdose.

B Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g. angioedema, hepatic injury, Stevens-Johnson Syndrome), one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture).

An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor or investigator to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

Both the sponsors and investigators decision on causality must be reflected in the safety report.

C Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

D Unexpected

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

E Serious

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

This definition permits either the sponsor or the investigator to decide whether an event is serious. The investigator’s perspective may be informed by having actually observed the event, while the sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. Because serious adverse events are critically important for the identification of significant safety problems, MCC believes taking into account both the investigator’s and the sponsor’s assessment as important. Therefore, if either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting.

F Life-Threatening

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

As with the definition of serious, the determination of whether an adverse event is life-threatening can be based on the opinion of either the investigator or sponsor. Thus, if either believes that it meets the definition of life-threatening, it must be considered life-threatening for reporting purposes.

3 REVIEW OF SAFETY INFORMATION

The sponsor is required to review promptly all information relevant to the safety of the drug. During the course of drug development, adverse event information is generally reported to a sponsor by investigators conducting clinical trials; however, a sponsor may become aware of new safety information from a variety of sources, both domestic and foreign. Some examples of sources are listed as follows, but safety information from any other source would also need to be reviewed and evaluated by the sponsor.

Animal studies or *in vitro* studies:

- Clinical or epidemiological investigations
- Reports in the scientific literature

Unpublished scientific papers:

- Information presented at scientific meetings
- Reports from foreign regulatory authorities

Reports from commercial marketing experience:

- Safety information presented at a professional meeting
- Foreign spontaneous reports

The sponsor's review should include examining data from all sources and deciding whether the information meets the criteria for expedited reporting (see section 4), as well as evaluating all accumulating data at regular intervals to update safety information and to identify new safety signals. Some types of information should be sought by the sponsor as part of its continuous pharmacovigilance on the safety of the drug. For example, the sponsor should conduct literature searches regularly with a frequency appropriate to the drug or study design to seek safety information and report that information if necessary.

4 MONITORING THE SAFETY DATABASE AND SUBMITTING SAFETY REPORTS

The sponsor is required to notify MCC in the following safety reports:

- Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports
- Six-monthly progress report
- Annual Development Safety Update Reports (DSUR)
- Final Safety Report

4.1 SAE Reporting timeframes

The sponsor is required to notify MCC and all participating investigators in a safety report.

A preliminary report should be provided to MCC within 7 calendar days followed by a follow-up/ expedited report within another 8 calendar days.

That is, the follow-up/expedited report must be received within 15 days after the sponsor obtained first knowledge of the adverse reaction.

MCC reserves the right to impose more stringent reporting timelines on an individual protocol basis.

Participating investigators include all investigators to whom the sponsor is providing drug under any of its trials. This includes, for example, all investigators participating in clinical trials at South African and non-South African sites, for the investigational drug.

In addition, the sponsor must identify in each safety report all safety reports previously submitted to MCC 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 and those that occurred in pre- and post-marketing studies.

Sponsors 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.

Sponsors-investigators are required to comply with both the sponsor and the investigator responsibilities. With respect to drug safety reporting, this includes examining data from reports in the scientific literature and reports from foreign commercial marketing experience. The MCC recognises that a sponsor-investigator may not have access to complete safety data maintained by a commercial sponsor or other sponsor-investigators, but sponsor-investigators are responsible for evaluating all safety information available to them. To protect human subjects, the MCC recommends that entities that provide drug to or receive drug from other entities share safety information with each other.

The sponsor must specifically submit a safety report in the following instances:

A Serious and Unexpected Suspected Adverse Reaction (SUSAR)

The sponsor must report in a safety report any suspected adverse reaction to study treatment (i.e. including active comparators) that is both serious and unexpected. Before submitting a safety report, the sponsor needs to ensure that the event meets all three of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as a safety report.

Deciding whether the adverse event meets the definition of a suspected adverse reaction is usually the most difficult determination, but this decision is critical to avoid the submission of uninformative safety reports. The sponsor and investigator should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction. The suspected adverse reaction must then be reported expeditiously in a safety report if it also meets the definitions of serious and unexpected.

Investigators are required to provide a causality assessment for each serious adverse event reported.

Both the investigator's and the sponsor's assessment of causality should be included in the report submitted to the MCC. If the investigator fails to provide a causality assessment and the sponsor is unable to obtain it, or if the investigator assesses the causality as unknown, the sponsor should evaluate the event without the investigator's assessment.

To assist sponsors with determining whether an adverse event meets the definition of suspected adverse reaction, the requirement specifies that sponsors are to report to MCC only if there is evidence to suggest a causal relationship between the drug and the adverse event and it provides examples of such evidence, described below.

Guidance for determining SUSARS:

I. Individual Occurrences

Certain serious adverse events are informative as single cases because they are uncommon and are known to be strongly associated with drug exposure. Some examples include angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome. The occurrence of even one case of such adverse events would meet the definition of suspected adverse reaction (i.e., there is a reasonable possibility that the drug caused the event).

II. One or More Occurrences

A single occurrence or a small number of occurrences, of a serious adverse event that is uncommon in the study population, but not commonly associated with drug exposure may also be informative. If the event occurs in association with other factors strongly suggesting causation (e.g. strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive to report. Often, more than one occurrence from one or multiple studies would be needed before the sponsor could determine that there is a reasonable possibility that the drug caused the event. Examples include tendon rupture or heart valve lesions in young adults, or intussusceptions in healthy infants.

III. Aggregate Analysis of Specific Events

Certain serious adverse events can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g. symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population). An example of the former would be a non-acute death observed in a trial in cancer patients. An example of the latter would be an acute myocardial infarction observed in a long-duration trial in an elderly population with cancer. Although these serious adverse events meet the definition of unexpected, as they are not listed in the investigator brochure, these events do not warrant expedited reporting as individual cases because it is not possible, based on a single case, to determine that there is a reasonable possibility that the drug caused the event. As a result, they do not meet the definition of a suspected adverse reaction.

MCC requires reporting in a safety report when an aggregate analysis of specific events observed in a clinical trial indicates those events occur more frequently in the drug treatment group than in a concurrent control group. In cases where a randomised comparison is not available, the estimate of whether the rate is greater than in a control population would have to be based on some other group not receiving the drug, such as the general population or populations similar to the drug population with respect to demographics and disease state but not receiving the test drug (e.g. a historical control). An aggregate analysis of specific events should reflect information from all relevant studies. Therefore, it should be performed both for individual studies (if there are enough events to be informative) and across all studies, to determine whether they meet the criteria for expedited reporting.

The following recommendations are intended to assist sponsors with protocol development and monitoring the safety database.

a) Reporting Study Endpoints

Generally, study endpoints refer to outcomes that sponsors are measuring to evaluate efficacy. For trials designed to evaluate the effect of a drug on disease-related mortality or major morbidity, endpoint information should be collected, tracked, and monitored, usually by a Data Monitoring Committee (DMC), during the course of the study. The protocol would pre-specify a monitoring plan for determining whether subjects receiving the drug treatment are at higher risk for the outcome (e.g. all-cause mortality), and such results would be reported according to the protocol. The study endpoints must be reported to MCC by the sponsor according to the protocol. For example, a death ordinarily would not be reported as an individual case in an expedited report from a trial designed to compare all-cause mortality in subjects receiving either drug treatment or a placebo. On the other hand, in the same trial with an all-cause mortality endpoint, if the death occurred as a result of an anaphylactic reaction that coincided with initial exposure to the drug, or as a result of fatal hepatic necrosis, the death must be reported as an individual case in a safety report because there would then be evidence suggesting a causal relationship between the drug and the event.

b) Serious Adverse Events that are not Study Endpoints

Other serious adverse events that are not study endpoints and are not “expected” (e.g. because they are not in the investigator’s brochure), can be anticipated to occur with some frequency during the course of the trial, regardless of drug exposure, depending on the patient population and disease under study. Examples of such “anticipated” events include known consequences of the underlying disease or condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pre-treatment baseline. In general, a limited number of occurrences of such an adverse event in a study population in which occurrences of the event are anticipated is not an adequate basis to conclude that the event is a suspected adverse reaction (i.e. that there is a reasonable possibility that the drug caused the event). Such events should not be reported individually as they occur because they are uninformative as single cases. Such anticipated adverse events should nonetheless be monitored at appropriate intervals, and the numbers of events in each arm of a controlled study should be compared. The adverse event must be reported to MCC expeditiously as a safety report if there is an imbalance between arms suggesting there is a reasonable possibility that the drug caused the adverse event. It is important to consider the entire clinical trial database in such analyses.

c) Safety Surveillance for Ongoing Clinical Trials

Because it is critical that a drug product’s risks be adequately assessed during development, sponsors should ensure that they have in place a systematic approach for safety surveillance. Such an approach should include a process for reviewing, evaluating, and managing accumulating safety data from the entire clinical trial database at appropriate intervals. In some cases, a specific independent committee with substantial external representation could be created to perform this function. In others, the sponsor may choose to create a safety team within the sponsor’s organization. In either case, this independent group would oversee the evolving safety profile of the investigational drug and evaluate, at appropriate intervals, the accumulating data from individual and multiple clinical trials, as well as other available information.

d) Findings from other sources

The sponsor must also report expeditiously any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk

in humans exposed to the drug. These reports are required for studies from any source. A finding that suggests a significant risk would ordinarily result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation. For example, actions often taken in response to a significant risk finding include immediate revision of the informed consent, intensification of subject monitoring, revised eligibility criteria or screening procedures, enrolment hold, or consideration of discontinuation of the trial.

I. 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.

II. 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.

5 OTHER SAFETY REPORTING ISSUES

A Investigator Brochure

The purpose of the investigator brochure is to provide the investigator with information (clinical and nonclinical) about the investigational drug that is relevant to the study of the drug in human participants.

The investigator brochure should include the information that is important for the investigator, who is administering the drug to human subjects, to know and understand. The investigator brochure is required to include information about the following:

- Drug substance and formulation
- Pharmacological and toxicological effects of the drug in animals (and in humans, if known)
- Pharmacokinetics and biological disposition of the drug in animals (and in humans, if known)
- Information relating to safety and effectiveness in humans obtained from prior clinical studies

Information about possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs

Precautions or special monitoring to be done as part of the investigational use of the drug.

I. Clinical Risk Information

With respect to clinical risk information, the investigator brochure should specifically and accurately list those adverse events that have been observed with an investigational drug and for which a causal relationship with the drug is suspected or confirmed. In addition, the investigator brochure should list adverse events that commonly occur with the class of drugs or may be predicted to occur based on the pharmacological properties of the drug, even if not yet observed with the drug under investigation, to alert the investigator to the possibility of their occurrence. Sponsors should use judgment in determining which terms accurately reflect a particular adverse event, including syndrome names if applicable. The investigator brochure should not list adverse events that are unlikely to have been

caused by the drug because such lists could dilute the importance of clinically meaningful risk information.

II. Updating the Investigator *Brochure*

During the course of the clinical trial, the sponsor must update the investigator brochure on an ongoing basis with new important safety information. Some updates to the investigator brochure should be made as soon as possible while others can be made on a routine basis. For example, a new safety finding that represents a significant risk to study subjects (e.g. a finding that patients with renal impairment are likely to experience a serious adverse reaction) should be communicated to investigators immediately, along with an update to the investigator brochure and possibly to the protocol (e.g., a change in screening procedures and eligibility criteria). On the other hand, an update to reflect a minor change in a suspected adverse reaction rate could be done on an annual basis.

The sponsor should exercise judgment when deciding whether the threshold has been reached for adding a newly observed adverse event to the investigator brochure. Criteria to consider usually include the strength of the evidence from individual or multiple cases and previous knowledge about the drug or drug class.

Until the investigator brochure is updated to include a new serious, suspected adverse reaction, subsequent occurrences of similar serious, suspected adverse reactions must be submitted expeditiously in safety reports to MCC and all participating investigators.

There is more than one acceptable approach for updating the investigator brochure with new safety information. For example, adding a new serious and unexpected suspected adverse reaction to the investigator brochure as an addendum, rather than reissuing the entire brochure, is an acceptable approach for keeping investigators informed of new observations. Sponsors should ensure that any addenda are incorporated into the next full revision of the investigator brochure.

B Development Safety Update Reports (DSURs)

There may be differences in the clinical safety profile for different presentations, for e.g., dosage form, formulation or delivery system of the pharmacologically active compound(s) or different indications/uses of a given product.

All adverse reactions which qualify for reporting should be cross-referenced with all other dosage forms and uses for that product.

The sponsor of a clinical trial in SA will be responsible for the submission of an annual Development Safety Update Report that includes information gathered from all clinical experience with the Investigational Medical product, whether in SA or elsewhere.

The DSUR should include the following:

Part 1: Analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its on-going risk: benefit

Part 2: A line listing of all suspected serious adverse reactions that have occurred in the trial(s) with the IMP.

Part 3: An aggregate summary tabulation of suspected serious adverse reactions that occurred in the trial(s) with the IMP.

An updated Investigator's Brochure including this information should be submitted to the MCC on an annual basis.

C Interim reports

The MCC requires that any trial of greater than 6 months duration must submit interim reports, starting from 6 months after the trial approval, that details the progress of the trial including:

- MCC study tracking number and Protocol number
- The suspected investigational medicinal product,
- Progress since trial approval
- Participant enrolment,
- Reported fatalities,
- Line Listing of Serious adverse events,
- Suspected Unexpected Serious Adverse Reactions
- and any other item specified during the MCC and Clinical Trials Committee (CTC) approval of the protocol application.

The interim report time frame may be adjusted depending on trial-specific factors as determined by the MCC.

D Unblinding

The blind should ordinarily be broken for safety reports submitted to MCC and all participating investigators. Knowledge of the treatment received is necessary for interpreting the event, may be essential for the medical management of the subject, and may provide critical safety information about a drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). The MCC does not believe that unblinding single or small numbers of serious and unexpected adverse event cases will compromise the integrity of the study, in part because such unblinding should be infrequent.

If a sponsor has concerns that unblinding of adverse events will compromise the integrity of the study, the sponsor can propose in advance an alternative reporting format or frequency to maintain the blind that must be agreed to by the MCC.

E Investigator Reporting

Most of the information about the safety of a drug prior to marketing comes from clinical trials. Therefore, adverse event reports from investigators are critically important, as they observe subjects' responses to the drug. Except for study endpoints, the investigator must immediately report to the sponsor all serious adverse events, regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population independent of drug exposure or in the investigator brochure as predicted to occur with the drug. The MCC recognises that it may take the investigator a short period of time (i.e., a day) to compile information about the event, but then expects the information to be immediately reported to the sponsor.

F Investigations of Marketed Drugs

A sponsor of a clinical study of a drug marketed or approved that is conducted must submit safety reports for suspected adverse reactions that are observed in the study, at either domestic or foreign sites. The sponsor must also submit safety information from the clinical study as prescribed by the relevant post marketing safety reporting.

G Duration of Safety Reporting

The purpose of sending safety reports to investigators is to provide investigators with information they need to protect their patients participating in clinical trials. Once they are no longer enrolling or monitoring patients, this information is no longer necessary.

Cut-off dates for sending safety reports to investigators may be described in the protocol. If no cut-off dates are specified, once a site has been officially closed out, the sponsor usually does not need to continue sending safety reports to that site, and an investigator does not need to receive or review them.

In unusual cases, safety information related to delayed toxicity may be reported after a site is officially closed out. For example, if a late toxicity is discovered that would affect subjects who received the investigational drug, the investigator should be notified so that patients could be followed up if necessary.

Safety Monitoring plan should include subsections on:

- Establishing a base-line for health before administration of study medicine
- Procedures for collection and recording of adverse events during the trial that occur following medicine administration (defined time period), and during the follow-up period
- A risk management procedure, including unblinding procedures, for dealing with serious, unexpected events or reactions which may arise during the conduct of the trial and which could significantly impact on the safety of the study participants
- Procedures for assessing and reporting the occurrence of adverse events to the sponsor, Independent Safety monitor, Ethics Committees and to the MCC
- Provisions for independent Safety Monitoring during the trial. Where a Data Safety and Monitoring Board/Committee is established, the membership and charter should be provided. The constitution of the DSMB should include representation or expertise from the patient population being studied and comply with the National Health Research Ethics Committee (NHREC) guide for DSMBs
- Monitoring the trial conduct (See SA GCP Guideline 2006)

6 REFERENCES

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

(2) Guidance for Industry and Investigators. 2012. Safety Reporting Requirements for INDs and BA/BE Studies. December.

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

(4) International Conference on 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.

(5) International Conference on Harmonisation (ICH) Topic E2F: 2010. Note for guidance on development safety update reports. September.

(6) ICH harmonised tripartite guideline on Clinical safety data management: Definitions and standards for Expedited reporting E2A. II D. Managing Blinded Therapy Cases.

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

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

7 SUBMITTING SAE REPORT

Where to Submit a Report

Reportable Safety Information as reflected in the Guidelines must be sent to:

Registrar of Medicines
Private Bag X828
Pretoria
0001

Tel: 0123958126

Fax: 0862484874

E-mail: nkambp@health.gov.za

Reporting of SAEs for medicines used under Section 21:
Registrar of Medicines
Private Bag X828
Pretoria
0001

Tel: 012 395 8241 or 012 395 8126

Fax: 012 395 8775 or 0862743073

E-mail: munbos@health.gov.za AND nkambp@health.gov.za

Appendix A

Initial Expedited reports

a) MCC study tracking number and Protocol number

b) The suspected investigational medicinal product,

c) An identifiable subject (e.g. study subject 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) Unique Case-identifier number

g) Identity of the sender of the report to MCC

h) Other comment or background information

Follow-up/Final Expedited Report

Within 15 days a complete report inclusive of the required administrative and clinical data must be submitted to the MCC:

Contents of the Follow-up/Final Expedited Report

Copy of the Initial Expedited report

A: Administrative and Identification Information

A.1 - Identification of the case safety report

A.2 - Primary source(s) of information

A.3 - Information on sender and receiver of case safety report

B: Information on the Case:

B.1 - Patient characteristics

B.2 - Reaction(s)/event(s) - time to reaction (immediate, latent, etc.)

B.3 - Results of tests and procedures relevant to the investigation of the patient

B.4 - Drug(s) information

B.5 - Narrative case summary and further information

8 UPDATE HISTORY

Date	Reason for Update	Version & Publication
May 2003	First publication released for implementation and comment - Title "Reporting Adverse Drug 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
28 Oct 2016	Fully revised document, publication under new title for comment Deadline for comment	v2 Aug 2016