Safety Reporting in Clinical Trials

Prof Paul Ruff

Clinical Trials Stakeholder Workshop

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Overview

- Background
- Revision – Safety Guidelines
- Definition of Key Terms
- Reporting Time Periods
- Pregnancy
- Overdoses

Background

- Safety Guideline – Previously published for comment in August 2019
- To address the gap in safety reporting - for example incomplete SAE forms received by SAHPRA
- Guideline revised in November 2019 on basis of comments from stakeholders

Safety Reporting

- Safety Reporting Guideline (Clinical Trials) - Applicable to all clinical trials approved by SAHPRA including HIV vaccines
- In the past HIV Vaccine had specific reporting timelines, but now the expectation is that they should comply with Clinical Trials Guideline for Safety Reporting
- All Clinical Trials are approved under Section 21 of Act 101 of 1965.
- All unregistered medicines fall under Section 21 and need to comply with the requirements of these guidelines

Safety Reporting

- SAHPRA/CTC requires stringent reporting criteria and timelines.
- Safety reporting should be defined by the Applicant in the protocol and CTF1.
- Certain clinical trials may require special and exceptional adverse event monitoring and reporting that will be specified by SAHPRA on a protocol-specific basis.
- Separate from guidelines on “Post Marketing Reporting of Adverse Drug Reaction to Human Medicines in South Africa” (2017) for registered medicines.

Revisions to Safety Guideline

Revised Sections:

- Section 6.1 – type of reports (Reference to SUSARs and clarification of final safety report format)
- Section 6.2 – Clarification on the reporting period for SUSARs, final safety and study Reports
- Section 7.5 – Reports Relating to Pregnancy and Breast-Feeding
- Section 7.6 – Overdoses and associated SAEs
- Other Administrative changes

Definitions of Key Terms

- Adverse events/experiences (AE)
- Adverse drug reaction or adverse reaction (ADR)
- Serious adverse event (SAE)
- Serious Unexpected Suspected Adverse Drug Reaction (SUSAR)
- All ADRs are AEs but not all AEs are ADRs
- All SUSARs are SAEs but not all SAEs are SUSARs.

Definition of Key Terms

- **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.

- **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.

Definition of Key Terms

A serious adverse event (SAE) is any untoward occurrence that:

- 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;
- is a medically significant / important event or reaction.

Definition of Key Terms

- **Unexpected (unlisted) Adverse Drug Reaction**:
- **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)

Definition of Key Terms

- **Serious unexpected suspected adverse reaction** (SUSAR):
- Adverse reaction that is unexpected but suspected to be drug related
- Fulfil criteria for “serious” as per SAEs.
- All SUSARs are SAEs but not all SAEs are SUSARs.

Definition of Key Terms

- **Investigational Product (IP):**
- IP is defined as any product used in a clinical trial being investigational, standard of care or concomitant that is not registered in South Africa by SAHPRA and/or has not been packaged and labelled for use in South Africa.
- Applicant may import medicines for clinical trials even though the same medicine is registered
- Adverse reactions to medicines registered in South Africa should be reported to Pharmacovigilance Reporting Centre based on Post-marketing ADR Guidelines

Submission Format - SAEs

- SAHPRA SAE Reporting Form or CIOMS Form acceptable
- No any other Company Specific Forms should be submitted to SAHPRA for SAE reporting

Submitting Safety Reports to SAHPRA

- Reports of SUSARs occurring in the clinical trial
- Reports of SUSARs and trends outside SA or in other clinical trials **only of special concern**.
- Standard six monthly Progress Report
- Annual Development Safety Update Reports (DSUR)
- Final Progress Report (Safety Report)
- Final Study Report

Reporting Timeframes

Type of Report	Initial Reporting Timeline	Follow up	Format
Preliminary reports - SAE: •Local Reports: •Fatal or life-threatening •Foreign Reports: Fatal or life-threatening (of special concern)	7 calendar days *first knowledge by Sponsor/Applicant 30 days (earlier if results in study closure)	8 calendar days 6 monthly as part of Progress Report	SAHPRA SAE Form/CIOMS Format Line listing
Local Reports: Other serious (unexpected, not fatal or life threatening	15 calendar days	6-monthly	SAHPRA SAE Form/CIOMS Format
Line listing of local reports • Serious (unexpected and expected) adverse events Any other issues of special concern Outside South Africa	6-monthly		Line listing

Reporting Timeframes

Type of Report	Initial Reporting Timeline	Follow up	Format
Other major safety concerns (change in nature, severity or frequency of risk factors)	15 days	6 monthly report.	Detailed report
New information impacting on risk-benefit profile of product or trial conduct	3 days and in 6-monthlyreport	6 monthly	Detailed report
Six-Monthly Progress report	6-monthly after the approval of the trial	6 monthly	SAHPRA Progress report form
Final Safety Report – Final Progress Report	30 days - completion or termination of clinical trial		Progress report form
Final study report	180 days of completion or termination of clinical trial.		

Post Marketing Reporting Requirements

- Reporting with registered product with local label ie. Phase IV trial:
- Post Marketing ADR reporting should be followed
- Send to National Pharmacovigilance Reporting Centre

Reports on Pregnancy/ Lactation

- The sponsor/applicant must report suspected adverse drug reactions related to pregnancy or breast-feeding as specified in section 6.2, 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.

Reports on overdoses

- Reports of overdoses should be submitted when the overdose was associated with an Serious Adverse Event according to Section 6.1
- Overdoses should be reported regardless as to whether they were intentional or accidental which must be specified
- Overdoses not associated with SAEs should be reported in Line Listing

Contact Details – Safety Reporting

Clinical Trials Unit:

Email: ctcsaes@sahpra.org.za

Section 21: section21@sahpra.org.za

SAE Reports should be emailed and no hardcopy should be submitted

Pharmacovigilance Unit* :

Post-marketing studies

Email: adr@sahpra.org.za

*Recommend that the post-marketing guidelines be reviewed for updates

Electronic Submission of other Safety Information

- Any other safety notifications – e.g. progress reports:
- E-mail ctcnotifications@sahpra.org.za
- Refer to the guideline on website: Electronic Submission of Clinical Trial Documents (Amendments, Bioequivalence Studies, Responses, Notifications, and Serious Adverse Events)