

AE Management (ClinO / KlinV)

Änderungshinweis: Anpassung an Details aus der Verordnungsrevision, Aktualisierung Referenzen, formale Änderungen.

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1. Purpose

The present document defines all types of Adverse Events and describes the documentation/assessment responsibilities in clinical trials (except for trials with medical devices) in compliance with Swiss regulatory requirements.

2. Abbreviations and Definitions

2.1. Abbreviations

General abbreviations are listed in the CTC Glossar.

(S)ADR	(Serious) Adverse Drug Reaction
(S)AE	(Serious) Adverse Event
AR	Adverse Reaction
ATMP	Advanced Therapeutical Medicinal Products
CA	Competent Authority
CIOMS	Council for International Organizations of Medical Sciences
ClinO	Ordinance on Clinical Trials with exception for trials with medical devices (KlinV)
CRF	Case Report Form
FOPH	Federal Office of Public Health (BAG)
HRA/ HFG	Human Research Act/ Humanforschungsgesetz
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethic Committee
IMP	Investigational Medicinal Product
SUSAR	Suspected Unexpected Serious Adverse Reaction

2.2. Definitions

The following definitions for IMPs are used analogously also for other clinical trials (except for ADRs/SUSARs) as well as for clinical trials with advanced therapy medicinal products (ATMPs).

ATMPs include transplant products according to the Transplantation Act (e.g. somatic cell therapy products and tissue-engineered products), gene therapy products and other nucleic acid-based products, as defined in the Therapeutic Products Act and taking into consideration the definitions in Article 5 paragraph 2 of the Gene Technology Act (GTA) and Article 3 paragraph 1 letter d of the Release Ordinance (RO). This also includes combinations of ATMPs with medical devices or xenogeneic cells or tissue. ATMPs are equivalent to medicinal products and are therefore also subject to the Therapeutic Products Act (TPA).

Adverse Event	Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (ICH E2A). <u>Comment:</u> An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product (ICH E2A). <u>Comment:</u> Please note that pregnancy is generally not to be considered an AE. Only if a pregnant study subject treated with an IMP has an untoward medical occurrence (complications during pregnancy or any congenital abnormality in the offspring) the AE or SAE form should be completed as appropriate.
Adverse Reaction (AR)/ Adverse Drug Reaction	All untoward and unintended responses to a medicinal product (including IMPs, TpPs, GTs, GMOs) or to a transplantation procedure related to any dose or procedure administered (ICH E2A). <u>Comment:</u> All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship (ENTR/CT 3).
Causal relationship	The assessment of causality of each (S)AE is defined in the study protocol and can be classified binomially as related or unrelated Related: - the event started in plausible time relationship to medicinal product resp. medical intervention applied and - the event cannot be definitely explained by underlying diseases or other situations. Unrelated: - the event started in no temporal relationship to medicinal product resp. medical intervention applied and - the event can be definitely explained by underlying diseases or other situations. Alternatively, the five different categories “not related - unlikely - possibly - probably – definitely” may be used. In case the five categories are used, it shall be defined which categories are considered as “related” and shall be reported as applicable.
Serious Adverse Event	Any untoward medical occurrence or effect that (ICH E2A, E2D): - results in death - is life-threatening - requires hospitalisation or prolongation of existing in-patients’ hospitalisation - results in persistent or significant disability or incapacity - is a congenital anomaly or birth defect - is a medically important event or reaction (for IMPs only) Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse (ICH E2D).
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Suspected adverse reaction which is related to the tested investigational product or the transplantation that is both unexpected and serious and subject to expedited reporting (ENTR/CT 3).

3. Responsibilities

All personnel involved in clinical trials according to ClinO are responsible for complying with this document.

The Sponsor is responsible for training of this document before conducting a clinical trial.

Each protocol author should incorporate a statement that specifies the procedures for reporting serious adverse events to Sponsor, IECs, and CAs, as applicable.

Investigator and Sponsor, respectively, are responsible for full investigation and thorough documentation of Adverse Events during the conduct of a clinical trial (see chapter 5.1 of this document). They are responsible for reporting reportable events as well as regular safety update reports to IECs and CAs in accordance with the respective Swiss regulations.

The responsible Investigator can also be the Sponsor of the clinical trial who will then have all responsibilities unified in his/her person.

4. References

General legal requirements and guidelines are listed in the form «Reference Documents» (CTC internal).

Respective current versions:

- Directive 2001/83/EC in its current consolidated version 01/01/2025 on the Community code relating to medicinal products for human use
- Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA);
- Human Research Act (HRA/HFG)
- Ordinance on clinical trials in human research with exception for trials with medical devices (Clinical Trials Ordinance, ClinO/KlinV)
- ICH Topic E6 (R3) Guideline for Good Clinical Practice, Note for Guidance on Good Clinical Practice
- ENCTR3: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')
- Swissmedic BW101_10_003_MB – Merkblatt Guideline Guideline Amendments Clinical Trials
- Swissmedic BW101_20_002e_MB_Safety reporting in clinical trials
- BW315_00_961_Swissmedic information sheet: Mandatory reporting of adverse reactions during a clinical trial with ATPs, other products (bacteriophages, etc.) and procedures
- ICH Topic E2A, Clinical safety data management: definitions and standards for expedited reporting
- ICH Topic E2D(R1), Post-Approval Safety Data Management, Definitions and Standards for Expedited Reporting
- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (Eudra-Lex CT-3' 2011/C 172/01)
- Entblindung klinische Versuche; DMSUSZ-1824642429-908
- Ungeplante Schwangerschaft während klinischen Versuchen; DMSUSZ-1824642429-911
- SAE Meldungen für übrige klinische Versuche; DMSUSZ-1824642429-916
- Meldung von AEs/SAEs für klinische Versuche mit IMP, TpP, GT, GVO (KlinV); DMSUSZ-1824642429-918
- Klinische Versuche der Transplantation menschlicher Organe, Gewebe und Zellen; DMSUSZ-1824642429-1187
- Studien mit Radiopharmazeutika und radioaktiv markierten Stoffen; DMSUSZ-1824642429-1213

5. Procedures

Study subject safety is a major objective during the conduct of clinical trials. The Clinical Trials Center (CTC) advises study teams conducting research projects involving human subjects regulated by the ordinance on clinical trials (ClinO) according to the Human Research Act (HRA). All clinical trials in Switzerland must be

conducted under the provisions of Swiss law and national regulatory requirements as well as medical and ethical obligations to collect, review, report and follow-up information about Adverse Events (AEs).

In the following, the procedures are defined for documentation and assessment of (S)AEs.

The respective documents accompany this present document, which describe all reporting duties of the Investigator resp. Sponsor including a summary flow chart, for the different types and categories of clinical trials.

Any pharmacovigilance / haemovigilance / biovigilance procedures for safety reporting to CA in Category A clinical studies must be conducted according to the current information published by the respective CA and the institutional regulations.

5.1. Documentation of data related to AEs/SAEs

Collection and documentation of clinical trial data regarding the safety and well-being of study subjects should be done completely and accurately by the Investigator/Sponsor.

Questioning for AEs should be done from the time of signing the informed consent form by the research subject until the time of last trial specific subject contact (including follow-up periods for self-reported SAEs, as applicable). In general, AEs occurring during the conduct of the clinical trial must be recorded according to the specifications in the protocol, which had been approved by IEC and CA.

5.1.1. Documentation of AEs

The Investigator must document non-serious AEs in the course of **Category C** clinical trials in a standardised manner in the case report form (CRF). In exceptional cases the sponsor can exempt specific adverse events, which are non-critical regarding the safety evaluation, from documentation. In **Category B** clinical trials, non-serious AEs must be documented in a standardized manner in the CRF, if this is defined in the protocol as being critical regarding safety evaluation or was requested by the authorities responsible for authorisation. For clinical trials of **Category A**, there is no obligation to document non-serious AEs in the CRF, unless differently specified in the protocol.

5.1.2. Documentation of SAEs

IMP/ATMP studies:

In clinical trials investigating medicinal products (IMPs, ATMPs) of any category the Investigator must document SAEs in a standardised manner in the CRF.

Other clinical trials:

In "other clinical trials" investigating medical interventions the Investigator must document only those SAEs, which are causally related to the trial-specific intervention, in a standardised manner in the CRF.

Responsibility	Procedure
Sponsor	Give definitions of what constitutes an AE or exemptions thereof in the protocol, as applicable.
Sponsor	Train Investigators on the handling of (S)AEs before the start of the trial.
Sponsor	Set up a quality system for safety management in a clinical trial by providing structures and written study specific documents. Ensure that the necessary quality standards are observed in every step of AE documentation, data collection, validation, evaluation, archiving and reporting.
Investigator	During the informed consent procedure, inform the study subject (resp. legal representative) to report all changes in health condition, which occur during the trial including follow-up periods, as applicable.

Responsibility	Procedure
Investigator	Document all data and information regarding (S)AEs in the source documents and on the (S)AE page of the CRF, as applicable. Ensure that all other members of the study team report to the Investigator any (S)AEs they are informed about by the study subject (resp. legal representative).
Sponsor	Keep detailed records of all (S)AEs reported by the Investigators and make regular updates, as applicable.

5.2. Assessment of AEs/SAEs

All identified and documented (S)AEs occurring in clinical trials have to be assessed. The assessment includes considerations about severity, seriousness, causal relationship to the medicinal product resp. medical intervention (relatedness) as well as expectedness (if applicable).

The Sponsor and the Investigator make the maximum effort to assess the event and collect as much information as possible.

Responsibility	Procedure
Investigator	Clinically assess the event and provide the subject with appropriate medical care according to the information gathered. The assessment includes severity, seriousness and causality of the event to the applied intervention.
Investigator	Classify the AE as serious, if it fits one or more of the respective criteria for SAE outlined in the protocol according to the definitions.
Investigator	Evaluate whether the (S)AE has a causal relationship to the applied study intervention.
Investigator	For each reportable SAE fill in the respective SAE Report Form and report the SAE to the Sponsor.
Sponsor	Check SAE Report Forms provided by Investigator for completeness and accuracy on the day of receipt. If any essential information is missing contact the Investigator immediately and ask for the outstanding information.
Sponsor	Evaluate all reported (S)AEs with respect to "causality" and identify serious adverse drug reactions (SADRs).
Sponsor	Evaluate all related (S)AEs with respect to "expectedness". Classify an SAE as "unexpected" if, by nature or intensity, it is not listed in the reference documents (e.g. Investigator's Brochure or summary of product characteristics).

The assessment of causal relationship by the Sponsor must be performed and documented in addition to the causality assessment by the Investigator. The Sponsor must not downgrade the Investigator's assessment. In case of disagreement with the Investigator's causality assessment, both assessments must be recorded in the study documents and mentioned in the reports to IEC and CA.

5.3. SUSARs/SADRs in Clinical Trials with IMPs/ATMPs

The "serious" plus "related" nature of an event defines a SADR, which has to be reported in clinical trials with IMPs or ATMPs urgently within predefined timelines to IEC and CA.

The "serious" plus "related" plus "unexpected" nature of an event defines a SUSAR in clinical trials with IMPs/ATMPs.

Responsibility	Procedure
Sponsor	Identify SAEs which are related to the IMP/ATMP and fill in a respective report form (if applicable).
Sponsor	Identify SAEs, which qualify as SUSAR, and fill in a CIOMS Form and report the SUSAR according to Swissmedic BW101_20_002_MB - Merkblatt and BW101_10_003_MB - Merkblatt.

Responsibility	Procedure
Sponsor	Break the blinding of treatment code for individual SUSAR before reporting a SUSAR to IEC and CA (no SUSAR, if treatment with placebo).
Sponsor	In multi-center studies, the sponsor should inform all investigators about any SUSAR occurring during the conduct of a clinical trial.

5.4. Reporting of individual SAEs to IEC and CA

Reporting of individual SAEs (SADRs, SUSARs, as applicable) should be done according to Swiss law and the corresponding documents by swissethics and CAs as applicable.

All details regarding safety reporting have to be defined in the study protocol.

5.5. Summary reporting of Safety Data

For clinical trials according to ClinO, a safety summary must be submitted to the responsible IEC and the CA once a year by means of a Safety and General Trial Progress Report.

Within one year after conclusion or premature end of the clinical trial, a final study report including all safety results has to be provided to the responsible IEC and the appropriate CA (Swissmedic or FOPH).

In studies with radiation, a final study report including the estimated final radiation dose must be sent to the FOPH by the Investigator except for studies investigating routine nuclear radiopharmaceuticals (Document *Studien mit Radiopharmazeutika und radioaktiv markierten Stoffen* (DMSUSZ-1824642429-1213)).

Responsibility	Procedure
Sponsor	Once per year compile a summary safety and general trial progress report including intensity and causality of the relevant events and send it to CA (if applicable), starting one year after study approval, including a list of all SAEs and SUSARs as well as a critical summary of the IMP's resp. medical intervention's safety profile. In international multi-center studies also events outside of Switzerland have to be included in the safety and general trial progress report. Additionally, send the safety and trial progress report to all responsible Investigators of all study sites.
Investigator	Once per year, send the safety and trial progress report compiled by the Sponsor to the responsible IECs, starting one year after study approval and inform the IEC about the general progress in the study.

5.6. SAE Management in multinational clinical trials

This document describes details regarding management and reporting of SAEs occurring within Switzerland. In case of multinational clinical trials SAE reporting needs to be done according to the respective national laws and regulations.

ATMP studies:

All cases of death, SUSARs and SADRs within and outside Switzerland have to be reported to appropriate CA (BW315_00_961_Swissmedic information sheet).