Information sheet
Safety Reporting in clinical trials

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1 Notification of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring with medicinal products in clinical trials of categories B and C (Art. 41 of the Ordinance on Clinical Trials in Human Research (ClinO, SR 810.305)

All Suspected Unexpected Serious Adverse Reactions (SUSARs), occurring in the framework of clinical trials of categories B and C at Swiss trial centres, must be reported to Swissmedic. Please note, that all three criteria (serious + related + unexpected based on the reference safety information) must be fulfilled for an adverse reaction to qualify as a SUSAR.

In addition to a fully completed submission form, the notification must contain the CIOMS form where the following information must be included:

- Trial subject identification code, gender and age/year of birth, details of the suspected trial medication (including the active pharmaceutical ingredient, indication, dosage and route of administration), beginning and end of treatment of the suspected trial medication, listing of concomitant medication(s) and concomitant diseases/medical history.

- The event must be described in sufficient details. This means, that in addition to body site and kind of adverse reaction, it is necessary to include information regarding degree of severity, its evolution over time, information on treatment interruption, treatment discontinuation, rechallenge (reduced or same dose), outcome.

- The assessment of the potential causal relationship between adverse reaction and medicinal product must be provided by investigator and sponsor, as well as the one on unexpectedness. For that purpose, the respective versions of the Investigator's Brochure or Product Information/ Summary of Product Characteristics for IMPs with a marketing authorisation defined as the primary Reference Safety Information (RSI) in the clinical trial application must be used as reference documents. Updates of these documents can be used as RSI if they have been approved by Swissmedic (substantial modifications). In particular, reference should be made to adverse drug reactions (ADR) that have already been documented for the corresponding system of organ class (SOC).

- All SUSARs from Swiss sites need also to be part of the Annual List of Events and Deficiencies or the Development Safety Update Report (Art. 43 para. 1 ClinO) of the respective reporting period.

For notifications relating to **blinded trials**, the treatment of the trial subject suffering from the SUSAR should be unblinded.

Important:

- Comparators and placebos administered in clinical trials are IMPs (independent of their registration status). Therefore, SUSARs associated with a comparator product or a placebo follow the same reporting requirements as the test IMP. Furthermore, events associated with placebo would usually not satisfy the criteria for a SUSAR and therefore for expedited reporting. However, in the rare cases, where SUSARs are associated with placebo (e.g. reaction due to an excipient or impurity), the sponsor should report such cases.
  After initial report of a SUSAR, follow-up reports (FUP) should only be submitted if they influence the causality assessment. Submitted follow-ups for SUSARs without influence on causality will not be processed.

- Death as follow-up to an initial non-fatal SUSAR should be reported as new initial SUSAR.

- SUSARs associated with unauthorized Auxillariary Medicinal Products (AxMPs) in Switzerland or with AxMPs authorized in Switzerland but coming from a market outside of Switzerland should be submitted as it is done with IMPs.

- For clinical trials of category A. i.e. with products marketed in Switzerland used according to the marketing authorisation, the sponsor is subject to the notification requirements specified in Article 59 paragraphs 1 and 2 of the Therapeutic Product Act (TPA, SR 812.21). These reports must be sent to Swissmedic Drug Safety Department. Same is true for SUSARs from authorized auxiliary medicinal products (AxMPs) used in category B and C studies, which are authorized in Switzerland, taken from the Swiss market and are used according to the local label.

- SUSAR notification is mandatory also if the investigator (or the sponsor) becomes aware of a suspected case after the clinical trial was completed and the suspected case occurred during or after the clinical trial was completed (Art. 41 para. 4bis ClinO).

Please do not send the following:

- Reports that do not fulfil the criteria stated in the SUSAR definition.
- Follow-up reports of SUSARs that do not influence the causality assessment.
- Individual SUSAR reports occurred in patients enrolled outside of Switzerland. These should be submitted with the Annual List of Events and Deficiencies or the Development Safety Update Report.
- Periodic lists or tables of SUSARs and/or SAEs. Lists/tables must be sent only with Annual List of Events and Deficiencies or the Development Safety Update Report.
- Copies of case report forms (CRFs) instead of CIOMS forms.

Submission Process of SUSARs:
SUSARs have to be submitted according to the general submission process.
For information on the submission please read the following sections of our Guideline BW101_10_003e_AA_Guideline_Amendments_Clinical_Trials. See on our wep page:

Home > Human medicines > Clinical trials > Clinical trials on medicinal products> Submission of changes during the clinical trial and reporting (LINK)
Follow > Guidelines for submission of changes during the trial > **Guidelines for submission of changes during the trial**:

- Section **1. In general**
- Section **2. Folder structure for submissions**
- Section **3.4 SUSARs**

Address for SUSAR notifications
To be submitted electronically and as of 01.01.2022 you have the option to minimize the previously required paper submission of your application by using the form "Confirmation electronic submission" as from below link:.
BW101_10_019e_FO Confirmation electronic submission (AM_KlinV)(AM_KlinV) (DOC, 182 kB, 11.11.2021)

This form allows sponsors/applicants to confirm for every submission that they agree to Swissmedic processing the application using the documents provided on CD/DVD.
Please send us the handwritten ("wet-ink") signed paper document ("Confirmation electronic submission") together with the CD/DVD. No other paper documents are required for this submission.
For each additional submission of application documents on CD/DVD (e.g. in connection with a response to formal deficiencies, etc.), this form must be prepared again and submitted with the CD/DVD.

If you have technical questions about the submission, please send them to:
esubmission@swissmedic.ch

Form: Please include the CIOMS form (.pdf) together with the completed Submission Form.
If you have to submit a follow-up report for a SUSAR, please mention the service order number of the initial SUSAR (included in the acknowledgment of receipt of the initial SUSAR) in the FO submission form in the available field (SA-Number).

Timelines (Art. 41, par. 4, ClinO)**:**

- Fatal and life-threatening SUSARs: Initial notification within 7 days, follow-up report within 8 days after initial notification (even if no influence on causality assessment), in cases where the initial notification is incomplete (e.g. narrative is incomplete).
- Other SUSAR events: Initial notification within 15 days.

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2 Notification of safety measures in clinical trials of categories B and C (Art. 37, par. 3, ClinO)

The most important tool for monitoring the safety of trial subjects is the immediate reporting, by the sponsor, of new events that could put the safety of trial participants at risk, taking both national and international data into account.

- All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures must be reported (e.g. a Dear Investigator Letter)
- The report must contain all the information in the form of a precise, critical summary, indicating the measures taken to minimise the risk.
- In case the urgent safety measure (USM) is based on a report of the minutes of the safety monitoring board (or similar), this document has to be submtted
- The report must be clearly highlighted as an important safety information and sent separately from the Annual List of Events and Deficiencies/DSUR.
- According to Art. 44 of ClinO regarding radiation protection for category B and C clinical trials with therapeutic products that emit ionising radiation, the sponsor shall notify Swissmedic within seven working days, if the permitted radiation dose guidance value is exceeded at any time.

Submission Process of safety measures in clinical trials:
Safety measures in clinical trials have to be submitted according to the general submission process. For information on the submission please read the following sections of our Guideline BW101_10_003e_AA_Guideline_Amendments_Clinical_Trials. See on our wep page:

Home > Human medicines > Clinical trials > Clinical trials on medicinal products> Submission of changes during the clinical trial and reporting (LINK)
Follow > Guidelines for submission of changes during the trial > **Guidelines for submission of changes during the trial**:

- Section **1. In general**
- Section **2. Folder structure for submissions**
- Section **3.2 Reporting to a running trial according to chapters 4.8 - 4.12 of this document**
- Section **4.9 Safety reporting in clinical trials of the categories B and C (Art. 37 ClinO)**

Timelines: Immediately following the occurrence of the circumstances that constitute a safety risk.

Address:

To be submitted electronically and as of 01.01.2022, you have the option to minimize the previously required paper submission of your application by using the form "Confirmation electronic submission" as from below link:
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Please send us the handwritten ("wet-ink") signed paper document ("Confirmation electronic submission") together with the CD/DVD. No other paper documents are required for this submission. For each additional submission of application documents on CD/DVD (e.g. in connection with a response to formal deficiencies, etc.), this form must be prepared again and submitted with the CD/DVD.

If you have technical questions about the submission, please send them to:
esubmission@swissmedic.ch

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3 Annual List of Events and Deficiencies or the Development Safety Update Report (Art. 43 para. 1 ClinO) for clinical trials of categories B and C (Art. 43 para. 3 ClinO)

The Annual List of Events and Deficiencies or the Development Safety Update Report are summaries of the current status of knowledge of the clinical investigation or of the development program with the specific investigation medicinal product (IMP) and describes the general progress of the clinical trial and new safety issues, identified and potential risks of active substances/medicinal products during clinical trials that could have an impact on the protection of clinical trial subjects (Art. 43 para. 1 ClinO).

The report may concern a single trial or several trials with the same IMP. In such a case the individual trials must be clearly identifiable.
Separate DSURs/ Annual List of Events and Deficiencies have to be submitted for each IMP. Alternatively, one Annual List of Events and Deficiencies / DSUR focusing on the combination treatment can be submitted instead. Trial-specific safety and progress reports can be submitted as well, where the safety updates about the trial are summarized (used in case the sponsor is not the manufacturer of the IMP).

In accordance with Art. 43, par. 3, ClinO, the Annual List of Events and Deficiencies/DSUR must be submitted for every clinical trial of categories B and C carried out in Switzerland.

The Annual List of Events and Deficiencies/DSUR is submitted once a year, from the date of study approval in Switzerland and throughout the duration of the clinical trial in Switzerland. The last Annual List of Events and Deficiencies/DSUR to be submitted must cover the Last Patient Last Visit (LPLV) in Switzerland for that specific trial. There is no need for further ASR/DSUR submissions after LPLV since the information on safety will be captured in the clinical study report.

The following details must be included in the Annual List of Events and Deficiencies /DSUR: report no. (consecutive numbering), product name, clinical trial code, time period covered by the report, date of the report, list of events or adverse reactions (including SUSARs), name and address of the sponsor.

The following information should be filled in the section List of Annual Events and Deficiencies /DSUR of the FO submission form, when sending the annual safety report:

- New SUSARs that have occurred in patients enrolled at clinical trial sites in Switzerland in the time period under review. Please include the service order number under SUSAR identification Number. The service order number is mentioned in the acknowledgment of receipt of the initial SUSAR, the reference number of the trial and the date of the CIOMS report.
- An updated statement from the Sponsor on the benefit/risk ratio of the trial in light of the new safety data collected over the reporting period

Submission Process of Annual List of Events and Deficiencies, Development Safety Update Reports (DSUR):
Annual List of Events and Deficiencies / DSURs for clinical trials have to be submitted according to the general submission process.
For information on the submission please read the following sections of our Guideline BW101_10_003e_AA_Guideline_Amendments_Clinical_Trials. See on our wep page:
Home > Human medicines > Clinical trials > Clinical trials on medicinal products> Submission of changes during the clinical trial and reporting (LINK)
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- Section **3.2 Reporting to a running trial according to chapters 4.8 - 4.12 of this document**

Form: Formats similar to DSUR (Development Safety Update Report), PSUR (Periodic Safety Update Report) / PBRER (Periodic Benefit Risk Evaluation Report), or Annual List of Events and Deficiencies according to Art. 43, par. 1, ClinO are accepted.

DSURs must comply with ICH E2F.
For Investigator initiated trials (IITs), the template “Annual List of Events and Deficiencies” published by swissethics may be used (www.swissethics.ch).

Please send the complete report, including the executive summary.

Timelines: The reference date for the Annual List of Events and Deficiencies/DSUR submission may differ from the authorisation date of the trial in Switzerland. If the clinical trial has started earlier in Switzerland than in the EU, the overall duration of the trial must be covered in the first annual safety report.

Address:
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esubmission@swissmedic.ch

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4 Information

Contact details:

Swissmedic
Swiss Agency for Therapeutic Products
Clinical Trials Division
Hallerstrasse 7
P.O. Box
3012 Bern

For any information please contact us:

Tel.: +41 58 462 03 87
E-mail: ct.medicinalproducts@swissmedic.ch

Change history

Version	Valid and binding as of:	Change	sig
18.0	01.11.2024	Updates associated with the revision of ordinances relating to the Human Research Act: new timeline included for the submission of life-threatening SUSARs and notification of SUSARs after completion of a clinical trial; Additional changes: new title in order to better describe the content of this guideline; updates in the submission procedure of SUSAR, USM and Annual List of Events and Deficiencies/DSUR and updates related to a new version of the submission form released on 01 November 2024	cac
17.0	09.09.2022	Minor corrections in V16.0	sec
16.0	07.07.2022	Alignment to the SAP related changes and to the new submission form introduced on 13.09.2022	sec/gav
15.0	15.02.2022	New esubmission guideline	sec
14.0	01.01.2022	Update to way of documents submission only by CD/DVD	sec
13.0	13.09.2021	Updates in line with upcoming new procedures for submission	sec
12.0	14.02.2020	Reporting of SUSARs associated with AxMPs, safety reporting for radiation protection in case of exceeding dose	sec
11.3		New layout, no content adjustments to the previous version	tsj
11.0	15.03.2019	Reporting of SUSARs associated with Placebo added	
10.0	10.10.2017	Addition of table of content / Clarification of submission requirements for ASR/DSUR and notification of safety measures / Availability of document in English only	sec
9.0	15.12.2016	Precisions concerning the ASR	jaf
8.0	21.11.2016	New QM ident: BW101_20_002e_MB Old QM ident: BW101_22_001e_MB The remaining content of the document was not reviewed and stays unchanged.	wkn
7.0	31.05.2016	Clarification of Reference Safety Information (RSI) Further clarification of safety reporting modalities	sec
6.0	05.05.2015	Clarification of submission modalities and format of SUSAR	sec
	17.09.2014	Demarcation between SAE and SAR, clarification SUSAR number	aju
	31.07.2014	New change history inserted in the document	wis