swissmedic

Information sheet
Mandatory reporting of adverse reactions during a clinical trial with ATMPs, other products (bacteriophages, etc.) and procedures

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1 Definitions and abbreviations

1.1 Definitions

Advanced therapy medicinal products (ATMPs)

Advanced therapy medicinal products (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; SR 814.91) and Article 3 paragraph 1 letter d of the Release Ordinance (RO; SR 814.911). 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).

According to Art. 3 let. b of the Release Ordinance (RO), biologically active genetic materials containing DNA and RNA are equivalent to microorganisms, but are not necessarily regarded as microorganisms. To take this legal environment into account and enable the application of a risk-based approach, the term ATMPs also refers to products with which genetic information is introduced into somatic cells, such as oligonucleotides, vectors, mRNA (including vaccines) and antisense RNA (asRNA). If ATMPs are released into the environment, the FOEN, SECB and FOPH must be notified and/or involved in accordance with Art. 81 TPO and Art. 43 RO.

This information sheet also applies to products and procedures such as autologous transplants and other therapies such as bacteriophages, blood and pathogen inactivation procedures and procedures for non-standardisable medicinal products and transplant products that do not meet the definition of an ATMP but employ similar processes.

1.2 Abbreviations

ASR	Annual Safety Report
ATMP	Advanced Therapy Medicinal Products

DSUR	Development Safety Update Report
GT	Gene therapy
GMO	Genetically modified organism
OOS	Out of Specification
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TpP	Transplant product

2 Introduction and objective

For the ATMP clinical trials, in accordance with Art. 21 and 22 ClinO, the provisions concerning clinical trials of medicinal products apply analogously.

This information sheet outlines the reporting obligations of investigators and sponsors during a clinical trial with ATMPs: reporting adverse events (according to Art. 41 ClinO) and urgent safety measures (according to Art. 37 para. 1 and 3 ClinO), and submission of annual safety reports (according to Art. 43 ClinO).

3 Legal basis

Switzerland

- Clinical Trials Ordinance (ClinO; SR 810.305)
- Gene Technology Act (GTA; SR 814.91)
- Medicinal Products Licensing Ordinance (MPLO; SR 812.212.1)
- Release Ordinance (RO; SR 814.911)
- Therapeutic Products Act (TPA; SR 812.21)
- Therapeutic Products Ordinance (TPO; SR 812.212.21)
- Transplantation Act (SR 810.21)
- Transplantation Ordinance (SR 810.211)

International

- EU Regulation 1394/2007 on Advanced Therapy Medicinal Products
- Eudralex Volume 4, Part IV, GMP requirements for ATMP of 22 November 2017
- ICH E2A Clinical safety data management: definitions and standards for expedited reporting - Scientific guideline
- ICH Guideline E2F on development safety update report Good Case Management Practice (CIOMS V)

4 Reporting of deaths, SUSAR and SADR with an administered ATMP during a clinical trial with ATMP

In accordance with Art. 41 para.4 ClinO, all unexpected and serious adverse reactions identified in Switzerland with a suspected link to the ATMP administered, so-called **S**uspected **U**nexpected **S**erious **A**dverse **R**eactions (SUSARs) must be reported to Swissmedic.

Due to the innovative nature and lack of experience with ATMPs, the sponsor, in accordance with Art. 41 para. 4 ClinO, must also report all **S**erious **A**dverse **E**vents (SAEs) that have a suspected link to the ATMP administered (so-called **S**erious **A**dverse **D**rug **R**eactions – SADRs) to Swissmedic

In addition, all cases of death that occur during the clinical trial in Switzerland must be reported to Swissmedic.

The report includes severe adverse drug reactions or events that could not only be linked to the ATMP itself but also to the following aspects:

- Serious events during the donation or during the preparation for the donation (including events that occur in connection with the administration of medicinal products that are given to a patient in view of an upcoming donation);
- Suspected viral, bacterial or other contamination from the ATMP;
- Serious events during the administration of a ATMP (e.g. during surgery for which the application of a transplant product is necessary, or an injection);
- Serious events that could be linked to a quality defect in the ATMP or its components (preservatives, media, viral vectors, etc.) or in the medical device or matrices that are components of the product;
- Exceptional Release of an ATMP «Out of Specification» (OOS) batch (*Guideline on Good Manufacturing Practice for Advanced Therapy Medicinal Products as a new Part IV of EudraLex Volume 4*).
- Release into the environment, transmission to other persons or animals of a medicinal product that consist of genetically modified organisms (GMO) or contain GMO.

Swissmedic reserves the right to also require the above reports from other countries in certain cases.

Notification timelines

Cases of death and SUSARs: Within 7 days for SUSARs leading to death or that are life-threatening and within 15 days for other events for which reporting is mandatory (Art. 41 para. 2 and 4 ClinO).

SADRs: Within 15 days.

Notification route

All reports must be submitted using the CIOMS form and / or the form "BW315_00_960e_FO Form Adverse Reaction Report CT ATMP" (own forms with comparable information are accepted). Additional information should be submitted as an accompanying letter.

All documents have to be sent via email using the **Filetransfer Service (FTS)**. To be able to use this service, please contact biovigilance@swissmedic.ch.

The documents must contain at least the following information:

- Name of the ATMP with composition, trial code, Swissmedic reference number, trial number (and country if report is from abroad);
- Details of the trial product (information regarding dose, rate of administration, duration of administration and dates of administration);
- Patient details (age, sex, medical history);
- For reports on SUSARs, unblinded data should be provided;

- Source of report, precise description of the SUSAR or SADR and its progression (date of event, symptoms, most important clinical signs, details on the degree of severity, chronology, and possibly details of dechallenges / rechallenges and outcome);
- Details on co-medications (including beginning and end of treatment);
- Analysis of the causal link between the event and the ATMP.

5 Reporting of urgent safety measures from clinical trials with ATMPs

Swissmedic must be informed immediately of current safety risks in order to guarantee the safety of the trial subjects (Art. 37 para. 1 and 3 ClinO).

Taking into account national and international data, the report must contain the following:

- Name of the ATMP with composition, trial code, Swissmedic reference number;
- All suspected new risks plus relevant new aspects of known adverse reactions that require measures relevant to safety;
- Source of report, precise description of the risks and of the measures taken.

The report must be submitted electronically and must include a critical, summarised assessment of the risk mitigation measures implemented.

The report must be separate from the annual safety report (ASR) and marked as urgent safety information.

Notification timelines

Swissmedic must be notified of the safety measures immediately, within 7 days at the latest.

Safety Signals must be submitted without delay once the circumstances that constitute a safety risk have occurred.

Notification route

Notifications of urgent safety measures must be submitted via Swissmedic Submissions/Portal using form “FO submission form”, see Applications for clinical trials for medicinal products (swissmedic.ch).

6 Submission of the annual safety report (ASR)

In accordance with Art. 43 ClinO the Sponsor is obliged to submit an **A**nnual **S**afety **R**eport (ASR) or **D**evelopment **S**afety **U**pdate **R**eport (DSUR). The report is a summary of the current status of knowledge and handling of identified and potential risks in relation to ATMPs in clinical trials.
The safety report should comply with ICH Guideline E2F and must include at least the following information:

- Name of the ATMP with composition, trial code, Swissmedic reference number (for national studies);
- Time period covered by the report;
- Accompanying letter or in the form with summary and the following information, if not evident in the report: status of the clinical trial in Switzerland and abroad (number of centres, number

of patients recruited/drop outs/completed, number of SAEs/SADRs/SUSARs/NSADR in Switzerland and abroad);

- Critical summary of the safety profile of the ATMP and new, relevant safety aspects and their effect on the clinical trial (including details regarding exposure);
- Table showing all serious adverse events (incl. SUSARs and quality defects) in Switzerland and abroad. The information presented should be as comprehensive as possible, and contain data on treatment groups and comparator groups. In the case of international multi-centre trials, the data on patients treated in Switzerland should also be presented separately;
- Additionally, for trials with healthy volunteers, tables showing **all** AE's occurring in Switzerland and abroad.

Notification timelines

The report must be submitted to Swissmedic once a year. Each report should cover 12 months of an ongoing clinical trial.

Notification route

Safety reports must be submitted via Swissmedic Submissions/Portal using form "FO submission form", see Applications for clinical trials for medicinal products (swissmedic.ch).

Change history

Version	Change	sig
6.0	Content updated, new reporting routes	pad
5.0	Transfer ATM processes in the area of authorisations New ID number assigned Formal adjustments, new layout	dei