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1 Objective

Medical devices, accessories for medical devices, and devices without a medical purpose listed in Annex I of the MedDO are referred to as 'medical devices' in this information sheet. This information sheet is valid under the new regulation that came into force on 26 Mai 2021 and it is intended for sponsors of clinical investigations of devices, contract research organisations (CROs), and investigators. It provides guidance on the authorisation process, reporting requirements of sponsors, and the surveillance of clinical investigations by the Swiss Agency for Therapeutic Products, Swissmedic.

This document does not cover performance studies with IVDs or clinical trials of medicinal products. For performance studies, please refer to information sheet BW600_00_0016_MB. For clinical trials with medicinal products, please refer to www.swissmedic.ch > Human medicines > Clinical trials on medicinal products.

2 Introduction

The Swiss Human Research Act (HRA, SR 810.30) regulates biomedical research on human subjects and is based on internationally recognised principles. It shall in particular ensure that

- the investigational medical device must demonstrate a sufficient stage of development for its intended use on humans.
- the investigation must satisfy scientific and ethical criteria
- the dignity, personality and health of human subjects must be protected.

Medical devices include, for example, implants, therapeutic devices, diagnostic devices for use on patients and other products[1], but neither medicinal products nor transplant products with living cells.

3 Legal basis, standards, and guidances

The information in this document is in summarised form. For that reason, please consult the valid legal texts, standards and guidelines in order to appraise a specific situation.

a) Legal texts

The following legal texts describe requirements applicable to clinical investigations of medical devices in Switzerland:

- HRA: Swiss Federal Act on Research involving Human Beings (Human Research Act; SR 810.30)
- TPA: Swiss Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act; SR 812.21)
- ClinO-MD: Swiss Ordinance on Clinical Trials with Medical Devices (SR 810.306).

These texts extensively refer to European requirements [Regulation (EU) 2017/745 on medical devices (the European Medical Device Regulation, MDR)]. For selected aspects, they also refer to requirements of the Swiss Ordinance on Clinical Trials in Human Research (ClinO; SR 810.305), the Swiss Ordinance on Organisational Aspects of the Human Research Act (HRA Organisation Ordinance, OrgO-HRA; SR 810.308), and the Swiss Ordinance on Medical Devices (MedDO; SR 812.213).

You can find Swiss legal texts in German, French and Italian together with English translations at www.fedlex.ch. As English is not an official language of the Swiss Confederation, English translations of legal texts are for information purposes only and have no legal force.

b) Guidance documents, templates, international conventions

- Swiss documents:

[1] Definition of the term medical devices: Art. 4 para.1 let. 1b Federal Act on Medicinal Product and Medical Devices (SR 812.21), Art. 1 Medical Devices Ordinance (SR 812.213)

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  - Guidance and templates published by Swissmedic: www.swissmedic.ch/ci.
  - Guidance and templates published by cantonal ethics committees: www.swissethics.ch.
- European documents:
  - Guidance under the MDR, including guidance document MDCG 2020-10/1 (Safety reporting in clinical investigations of medical devices), guidance document MDCG 2020-10/2 (Summary safety report form) are published at ec.europa.eu/health/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en.
- Standards:
  - ISO 14155, Clinical investigation of medical devices for human subjects – Good Clinical Practice
  - Other standards that reflect the status of science and technology with regard to the development and manufacturing of medical devices
- International conventions: Declaration of Helsinki, Biomedicine Convention, Additional Protocol by the Council of Europe to the Biomedicine Convention, CIOMs Guidelines, etc.

4 ISO 14155 standard

Art. 3 to 5 ClinO-MD, Chapters 2 and 4 ClinO-MD; Art. 72 and Annex XV of Regulation (EU) 2017/745

The ISO 14155 standard describes *'principles of good clinical practice in the field of clinical investigations of devices'*. For example, it defines internationally recognised terms, describes the content of the necessary documents and the obligations of involved persons.

For clinical investigations involving particularly low risks, certain deviations are possible, particularly for post-market trials. However, the protection of the participants and data quality and security must not be affected by such deviations.

The sponsor is required to address compliance to the standard and disclose any deviations from the standard in the following documents: *Clinical investigation plan'* (CIP)[2], *'list of standards'* [3], *Swissmedic authorisation application form*.

5 Authorisation of clinical investigations with medical devices

5.1 Trial categories and responsible authorities

Arts. 2, 6-7, 16-18, 21, 33-34, 38-39, 42, 49 and Annexes 1-5 ClinO-MD

In case of doubt contact the cantonal ethics committee, which in Switzerland is the responsible entity for the delimitation and of research projects.

a) Terms and definitions

- 'Clinical trial' in Swiss legal texts is an umbrella term used for clinical investigations with medical devices, performance studies with IVD, clinical trials of medicinal products, and clinical trials conducted with other interventions (e.g. surgical interventions, other therapies).
- A clinical investigation with a medical device is any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.
  Devices without a medical purpose listed in Annex XVI of the MDR and Annex I MedDO also fall under the clinical investigations regulations. Examples include contact lenses, other products introduced into or onto the eye, products totally or partially introduced surgically into the body (except tattooing products and piercings), fillers, devices for liposuction, lipolysis or lipoplasty, high intensity lasers and intense pulsed light, brain stimulation equipment.

[2] Expected contents of a CIP are listed in Annex XV of the MDR, and in the Annex to EN ISO 14155.

[3] A template for the list of standards is available in guidance document MDCG 2021-8 under 'Checklist of general safety and performance requirements, standards, common specifications and scientific advice'.

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In order to establish whether your research project is a clinical investigation of a medical device, you should check whether you are developing a device for a purpose listed in art. 3 of the MDO, whether the device or its output (e.g. the output of a software) will be applied to human subjects as part of the project, whether the investigation is systematic[4], and whether you will investigate performance and/or safety aspects.

The following aspects are not relevant for the delimitation of research projects: Whether there will be few or many human subjects, high or low expected risks, prototypes or devices with a mature design, patients treated with the device or volunteers without medical benefits, whether the sponsor intends to place the device on the market.

For example, a feasibility study with healthy students can be a clinical investigation of a medical device, while a retrospective study based on hospital records is not.

b) Applicable procedures

The applicable procedure for approval of a clinical investigation depends on the categorisation.

- Category A clinical investigation
  Such investigations are often termed "post-market". The investigational devices may be placed on the Swiss market (i.e. the CE mark has been obtained) and the devices will be used exclusively as stated in the CE-marked instructions for use. In particular, for example, the relevant indications, contraindication, device settings and precautions must be observed.
  These clinical investigations must be submitted to and authorised by the competent cantonal ethics committee only. In Switzerland, the cantonal ethics committee also decides alone whether it is acceptable to carry out additional procedures that are invasive or burdensome. For your applications, please follow the instructions of the cantonal ethics committee[5].

- Category C clinical investigation
  Such investigations are often termed "pre-market". The medical device bears either a CE-marking but will not be used in accordance with the CE-marked instructions for use (off-label use, Category C1), or is not CE-marked (Category C2), or its placing on the market or use is prohibited in Switzerland (Category C3).
  They can start in Switzerland once the authorisations of the cantonal ethics committee and Swissmedic have been obtained. Applications for authorisation must be transmitted on the same day to both institutions via the respective webportals: eMessage for Swissmedic (see Annex 6), BASEC for ethics committees.
  Before beginning a trial, please ensure that you have received Swissmedic authorisation and fulfilled any conditions stipulated in the letter of authorisation.

In Annex A7 of this information sheet, you can find considerations concerning special groups of products:

- Medical devices that are made to an individual patient's specifications, including patient matched, patient-adapted and custom made medical devices.
- Software
- Therapeutic products with devitalised human tissues or cells
- Radiation sources, ionising radiation, radiation protection
- Combined clinical trials with several types of products
- Products that are combinations
- Examples of combined clinical trials and products that are combinations

[4] Example of non-systematic activities: Disabled persons providing design input for the development of a wheelchair during a workshop. Be aware, however, that it is illegal to supply patients or professionals with non-conforming medical devices for use.

[5] Information available at www.swissethics.ch

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5.2 Applications to Swissmedic for the authorisation of category C clinical investigations

Arts. 16-20 and Annex 1 ClinO-MD; Art. 54 TPA; FeeO-Swissmedic

5.2.1 First submission to Swissmedic of an authorisation application

First submission of an authorisation application
Use the form BW610_10_021e_FO. This form also contains a list of required documents. See Annex A6 for instructions on how to create an eDok and submit an application.

EMDN code for medical devices:

In the authorisation application form, you are required to enter the European Medical Device Nomenclature (EMDN) code applicable to the devices. The EMDN has been published by the European commission and is available free of charge at https://webgate.ec.europa.eu. You can also consult a questions and answers document on EMDN published by the European Commission (*md_q-a_emdn_en_0.pdf*).

Simplified review:

Under the conditions listed in article 17 para. 2 ClinO-MD, you may ask Swissmedic to perform a simplified review of your submission:

a) The clinical investigation falls under category C1 or C2 and concerns the investigation of a non-invasive device classified as risk class I or IIa according to Art. 15 MedDO[6].
b) The use of the investigational device is, at most, associated with minimal risks to the subjects.
c) The investigators have agreed in written form to inform the Sponsor without delay of all serious adverse events or other (new) circumstances that could threaten the safety of subjects or device users according to Art. 32 ClinO-MD (see also sections 7.2.2 and 7.2.3 of this information sheet).
d) The Sponsor has a risk management system in place to monitor safety.

To check if your project meets these conditions and to apply for a simplified review, please complete and submit the form BW610_10_023e_FO in addition to the form BW610_10_021e_FO (active pdf format, some questions will pop up as you fill in the fields).

In case Swissmedic deems the application for a simplified review to be unsubstantiated or unjustified, you will receive a preliminary letter from Swissmedic (explaining that a rejection of the application for simplified review is foreseen, including the reasons). Upon receipt of the preliminary letter, you will have the opportunity to clarify any misunderstandings, submit corrections and missing information. You will also have the option to withdraw the application for simplified review and switch to a regular review of the submission (fees for regular reviews will then be applicable, see below) or the option to withdraw the application for the clinical investigation altogether. Swissmedic will initiate a regular review only after you have submitted a request for a regular review.

Incomplete submissions:

In case of incomplete requests, stringent deadlines will apply for the end of the application. Please make sure you or your deputy will be available for handling requests after the submission.
While the following documents are essential, they are regularly missing in applications, leading to delays. Please make sure you submit the following documents, they need to show the name of the investigational device and identification of exact models and versions that are foreseen in the clinical investigation:

- List of applicable standards and GSPR information, a template for the list and GSPR information is available in guidance document MDCG 2021-8 under 'Checklist of general safety and performance requirements, standards, common specifications and scientific advice'.

[6] Consult the latest revision of the European document MDCG 2021-24 for guidance of classification of medical devices.

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- The statement of the manufacturer according to Annex XV of the MDR, and declaration for access of Swissmedic to additional technical documents during 10 years, or 15 years for implants (dated and signed by the manufacturer).
- For category C clinical investigations of devices that emit ionising radiation, please also submit documents according section 5.4 and Annex 7 of this information sheet.

5.2.2 Validation

A formal check of every new application will be carried out within 10 days to ensure that the clinical investigation falls under the competence of Swissmedic and that documents have been provided as required. Submissions that fail the validation step are considered to be incomplete, and will not be processed by Swissmedic. In such cases, Swissmedic requests you to complete the information/documentation within 10 days. If needed, you may request an extension of up to 20 days.

Swissmedic will acknowledge the successful validation in writing, and inform that the application is proceeding to the content review stage.

Always send additional submissions to Swissmedic and to the ethics committee (on the same day).

5.2.3 Review and authorisation

During and/or after the content review, Swissmedic can ask for additional information. If a positive assessment is possible on the basis of the documentation submitted, Swissmedic will inform you and wait for the decision of the cantonal ethics committee. Swissmedic is only allowed to authorise a clinical investigation after ethics committee approval.

5.2.4 Rejection, restrictions, conditions

If a positive assessment is not possible, you will receive a preliminary decision within 45 days of the validation acknowledgment of the application. The review of the contents by Swissmedic may, in certain cases, take up to 65 days (for first-in-man investigations or manufacturing using a new procedure). The cantonal ethics committee carries out its review independently. Swissmedic and the ethics committee will therefore send separate letters to you.

The two preliminary decision letters (of Swissmedic and of the ethics committee) will list the findings leading to rejection, restrictions or conditions, any missing information that must be provided, references to the current requirements.

Based on the two letters, you can clarify any misunderstandings, submit any missing information, and will also be allowed to correct application documents and resubmit these to Swissmedic and the cantonal ethics committee within approximately 30 calendar days. Please make sure you submit the same information and updated document versions on the same day to both institutions.

You may contact Swissmedic, if necessary, to ask questions regarding the identified shortcomings and discuss required changes. If issues cannot be addressed in due time, you can either request Swissmedic and the ethics committee for an extension of the deadline or retract the application. After a retraction or a rejection, a new submission with corrected documents is possible at any later point in time.

At the end of the authorisation procedure, you will receive letters of decision.

5.2.5 Fees

The flat rate fee for handling an application for the authorisation of a clinical investigation with a medical device is CHF 5000.- (FeeO-Swissmedic) and will be invoiced by Swissmedic. Relevant additional workload caused by shortcomings and corrections will be invoiced at a rate of CHF 200.- per hour.

The flat fee is not applicable to simplified reviews, or in case of withdrawal of an application before review has started. The actual work performed for the simplified review or until withdrawal will be invoiced at an hourly rate of CHF 200.-.

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5.3 Submissions to Swissmedic for combined clinical trials

In combined trials, multiple products can be subject to investigation (medical devices, medicinal products, advanced therapy medicinal products/ transplant products). The requirements for both product types must be fulfilled. You can find detailed information for your submissions in Annex A7.

5.4 Radiation sources, ionising radiation, radiation protection

Additional documents are necessary in case of radiation and Swissmedic will consult with the Federal office of Public Health for radiation protection aspects. You might receive questions from FOPH during the authorisation procure. See Annex 7 for details.

6 Review and surveillance activities by Swissmedic

Art. 54, 54b and 66 TPA; Art. 3 para 1 section f and Art. 17 ClinO-MD; Arts. 46-48 ClinO

In order to authorise category C clinical investigations, Swissmedic checks the status of the fulfilment of General Safety and Performance Requirements (Annex I of Regulation (EU) 2017/745), if the product risks are duly considered in the clinical investigation, and if the product data is in line with current scientific knowledge and correctly indicated in the protocol.

It is mandatory for sponsors of clinical investigations to operate an appropriate quality assurance system and check the following (not a complete list):

- whether all duties have been assigned to specific persons,
- whether written procedures are available and up to date,
- whether the notification duties and authorisation requirements for Switzerland are correctly implemented in the written procedures,
- whether the job descriptions of personnel are complete and up to date,
- whether written contracts are available with external parties,
- the appropriateness of the basic and advanced training of involved personnel.

6.1 Frequent objections

In category C clinical investigations the following aspects have recurrently led to objections. Additional information regarding each of these aspects can be found in the Annex:

- CRF for documentation of adverse events and device deficiencies
- Risk reduction measures
- Handling of mortality, disabilities, patients lost to follow-up
- Inclusion and exclusion criteria, particularly vulnerable persons
- Reflection period when consenting for invasive procedures

6.2 Inspections

Like other authorities in Europe, Swissmedic may carry out inspections. Clinical investigations of all categories, compliance with all requirements, and all companies, institutions and persons involved may be inspected. If necessary, Swissmedic may withdraw or suspend an authorisation that has been granted, or make the continuation of an investigation dependent on additional conditions.

7 Submissions during clinical investigations (notification duties, authorisations)

Sponsors must send spontaneously and without solicitation information to Swissmedic and the ethics committee. The following sections describe duties of the sponsor in regard to Swissmedic. The requirements of cantonal ethics committees are not addressed in this information sheet; please follow the instructions of the cantonal ethics committees.

Fulfilment of statutory reporting duties needs to be organised as part of the sponsor's quality assurance system (see chapter 6 of this information sheet).

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7.1 Category A clinical investigations

Art. 33-39 ClinO-MD; art. 66, para. 4 MedDO; art. 67, para 2 MedDO

7.1.1 Reporting duties to Swissmedic

- Materiovigilance reporting is mandatory for category A clinical investigations of medical devices.
- If the sponsor is the manufacturer of the investigational device or Swiss representative of the manufacturer: According to art. 66 para. 1 to 2a MedDO, the sponsor has to send reportable incidents to Swissmedic. Use the form available at www.swissmedic.ch/swissmedic/en/home/medical-devices/reporting-incidents---fscas/hersteller---inverkehrbringer.html and send it to materiovigilance@swissmedic.ch.
- If the sponsor is not the manufacturer of the investigational device or Swiss representative of the manufacturer: In case of incidents, check whether the event is subject to materiovigilance reporting duties for users (art. 66, para. 4 MedDO). Use the guidance MU680_20_008e_WL for checking reporting duties. If the clinical investigation is conducted in a hospital, you can also ask the materiovigilance contact person of the hospital (art. 67 para. 2 MedDO). The sponsor has to ensure that reportable incidents are sent to Swissmedic. Use the form MU680_20_015d_FO and send it to materiovigilance@swissmedic.ch. The guidance and the form are available at www.swissmedic.ch/swissmedic/en/home/medical-devices/reporting-incidents---fscas/users---operators.html. Additionally, please note that users are legally obliged to inform the suppliers of the devices about serious incidents (art. 66 para. 4 MedDO).

7.1.2 Reporting duties to the ethics committee

- Consult information at www.swissethics.ch for preparing and sending reports to the ethics committee.
- In line with Art. 33 ClinO-MD, report to the ethics committee all serious adverse events (SAE) for which a causal ralationship between the event and the test proceure used in the clinical trial has been ascertained. Use the form BW610_20_023e_FO.
- For safety and protective measures, annual safety reports, and final reports, refer to art. 35 to 37 and Art. 39 ClinO-MD.

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7.2 Category C clinical investigations

Table: Overview of submissions after authorisation of a clinical investigation.

Type of submission	Deadlines
Modifications (Art. 15 and 20 ClinO-MD) - requiring authorisation	Substantial modifications can be submitted anytime. Note: If safety and protective measures are necessary, such as a temporary suspension of product use, they must be taken immediately and notified to Swissmedic and the ethics committee. Modifications can be submitted later on.
- requiring notification	Submit non-substantial modifications to Swissmedic asap. Submit to the ethics committee either together with the next annual safety report or asap according to the document *'Substantial modifications to clinical investigations of medical devices'* [1]
Reportable SAE and device deficiencies (Art. 33 ClinO-MD)	7 days
Safety and protective measures (Art 34, 36 and 38 ClinO-MD) - temporary halt or early termination on safety grounds (Art. 36 and 38 ClinO-MD) - other measures (art. 34 ClinO-MD)	24 hours 2 days
Annual Safety report (Art. 35 and 38 ClinO-MD)	Not later than 1 year after the date of authorisation / the last annual safety report
Interruption and early termination (Art. 36 and 38 OClin-MD) - on safety grounds - not on safety grounds	24 hours[2] 15 days[2]
End of the clinical investigation in Switzerland[3] (Art. 36 ClinO-MD)	15 days
Final report and summary for lay persons (Art. 37 and 38 ClinO-MD) - after regular study end - after interruption or early termination	Within 1 year, exceptions are possible if motivated by scientific reasons[4] Within 3 months
Radiation incident (Art. 39 ClinO-MD, the permissible dose guide value has been exceeded in a subject)	7 days

1 Available at www.swissethics.ch

2: In case of multiple Swiss centres, send the information to all ethics committees involved.

3: Last patient last visit, except if defined otherwise in the CIP.

4: The scientific reasons and the deadline need to be described in the CIP.

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7.2.1 Modifications (amendments)

Art. 15, 20 and 48 ClinO-MD; FeeO-Swissmedic

Modifications require Swissmedic authorisation/notification as well as ethics committee authorisation/notification. Before submitting a modification, please check which documents and what information has already been provided to Swissmedic, which of the documents are affected by modifications, and if the modifications must be considered substantial. You only need to submit documents that are new or have been modified.

For modifications, you need to submit the following documents to Swissmedic:

- A cover letter explaining the reason for the modification.
- Documents affected by the modification, with all modifications compared to the earlier version highlighted in the text. Please only submit the versions with the modifications highlighted/track-changed in the text; clean versions are not required.

a) Modifications that must be submitted for authorisation (substantial modifications)

Submission of modifications requiring authorisation
Use the form BW610_20_021e_FO. See Annex A6 for instructions on how to create an eDok and submit an application.

Modifications that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated in the clinical investigation must be authorised by the ethics committee and Swissmedic before they can be implemented. Substantial modifications notably include the following: design modifications and modifications of product administration or use; modification of safety procedures, additional interim analyses, modification of selection criteria or subject numbers foreseen; new Swiss sites or new principal investigators; changes to a primary or secondary endpoint, mode of measurement of endpoints or other aspects of the design of the clinical investigation with a possible impact on investigation results; changes in the subject information and consent forms; etc.

You can find examples of substantial modifications in the annex of the European guidance document MDCG 2021-6, and in the national guidance document on "Substantial modifications to clinical investigations of medical devices" published at www.swissethics.ch.

According to Art. 48 ClinO-MD, and if a clinical investigation was approved in Switzerland before 26.5.2021 (under the old regulation), you need to ask for a re-categorisation of the project and deliver information according to Art. 4 ClinO-MD when submitting a substantial modification.

Submit the application to Swissmedic and to the ethics committee on the same day. Once a complete documentation has been submitted, it will be reviewed within 38 days. Within 10 days of your submission, you will receive a confirmation of receipt of complete documentation or a request to provide any missing documents. Swissmedic may extend its review period by 7 days if needed.

b) Change of sponsor, issuing of a letter of authorisation for the new sponsor

Submission of a change of sponsor
Use the form BW610_20_021e_FO. See Annex A6 for instructions on how to create an eDok and submit an application.

Submit documents at least 38 days before the scheduled change date.

The following documents should be submitted:

- Cover letter signed by the previous sponsor, date when its activities in the investigation end, explanations about the changes.
- The completed form BW610_10_021e_FO, with all the details of the new sponsor.

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- Modified investigation documents in “Track changes” mode.

c) Modifications subject to notification only

Submission of modifications requiring notification
Use the form BW610_20_021e_FO. See Annex A6 for instructions on how to create an eDok and submit an application.

Modifications that neither fall under a) nor b), must be notified to Swissmedic and will normally lead to no further correspondence. Please be aware that Swissmedic does not issue manual acknowledgements of receipt. Immediately after a submission, you can find two automatic acknowledgements in eMessage (for successful upload and technical validation). See Annex 6 for additional information.

If modifications are found that are subject to approval (instead of notification), Swissmedic will contact you. If this is the case, you will need to stop implementation of the modifications in the study and wait for authorisation. In case of gross errors or repetition, Swissmedic may open surveillance activities and asks you to check your quality assurance system and implement corrective and preventive action (CAPA) to improve submissions.

Fees: The flat rate fee for handling modifications that are subject to authorisation amounts to CHF 1000.- and is invoiced by Swissmedic. Relevant additional workload caused by shortcomings regarding the documentation and corrections will be invoiced at an hourly rate of CHF 200.-.
In case of withdrawal of a modification before review has started, the flat rate fee is not applicable. In this particular case, the work performed until withdrawal will be invoiced at a rate of CHF 200.- per hour. Likewise, in case of change of sponsor requiring authorisation the provided work will be charged to the hourly rate of CHF 200.-.

7.2.2 Safety (risks and safety measures)

Arts. 12 and 15 HRA; Art. 34 and 36.4 ClinO-MD

Submission of new circumstances that could threaten the safety of the subjects, and the corresponding safety and protective measures
Use the form BW610_20_022e_FO. See Annex A6 for instructions on how to create an eDok and submit an application.

A risk mitigation responsibility lies with the sponsor and the clinical investigator. The sponsor and the investigator themselves must take all necessary measures without delay in order to protect the subjects from immediate danger. Expedited reporting to Swissmedic lies in the responsibility of the sponsor.

The reporting deadline is 2 days for measures concerning ongoing investigations and 24 hours for a temporary halt or early termination on safety grounds. The following situations in particular must be reported:

- device deficiencies requiring measures.
- previously underestimated risks, safety-related measures, modifications of the CIP abroad (includes modifications agreed upon with foreign authorities or ethics committees or those imposed by them).
- temporary halt or early termination on safety grounds in Switzerland or abroad.

7.2.3 Serious adverse events (SAEs) and device deficiencies

Art. 4, 12 and 15 HRA; Art. 4, 32 and 33 ClinO-MD and Annex XV chapter III MDR; MDCG 2020-10; sections 3.1, 3.2, 3.45, 6.2, 7.4.3-7.4.4, C.2.4 and Annexes E and F of standard ISO 14155:2020

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a) General considerations

- Sponsors have to fully record adverse events and device deficiencies described in Art. 32 ClinO-MD (or Art. 80 of the MDR) and have a duty of diligence. Notably, they need to be able to quickly identify unexpected situations during category C clinical investigations, including higher than expected frequency or severity of harm, and unexpected types of harm, in order to take appropriate measures and stop undue risks. The sponsor needs to be in a position to temporarily stop device use in the sites and/or take other measures. Swissmedic and ethics committees can request records according Art. 32 ClinO-MD at any time.
- Adverse events (AE) and device deficiencies must be recorded by the investigator on the case report forms (CRFs). For all SAE and for all device deficiencies with an SAE potential[7], please make sure that all data necessary for timely fulfilment of the reporting duty with Swissmedic are collected on the CRFs. You can find examples of templates in Annex 1 of this information sheet.
- For pre-market investigations, CRF concerning SAE and device deficiencies must be sent to the sponsor rapidly, normally within 24 hours to 3 days, and malfunctioning or explanted devices should normally be returned for examination.
- The information needs to be monitored continuously by the sponsor. Queries for incomplete or non-plausible entries need to be issued rapidly. For unexpected SAEs (with regard to type, severity or frequency of harm) and device deficiencies, it may be necessary to take precautionary measures. Typically, device use may need to be temporarily suspended by the investigator and/or the sponsor. During suspension, the sponsor can carry out necessary analyses, check the design of the device, hypotheses for the clinical investigation, or adequateness of investigation procedures with no additional risks to patients. See also section 7.2.2 (measures for safety reasons).

The following events must be reported to Swissmedic within 7 days

- any SAE in Switzerland or abroad that has a causal relationship with the investigational device, the comparator or investigation procedures or where such causal relationship is reasonably possible (i.e. serious and not obviously unrelated to the investigation);
- any device deficiency with an SAE potential noted in Switzerland or abroad;
- any new finding in relation to events above.

To assess whether sending a report is mandatory, it is therefore necessary to clarify whether the issue is serious, and whether a causality with the investigational device or intervention/procedure can be excluded.

In case of a device deficiency that causes several SAE, every single SAE need to be reported separately. Follow-up information concerning the patients also need to be submitted separately.

Seriousness criteria applicable to clinical investigations of medical devices are more stringent than criteria used in clinical practice or those used in clinical trials of medicinal products. Therefore, please make sure

- study personnel are trained accordingly and use medical device criteria only;
- members of events committees or safety monitoring boards are trained accordingly and use medical device criteria only.

b) Is the event an adverse event, is it serious, what is the causal relationship between the event and the device or study procedures, does a device deficiency have potential for causing SAE?

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational

[7] A device deficiency with an SAE potential is a device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate

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device.

Seriousness criteria for adverse events[8] in clinical investigations of medical devices are:

- ☐ death
- ☐ life-threatening illness or injury
- ☐ permanent impairment of a body structure or a body function
- ☐ hospitalisation or prolongation of patient hospitalisation
- ☐ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- ☐ chronic disease
- ☐ foetal distress, foetal death or a congenital physical or mental impairment or birth defect

A planned hospitalisation for a pre-existing condition or a procedure required by the CIP without a serious deterioration in health is not considered to be a serious adverse event.
While continuation of a pre-existing condition is not an 'event', increased severity or clinically relevant progression of a pre-existing disease in a patient need to be documented as adverse events (e.g. increased severity of migraine, clinically relevant worsening of arrhythmia, clinically relevant progression of renal disease, etc.).

The causal relationship of each SAE with investigational devices, comparators and study procedures must be assessed by the investigator and the sponsor. For the causality assessment, the sponsor must take into account the complete data that are available (including the technical documentation, literature, all study sites involved). Four levels of causality are used in Europe in order to correctly describe the causal relationship:
- not related,
- possible,
- probable,
- causal relationship.

Also consult MDCG 2020-10/1 for definitions. Unknown causes (e.g. insufficient data available) must be adjudicated as possibly related.

Causality cannot be ruled out and you must not describe an event as "not related" if for example

- there is insufficient information for causality assessment,
- no other clear cause can be identified, and there is a correlation in time or with the bodily part concerned,
- the investigational device or a procedure could affect the bodily part concerned,
- similar events have already been recorded as side effects or complications with other, similar devices and procedures, or
- user errors are involved, e.g. in case of an injury due to an operating error.

c) Timelines and forms for notifications of sponsors to Swissmedic, forms for sponsors:

- Reportable SAEs and device deficiencies with an SAE potential must be reported to Swissmedic within 7 days.
- For multi-centre studies, submit a table in accordance with the MDCG 2020-10/2 template to clinicaltrials.devices@swissmedic.ch. Complete the Excel table cumulatively over the course of the investigation, and highlight all changes compared with the last version.
- If a reportable SAE or a device deficiency with an SAE potential occur in a Swiss site, please also fill in and submit the following form that contains more detailed information:

Notification of serious adverse events and device deficiencies that occur in Swiss centres

[8] See also MDCG 2020-10/1

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Use the form BW610_20_023e_FO. See Annex A6 for instructions on how to create an eDok and submit an application.

7.2.4 Annual safety report

Art. 35 and 38 ClinO-MD

Submission of the annual safety report
Use the form BW610_20_021e_FO. See Annex A6 for instructions on how to create an eDok and submit an application.

From the date of approval of the clinical investigation, a report must be submitted annually to the cantonal ethics committee and Swissmedic. A typical report includes the following information:

- Data cut-off date up to which study data has been considered in the report, and the reporting period
- Status of recruitments: Current number of subjects worldwide and in Switzerland, duration of the currently existing follow-up observations
- Status of the clinical investigation abroad (countries involved, any study interruptions or early terminations)
- Anticipated serious adverse events: Description, occurrence in the trial arm versus control arm and medical literature, evaluation by the sponsor
- Unanticipated serious adverse events: Causality with the investigational device or a procedure, possible causes
- Any device deficiencies: Includes malfunctions, use errors, inadequacies in the information supplied by the manufacturer including labelling
- Safety-relevant measures taken by the sponsor or imposed by ethics committees or authorities anywhere in the world
- Results from other clinical investigations with the investigational device (if applicable)
- Sponsor's conclusions regarding the safety of the subjects and the continuation of the investigation
- Annex with the cumulative list per cut-off date of reportable serious adverse events and device deficiencies

The report must be up to date, a cut-off date older than 2 months is generally not considered adequate for pre-market clinical investigations. You are allowed to submit annual reports to Swissmedic before the specified deadline, which especially in multinational investigations allows to write and submit a joint annual report for all authorities and ethics committees involved.

7.2.5 Completion, discontinuation, interruption of the investigation

Art. 36 to 39 ClinO-MD

Notification of end, early termination or temporary halt for reasons not related to safety
Use the form BW610_20_021e_FO. See Annex A6 for instructions on how to create an eDok and submit an application.

The sponsor must notify Swissmedic of the end of a clinical investigation within 15 days (as of last patient, last visit). A discontinuation or an interruption of the investigation for reasons not related to safety, and the reasons for this, must also be notified within 15 days.

The final report, with contents in accordance with Annex XV, Art. 77(5) and 77(6) of the MDR ("clinical investigation report" and summary presented in terms understandable to the intended user) must generally be submitted within one year of end. Additional information concerning contents of the report are available in ISO 14155. Guidance regarding the summary of the clinical

investigation report will be published on the website of the European Commission. In case of a temporary halt or early termination, the report is due within 3 months.

For clinical investigations with radioactive sources, and in accordance with Art. 39 ClinO-MD, the final report needs to provide all relevant information concerning radiation protection, including – in particular – a retrospective estimation of the dose to which participating persons have been exposed to. Exemptions to the reporting requirement may be granted on request by the Swiss Federal Office of Public Health.

8 Data retention requirements

Art. 40 ClinO-MD

An archiving period of at least 10 years after the end of the investigation is generally required and is applicable to sponsors and investigators; the period is at least 15 years for implants.

9 Databases used in Switzerland

Availability of a module for clinical investigations in the European database (new EUDAMED IT system) under the MDR is expected in 2023. However, the access of Swissmedic to that database might be postponed. Until further notice, the sponsor has the obligation to submit requests and reports via the Swissmedic portal eMessage, including information about different CIP versions used abroad, or safety measures taken abroad such as study interruptions and early terminations on safety grounds. In Annex 6 you can find information explaining how to make a submission to Swissmedic. BASEC must be used for submissions to cantonal ethics committees.

EUDAMED permits the identification of multinational clinical investigations and the coordination among national surveillance authorities in Europe. EUDAMED is currently a depository for basic data on clinical trials with medical devices and any modifications and national measures and is currently only available to competent authorities. It will be updated according to new requirements introduced by the MDR. Pre-market clinical investigations are assigned a EUDAMED identification number (the so-called EUDAMED CIV-ID). The number is always attributed by the first authority to process a clinical trial application within Europe, and is communicated to the sponsor. If a EUDAMED CIV-ID has already been assigned to your clinical investigation, when submitting an application for authorisation in other countries you need to inform the competent authorities accordingly.

10 Sponsors with registered offices abroad, submissions by third parties

Art. 4 para 3 und Annex 1 Section 2.1 ClinO-MD

Sponsors headquartered in another country must specify an agent that is domiciled or has a place of business in Switzerland as an address for correspondence. Preliminary decisions, official decisions and invoices from Swissmedic are sent to the agent. Legal and natural persons domiciled or headquartered in Switzerland can be specified as agents, e.g. distribution companies, a lawyer or the clinical investigator.

Swissmedic accepts submissions made by

- the sponsor,
- a third party, for example a clinical research organisation. When submitting an authorisation application, list third parties that are authorised to communicate with Swissmedic in the application form.

11 Liability in the case of damage, coverage in the form of insurance

Arts. 19-20 HRA; Arts. 13-14 ClinO; Art. 15 Insurance Oversight Act (Versicherungsaufsichtsgesetz, VAG, SR 961.01) and implementing provisions in the Oversight Ordinance

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An insurance company headquartered in Switzerland or with a branch office in Switzerland can be considered to offer an acceptable coverage as the subjects are able to assert their legal right of direct claim and the associated legal enforcement claims within Switzerland.
The cantonal ethics committee will review the fulfilment of the liability and coverage obligations. Cantonal ethics committees have published information on insurance coverage requirements including templates for insurance policies (see www.swissethics.ch > Templates/Checklists).

12 Penal provisions

Penal provisions in the case of offences and infringements are described in the HRA and the TPA *(Arts. 62-64 HRA; Arts. 86-90 TPA)*.

ANNEX

A1: Recording of adverse events and device deficiencies

Art. 12 and 15 HRA; Art. 32-33 ClinO-MD and statement of the manufacturer according to Annex XV Chapter II Section 4.1 of Regulation (EU) 2017/745; ; MDCG 2020-10; Sections 3.1, 3.2, 3.45, 6.2, 7.4.3-7.4.4, and Annexes C, E and F of standard ISO 14155:2020

The sponsor needs to prepare adequate case report forms (CRF). He receives CRF filled in by the centres and must satisfy risk management requirements and reporting requirements in respect of adverse events and device deficiencies. Boxes 1 to 3 show typical examples of CRF for category C clinical investigations of medical devices.

Box 1: Documentation of occurrence of adverse events and device deficiencies
Texts need to be integrated in the following CRF: procedure CRF, CRF for follow-up visits, unscheduled visits, contacts by phone.

Have there been any adverse events?
☐ *Yes, please fill in an "Adverse events" form.* ☐ *No*

Have any device deficiencies been noted (e.g. malfunctions, use errors, inadequate labelling)?
☐ *Yes, please fill in a "Device deficiency" form.* ☐ *No*

Box 2: Adverse events form

Study title
Name of sponsor

Investigation site: ……...
Subject ID code: ……...
Age of the patient on date of event onset: ……..
Patient gender: ……..
Date the centre became aware of event:
Date of procedure/ First use: ……...
Date of event onset: ……...
Current location of the device: ……..

Type of information
☐ *new event*
☐ *follow-up information*

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Criteria for seriousness

- ☐ *death*
- ☐ *life-threatening illness or injury*
- ☐ *permanent impairment to a body structure or a body function*
- ☐ *led to in-patient hospitalisation or prolongation of existing hospitalisation*
- ☐ *led to a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function*
- ☐ *led to chronic disease*
- ☐ *led to foetal distress, foetal death or a congenital abnormality or birth defect*

Description of event
[blank space for extensive descriptions]

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Action/treatment/patient outcome
[blank space for extensive descriptions]

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Relationship to procedure

- ☐ *not related*
- ☐ *possible / unknown*
- ☐ *probable*
- ☐ *causal relationship*

Relationship to device

- ☐ *not related*
- ☐ *possible / unknown*
- ☐ *probable*
- ☐ *causal relationship*

Expectedness

☐ *Anticipated* ☐ *Unanticipated*

Investigation arm

☐ *Investigation arm* ☐ *Comparator arm*

Outcome

- ☐ *ongoing, medical condition is not stable, please provide updates on a regular basis*
- ☐ *resolved without sequelae, date of event resolution: ……...*
- ☐ *resolved with sequelae, medical condition is stable, date of event resolution: ……...*

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Box 3: Device deficiency form (malfunction, use error, inadequate labelling)

Study title
Name of sponsor

Investigation site: ……...
Subject ID code: ……...
Date the centre became aware of event:
Date of procedure/ First use: ……...
Date of event: ……...
Current location of the device: ……..

Type of information
- ☐ *new deficiency*
- ☐ *follow-up information*

Nature of the problem (tick all that apply)
- ☐ *Malfunction*
- ☐ *Use error*
- ☐ *Inadequate labelling*
- ☐ *Other: ……...*

SAE potential
- ☐ *Led to a serious adverse event. Please complete an Adverse Event CRF.*
- ☐ *Is a Device deficiency that did not lead to an adverse event but could have led to a medical occurrence*
  a) if appropriate action had not been taken
  b) intervention had not occurred, or
  c) circumstances had been less fortunate
- ☐ *None*

Description of the deficiency (occurrence, measures taken, outcome of investigation):
[blank space for extensive descriptions]

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A2: Risk mitigation measures

In line with the stage of clinical development, innovation and the risk potential, the sponsor is obliged to implement risk mitigation measures. Box 4 shows safety measures that need to be considered and, where necessary, included in the clinical investigation plan for pre-market clinical investigations. The aim is to avoid problems, or identify them at an early stage, so that the subjects are not exposed to unnecessary risk. Additional measures may be necessary, depending on the specific project.

Box 4: Safety measures for pre-market clinical investigations

a. Prior training of every user: Possibly with models, animals, cadavers.
b. On-site supervision of every user: Supervision (proctoring) in the first subject/ while using the devices for the first time.
c. Single patient release in first-in-man studies: Define the duration of the follow-up between individual patients. Before you release the next patient, obtain fully monitored data, resolve any queries (AE, SAE, device deficiencies, missing data), evaluate whether the data meet expectations. If necessary carry out additional product tests, improve product design, the IFU, selection procedures, other aspects as needed.
d. Risk-adapted recruitment, interim analyses: Do not expose an unnecessarily large number of subjects. Define phases, e.g. feasibility phase/ pivotal phase. Before each new phase, carry out an interim analysis. Define the data needed for the interim analysis, incl. the minimum required follow-up of subjects who have already been treated. For interim analysis, 100% source data verification and resolution of queries (AE, SAE, device deficiencies, missing data) normally needs to be foreseen.
e. Handling of CRF: Foresee short deadlines for submission of safety relevant data to the sponsor. Readily verify the clarity of descriptions and attributes (serious/not serious, anticipated/unanticipated, relatedness to devices and procedures, device deficiencies with/without an SAE potential), rapidly issue queries. Maintain the list of AE/SAE/device deficiencies as required by law. Retrain the sites if you see repetitive errors in the CRF. Immediately evaluate measures in case of unexpected nature, severity or frequency of problems. If necessary, suspend device use until measures are completed.
f. Safety committees, e.g. data monitoring committees (DMC), data safety monitoring boards (DSMB) or data safety monitoring committees (DSMC): In double-blind randomised investigations with relevant risks, unblinded data need to be assessed periodically and in case of unexpected events. The committees oversee attributions made by investigators, may evaluate unblinded data and are expected to make independent evaluations; investigators should therefore not be part of the committees. Make sure members have been trained on European seriousness criteria and causality assessment for clinical investigations of medical devices (guideline MDCG 2020-10).
g. Stopping criteria: Define the type and number of incidents that will lead to the suspension of further use.
h. Implant card for subjects: In addition to standard information the card also needs to include information on participation in the research project, title of the investigation, contact details of the investigator.
i. Systematic return and examination of devices in case of problems or explantation, if applicable evaluation of excised tissues.
j. Sufficient duration of follow-up of subjects: While short term observations may be the primary goal of certain feasibility studies, information that ensure the safety of the subjects and their adequate further management also need to be collected. Problems should be identified e.g. by observation of the entire healing process, any subsequent procedures and adaptations to the device intended by the manufacturer, the short, medium, longer-term outcomes of the subjects. Unforeseen issues need to be analysed centrally and communicated to the investigators in charge of the patients.
k. Contact persons, retrieval of information on serious incidents: Procedures to be followed before subjects are declared lost to follow-up should be determined in a risk-based approach. They should be timely, effective and in line with the data analysis that is planned. For details see Annex 3.
l. Restrictions for access to individual diagnostic data: Incorrect diagnostic data obtained with non CE-marked devices can cause wrong decisions on patient care. If feasible, foresee standard of care diagnostics to be used in parallel. Do not unnecessarily report investigational test results to treating doctors, nurses, patients or others. Do not unnecessarily include investigational data in medical records. Justify exceptions and define communication including recommendations for additional testing in case of alarming results and incidental findings.

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A3: Patients lost to follow-up, mortality, permanent impairment

Art. 4, 5, 10, 12 and 15 HRA; Art. 4, 32 and 33 ClinO-MD; Annex XV chapter II sections 3.6 and 4.1 and chapter III MDR; MDCG 2020-10; sections 3.1, 3.2, 3.45, 6.2, 7.4.3-7.4.4, C.2.4 and Annexes E and F of standard ISO 14155:2020

The investigations must be planned in such a way that the endpoints foreseen by the sponsor can be recorded correctly. The course of various diseases and different interventions can lead to mortality, and to physical or mental disability. Such events are often foreseen as endpoints and need to be retrieved.

During pre-market investigations with relevant risks, the events must be monitored continuously by the sponsor. It is the duty of the sponsor to rapidly identify and avert excessive risks. Deficient investigation planning and missing data can moreover threaten the validity of the results.

Important aspects can be found in Boxes 5 and 6.

Box 5: Organisational aspects for investigations with a mortality endpoint or endpoints that lead to a loss of independence

- Informed consent form: The form should include the consent for the sharing of medical information with a contact person, e.g. that the investigator may clarify the state of health with the subject's general practitioner and/or named individuals.
- Clinical Investigation Plan:
  - Procedures for follow-up visits: If a subject can no longer be traced, its address and state of health should quickly be clarified by the investigator with the contact person.
  - Monitoring plan: If a subject can no longer be traced, the monitor should check with the centre on the appropriateness of attempts made to contact the subject and his contact person.
  - Missing data and statistical considerations: If the occurrence of a death or other endpoints cannot be established, sensitivity analyses should usually be provided for (analyses on the effect of the missing data on the results).
- Reports: The number of *patients lost to follow-up* and the results of the sensitivity analyses should be included in final reports and publications.

Box 6: Examples of inadequate investigations planning in the case of investigations with a mortality endpoint or endpoints that lead to a loss of independence

- Clinical investigation plans that describe no measures for patients lost to follow-up.
- Insufficient measures e.g.
  - failing to obtain the written consent of the subject with regard to obtaining health information from third parties.
  - no sensitivity analysis (failure to take into consideration that subjects lost to follow-up may have experienced a fatal outcome or severe disabilities).

A4: Inclusion and exclusion criteria, particularly vulnerable persons

Arts. 11 and 21-31 HRA; Arts.15-17 ClinO; Arts. 64-68 MDR

A research project involving particularly vulnerable persons may only be carried out if equivalent findings cannot be obtained in any other way. Particularly vulnerable persons are, for example, minors (children, adolescents), adults lacking the capacity in the consent procedure, patients in emergency situations, pregnant women or embryos / foetuses. Investigations with own employees are considered as problematic due to financial dependence.

For that reason, please check the wording of the inclusion and exclusion criteria. If particularly vulnerable groups of persons are not explicitly excluded from the investigation, the necessary

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justifications must be in the documentation. Information texts and consent forms are needed for all persons taking part in the investigation, as is a written description of the procedure for enrolment / consent / post hoc consent.

Flow charts or diagrams, for example, may also be appropriate as a written description. These should show which person, at which point, using which documents, carries out which activities that lead to inclusion in the investigation and, if in case of enrolment in an emergency situation, to obtain a correct post hoc consent.

In practice, investigations under mixed conditions present particular difficulties, and especially if both vulnerable and non-vulnerable subjects are to be enrolled or if a temporary, particular vulnerability exists. In such cases, please pay particular attention to correct investigation planning. Considerations and examples can be found in Box 7.

Box 7: Considerations regarding clinical trials with both vulnerable and non-vulnerable subjects

Example 1, mixed populations
An investigation of a coronary stent is to be conducted. The devices can in principle be used for elective interventions and for emergency patients with acute myocardial infarction. According to inclusion and exclusion criteria, emergency patients are not excluded from the investigation:
- Are you sure the investigation should involve emergency patients with acute myocardial infarction?
- Does the documentation state which research question can only be investigated using the emergency patients, and why?
- Has the necessary number of emergency patients, that is needed to investigate these particular research questions, been calculated?
- For enrolment, how do you make sure that the correct number of emergency patients and elective patients will be included (stratification)?

Example 2, emergency situation at the beginning of an investigation
A coronary stent is used on emergency patients with myocardial infarction, and the investigation is then continued with a follow-up under regular clinical conditions.
- Who clarifies the emergency patient's capacity to consent, and how?
- When and how are the patients themselves and / or their representatives involved?
- At what point is the independent doctor involved?
- When and how, after implantation, does the post hoc consent and the consent to continue taking part in the clinical investigation take place (now administered with the appropriate reflection period)?
- Is the written description of the whole consenting procedure available?
- Are the necessary documents for the various steps available (information and consent forms for use under emergency conditions, documented decision of the independent doctor, post-hoc information and consent forms for use of previously collected data and continued participation in the investigation)?

Specific provisions also apply regarding research involving prisoners *(Art. 28 HRA)*.

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A5: Reflection period when consenting for invasive procedures

Art. 16 HRA

The subject must be given an appropriate reflection period. For procedures that can be planned, the question of the time required arises in particular in the case of

- implants,
- a permanent modification to bodily parts or
- invasive examinations with relevant risks.

The reflection period should in general be rather too generous than too short, and must be described by the sponsor in the CIP. Guidance and case descriptions are available on the subject:

- Swissethics: „Leitfaden Bedenkfrist“ (available at www.swissethics.ch).
- Decisions of the Federal Supreme Court: As a result of legal disputes, the Federal Supreme Court has commented on aspects regarding consent to invasive procedure in daily clinical practice (considerations available e.g. in the judgement of the Federal Supreme Court no. 4P.265/2002, free of charge at www.bger.ch). These aspects can also be taken into consideration when determining the reflection period for clinical investigations.

Box 8: Consent to invasive procedures: the following procedures are not considered appropriate for elective invasive interventions and will be classified by Swissmedic as critical findings when carrying out inspections of clinical investigations

- Give information regarding an investigation and obtain the written consent during the same consultation.
- Give information regarding an investigation only after the patient has admitted to the hospital for an elective intervention.

A6: How to make a submission

You can find information on the eGovernment Service eMessage in various languages at

- *www.swissmedic.ch/ci* and *www.swissmedic.ch/ci* > EN > Clinical investigations > How to submit
- OS000_00_005e_MB eMessage functions

The following items can be sent by email to clinicaltrials.devices@swissmedic.ch:

- Tabular listings of reportable serious adverse events and device deficiencies according to the European reporting formats.
- Communications during an ongoing procedure with no documents attached, e.g. for extension of deadlines, other coordination needs, questions concerning the procedure.

In all other cases, you must follow the eGovernment submission procedures. In order for your submission to be handled correctly, standardised forms and a standardised folder structure are necessary and must always be used. Electronic submissions consist of three steps:

a) **Prepare the standardised form and download the standardised folder structure**
To prepare a submission, go to www.swissmedic.ch/ci > Forms and templates, choose and fill in the correct form. Go to www.swissmedic.ch/ci > EN > Clinical investigations > “How to submit” > “eDok electronic folder structure (ZIP)”, and download the standardised folder structure.

b) **Generate an eDok**
Copy the form, an accompanying letter if needed and every document into the correct folder. Your files should be in pdf or Excel format. Zip the whole structure (the standardised folders with all your files). This is called an “eDok”. One eDok includes one entire submission. In rare cases of errors due to size overload, you can split the documents (two eDoks for one submission).

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c) **Submit the eDok**
Send eDoks for clinical trials of devices to Swissmedic via the Swissmedic Portal eMessage (www.swissmedic.ch/emessage-en). Swissmedic also runs a second portal, eSubmission, which cannot be used for devices.

In order to create an eGovernment accout, you need an email-address and a mobile phone. Immediately after the registration step, you can submit to Swissmedic. A two-way identification procedure will be carried out for safety reasons each time you access the portal, with a code that is sent to your mobile phone. For a submission, answer the questions on the screen, select your eDok, select the “Upload” button and confirm. You will receive two automatic communications. The first one shows whether the 'submit' step was successfull ('delivery confirmation'). Immediately afterwards, a second communication will show whether your files passed the automatic technical validation ('acceptance of delivery' or 'acceptance of delivery denied'). Confirmations and error messages will be stored in eMessage for you. Always check the messages you receive.
You should not store files in the portal. Instead, download correspondence of Swissmedic and store your submissions and the correspondence in your trial master file, so all authorised persons can access them during the clinical trial and the mandatory archiving period.

Troubleshooting: The error message 'acceptance of delivery denied' mostly occurs when the eDok format is not respected.
- Always provide your files in the standardised folder structure and accompanied by the corresponding Swissmedic form.
- In your eDok, include pdf and Excel files only (xlsx, xls, ods). Files from digital sources are preferred. When scanning documents you must use the OCR standard in order for the texts to be machine-readable.
- If the file name is too long or contains unforeseen characters, the system will not be able to process your submission. The maximum recommended length is 60 characters with the file extension. File names can include 'A' to 'Z', 'a' to 'z', '0' to '9', '.', '-', and '_'. You may not use a blank space at the beginning or end of a file name and you should not use the following characters: « * : < > ? / \ | ~ # % & " { }.
- If you do not see messages from Swissmedic, you can adapt the filter option in eMessage to see unread messages only (default setting), or all messages. Please be aware that you will only see messages and other correspondence made under your ID, not correspondence concerning the same clinical trial sent to other users that have used a different ID.

If you are unable to register or submit, you can contact eSubmission@swissmedic.ch for help.

A7: Considerations concerning special groups of products

a) Personalised medical devices (patient-matched medical devices, patient-adapted medical devices, custom-made medical devices)

Consult the European guidance document MDCG 2021-3 in order to determine whether a device that is made to an individual patient's specifications is a patient-matched, patient-adapted, or custom-made medical device.

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Table: Types of personalised medical devices and categories of clinical investigations

Type of device	Applicable GSPR must be fully met*	Type of declaration*	Device classes where notified body involvem. is required*	CE marking is required*	Possible categories of clinical investigations
patient matched	Yes	Declaration of conformity	Im, Ir, Is, IIa, IIb, III	Yes	A, C1, C2, C3
patient-adapted	Yes	Declaration of conformity	Im, Ir, Is, IIa, IIb, III	Yes	A, C1, C2, C3
custom made	No (justified exceptions permitted)	Statement for custom made devices according to Annex XIII of the MDR	class III implantable devices	No	Mainly C2**

* In order to place devices on the market and use them in category A clinical trials.

** In most clinical investigations, there are relevant design aspects that are determined in advance (not by individual decisions of prescribers), these projects do not generally fall under category A.
Clinical investigations can be acceptable for category A if the following conditions are met, always include corresponding descriptions and a summary of available clinical data in the clinical investigation plan:

(a) all devices will fully comply with the applicable general safety and performance requirements of the MDR with no exceptions (notably, sufficient clinical data and a positive benefit-to-risk determination must be available; anecdotal cases and results of pilot studies are not normally considered to be sufficient clinical data) and

(b) a valid notified body certificate is available in case of class III implantable devices.

b) Software

Consult the European guidance document MDCG 2019-11 in order to determine whether a software is a medical device and to determine its risk classification.

Is it necessary, for software based on machine learning methods, to receive an authorisation for a clinical trial of the software in order to collect data sets needed to train the software?
No, collecting biomedical data in humans for research purposes normally falls under the Swiss Human Research Ordinance (HRO, RS 810.301). If in doubt, please consult the cantonal ethics committee in charge of your study. HRO applications need to be submitted to and are treated by cantonal ethics committees. You can file an application for a clinical investigation with the software when the software is ready and all required information is available (description of training data sets, validation and technical tests, input required by the software and conditions of use, technical performance with the said input and under the said conditions of use, residual risks, information on adherence to standards, GSPR checklist, measures taken for minimising risks to study subjects during the investigation, etc.).

c) Therapeutic products with devitalised human tissues or cells

These products contain non-viable tissues or cells of human origin or their derivatives; they do not contain any living cells.
Where the principal mode of action is achieved by pharmacological, immunological or metabolic means or in case of doubt about the principal mode of action, rules for clinical trials of medicinal products must be followed.
Where the principal mode of action is not achieved by such means, four types of products need to be distinguished:

1. Derivatives (extracted from human tissues or cells, not containing such tissues or cells).
2. Integral combinations, where non-viable tissues or cells or their derivatives contribute an action ancillary to that of a medical device.
3. Non-viable tissues and cells.
4. Integral combinations with a medical device, where non-viable tissues or cells exert a principal mode of action.

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Product types 1 and 2 in Europe fall under the MDR and need to fulfil the General Safety and Performance Requirements of the MDR. In Switzerland, clinical investigations currently fall under the ClinO-MD. There is a transitional period for devices duly notified to Swissmedic until 26.5.2021; it is permissible to market and conduct category A clinical trials with such devices until 26.5.2025. Swissmedic authorisation is necessary for the conduct of category C clinical trials.
Product types 3 and 4 on the Swiss territory are currently considered medical devices. Please contact clinicaltrials.devices@swissmedic.ch if you plan to conduct a category C clinical trial with these products. Corresponding forms and updated information will be provided to you. The products currently need to fulfil Essential Requirements of directive 93/42/EEC and clinical trials in Switzerland fall under the ClinO. Please be aware that regulatory changes are being foreseen. As soon as new legislation and new transitional regulations have been issued, Swissmedic will publish the information on its website. Category A clinical trials can be conducted with products duly notified to Swissmedic (extensive documentation is required for the notification, please refer to the Swissmedic website Notification of devitalised human tissue). Swissmedic authorisation is required for the conduct of category C clinical trials.

d) Radiation sources, ionising radiation, radiation protection
When using radiation sources, please note the dose levels, the procedures and the additional application documentation required in accordance with *Art. 18 and Annex 1 section 5 ClinO-MD, and Art. 28 of the Radiation Protection Ordinance (SR 814.50)*.

For category C clinical investigations with therapeutic products that can emit ionising radiation, the documents must be submitted to the ethics committee and Swissmedic. Swissmedic will forward a complete copy of the application to the Swiss Federal Office of Public Health.

For category A clinical investigations these documents must be submitted to the cantonal ethics committee and, if required, to the Swiss Federal Office for Public Health.

e) Combined trials with multiple types of products
In combined trials, multiple products can be subject to investigation: medical devices, medicinal products, advanced therapy medicinal products/ transplant products. The requirements for clinical trials with medicinal products and those for clinical investigations with medical devices must both be fulfilled. Submission routes are shown below.

- Submissions when medical devices and medicinal products (excluding ATMP) are under investigation:

Conforming medical device*	Conforming medicinal product**	How to submit to Swissmedic
No	No	Submit a full documentation for clinical investigations with medical devices with the form BW610_10_021e_FO and the standard folder structure as described in Annex A6. In addition, insert the form for clinical trials with medicinal products and all the additional documents required for medicinal products in folder 18 of the standardised folder structure for medical device applications. The submission has to be uploaded via the eMessage portal.
No	Yes	Make a submission with the form and according to requirements for clinical investigations with medical devices as described in Annex A6. In the CIP, describe the regulatory status of the medicinal product and pharmacovigilance reporting duties for the medicinal product.

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Yes	No	Make a submission with the form and according to requirements for clinical trials of medicinal products. In the CIP, describe the regulatory status of the medical device and materiovigilance reporting duties for the medical device.
Yes	Yes	No submission to Swissmedic. Refer to section 5.1 of this information sheet (information on category A clinical investigations). In the CIP, describe the regulatory status of the products, materiovigilance and pharmacovigilance reporting duties.

* CE-marked, is used in the clinical trial according to its CE-marked instructions for use, has not been prohibited in Switzerland

** Authorised by Swissmedic and used in the clinical trial according to its authorised label

During the trial, please send reports about adverse events to Swissmedic as follows:
Send reports relating to medicinal products to SUSAR@swissmedic.ch, please observe the Information sheet "Safety relating to clinical trials - Compulsory notification".
For Reports relating to medical devices the forms can be found at www.swissmedic.ch/ci > EN > Clinical investigations > Submissions during ongoing clinical trials. Send tabular SAE reports according to MDCG 2020-10/2 by e-mail to clinicaltrials.devices@swissmedic.ch and other reports via the Swissmedic portal (see Annex 6).

- Submissions when medical devices and advanced therapy medicinal products (ATMP, transplant products) are under investigation:

Conforming medical device*	Conforming ATMP**	How to submit to Swissmedic
No	No	Make a submission with the form and according to requirements for clinical trials with ATMP. As part of the documentation, also submit the authorisation application form for clinical investigations of medical devices BW610_10_021e_FO and the documents that are listed in that form.
No	Yes	Make a submission with the form and according to requirements for clinical investigations with medical devices. In the CIP, describe the regulatory status of the ATMP and pharmacovigilance reporting duties for the ATMP.
Yes	No	Make a submission with the form and according to requirements for clinical trials with ATMP. In the CIP, describe the regulatory status of the medical device and materiovigilance reporting duties for the medical device.
Yes	Yes	No submission to Swissmedic. Refer to section 5.1 of this information sheet (information on category A clinical investigations). In the CIP, describe the regulatory status of the products, materiovigilance and pharmacovigilance reporting duties.

* is CE-marked, is used in the clinical trial according to its CE-marked instructions for use, and has not been prohibited in Switzerland

** is authorised by Swissmedic and is used in the clinical trial according to its authorised label

f) Products that are a combination
A product that is a combination is either a medical device (with an ancillary medicinal substance), a medicinal product (that includes a medical device component), or a transplant product (that

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includes a medical device component). The corresponding regulation is applicable to these trials. For borderline issues and combinations, Switzerland takes into account the European delimitation criteria between medicinal products and medical devices. You can find additional information with the following links:

- EU guidance on medical devices: MDCG endorsed documents
- EMA guidance on medical devices and combination products: www.ema.europa.eu
- Swissmedic website "Frequently Asked Questions on medical devices – FAQ MD"
- Swissmedic website "Questions on delimitation"

Examples

- Example 1: Vials of a new parenteral hormone product (medicinal product) and a new pen injector (medical device) will both be tested in a clinical trial. This is a combined clinical trial involving a medicinal product and a medical device.
- Example 2: A drug-eluting coronary stent is considered a medical device. Clinical trials of these products are clinical investigations of medical devices. They do not need to be handled as combined trials nor as trials of medicinal products.
- Example 3: A single-use infusion device prefilled with a drug is considered a medicinal product. Clinical trials are medicinal product trials. They do not need to be handled as combined trials nor as clinical investigations of medical devices.

Contacts in case of questions

- General questions: questions.devices@swissmedic.ch.
- Questions concerning an ongoing procedure or an approved clinical investigation: Contact the person that is mentioned on Swissmedic correspondence or clinicaltrials.devices@swissmedic.ch
- Questions concerning the Swissmedic eMessage portal: eSubmission@swissmedic.ch

Further information from Swissmedic on clinical investigation with medical devices can be found on the Internet: www.swissmedic.ch/ci

Change history

Version	Valid and binding as of:	Description, comments (by author)	Author's initials
3.2	27.07.2022	Section 7.2.4: Clarification, the list of reportable SAE and DD needs to be a cumulative list. Section 10: Use of the term 'agent' for a clearer distinction between agents for foreign sponsors and legal representatives of manufacturers or study subjects.	sci
3.1	08.06.2022	Updated links and references throughout the document. Regulatory references updated and reporting form included in chapter 7.1.2.	sci
3.0	26.05.2022	Revision due to national implementation of the European IVDR. Document code changed to BW600_00_015e_MB (previously BW610_00_0015e_MB)	sci

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