

Information sheet
Clinical investigations of medical devices

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Contents

1	Objective	3
2	Introduction	3
3	Legal basis, standards, and guidance documents	4
3.1	Legal texts	4
3.2	Guidance documents, templates, international conventions	4
4	ISO 14155 standard	5
5	Approval of clinical investigations of medical devices	5
5.1	Trial categories and responsible authorities	5
5.1.1	Terms and definitions	5
5.1.2	Applicable procedures	6
5.2	Applications to Swissmedic for the approval of category C clinical investigations	8
5.2.1	First submission to Swissmedic of an approval application	9
5.2.2	Validation.....	10
5.2.3	Review and approval	10
5.2.4	Shortcomings	10
5.2.5	Fees	11
5.2.6	Submission in case of confidentiality restrictions	11
5.3	Submissions to Swissmedic for combined studies	12
5.4	Devices emitting ionising radiation, radiation protection.....	12
6	Review and surveillance activities by Swissmedic	12
6.1	Frequent objections	12
6.2	Inspections	12
7	Submissions during clinical investigations (reporting duties, notification duties, approvals)	13
7.1	Category A clinical investigations	13
7.1.1	Reporting duties to Swissmedic.....	13
7.1.2	Reporting duties to the ethics committee	13
7.2	Category C clinical investigations	13
7.2.1	Modifications (amendments).....	15
7.2.2	Safety (risks and safety measures).....	17
7.2.3	Serious adverse events (SAEs) and device deficiencies.....	17
7.2.4	Annual report.....	20
7.2.5	Completion, premature termination, interruption of the investigation	21

8	Data retention requirements	22
9	Databases used in Switzerland	22
10	Sponsors with registered offices abroad, submissions by third parties	22
11	Liability in the case of damage, coverage in the form of insurance	22
12	Penal provisions	23
	ANNEXES	24
	A1: Recording of adverse events and device deficiencies	24
	A2: Risk mitigation measures	27
	A3: Patients lost to follow-up, mortality, permanent impairment	28
	A4: Inclusion and exclusion criteria, particularly vulnerable persons	29
	A5: Reflection period when consenting for invasive procedures	31
	A6: How to make a submission	31
	A7: Special groups of products	33
	Contacts in case of questions	36

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 approval 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 of IVDs or clinical trials of medicinal products. For performance studies, please refer to information sheet [BW600_00_0016e_MB](#). For clinical trials of medicinal products, please refer to www.swissmedic.ch > Human medicines > Clinical trials on medicinal products.

For submissions regarding a combined study, where several clinical trials mentioned above are conducted in parallel, please also refer to information sheet [BW600_00_017e_MB](#).

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 products¹, but neither medicinal products nor transplant products with living cells.

3 Legal basis, standards, and guidance documents

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

3.1 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 of 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.

3.2 Guidance documents, templates, international conventions

- Swiss documents:
- Guidance and templates published by Swissmedic: www.swissmedic.ch/ci.
- Guidance and templates published by cantonal ethics committees: www.swissethics.ch/en/ethikkommissionen.
- 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

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)

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*², *'list of standards'*³, *Swissmedic approval application form*.

5 Approval of clinical investigations of medical devices

5.1 Trial categories and responsible authorities

Arts. 2, 2a, 6-7, 16-18, 33-34, and Annexes 1, 2, 4 and 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.

5.1.1 Terms and definitions

- 'Clinical trial' in Swiss legal texts is an umbrella term used for clinical investigations of medical devices, performance studies of IVD, clinical trials of medicinal products, and clinical trials of other interventions (e.g. surgical interventions, other therapies).
- A clinical investigation of 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, see annex A7 for additional information.

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 MedDO, 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 systematic⁴, 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,

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 MDCG 2021-8 under 'Checklist of general safety and performance requirements, standards, common specifications and scientific advice'.

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.

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

5.1.2 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.

In Switzerland, these clinical investigations must be submitted to and approved by the competent cantonal ethics committee only, no submission to Swissmedic is required. The cantonal ethics committee decides 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 committee⁵.

- 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).

These clinical investigations can start in Switzerland once the approvals of the cantonal ethics committee and Swissmedic have been obtained. Applications for approval must be transmitted on the same day to both institutions via the respective webportals: eMessage for Swissmedic (see annex A6), BASEC for ethics committees.

Before beginning a trial, please ensure that you have received Swissmedic approval and fulfilled any conditions stipulated in the letter of approval.

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
- Devices emitting ionising radiation, radiation protection
- In-house manufactured devices
- Devices without an intended medical purpose
- Products that are a combination
- Examples of combined studies versus products that are a combination.

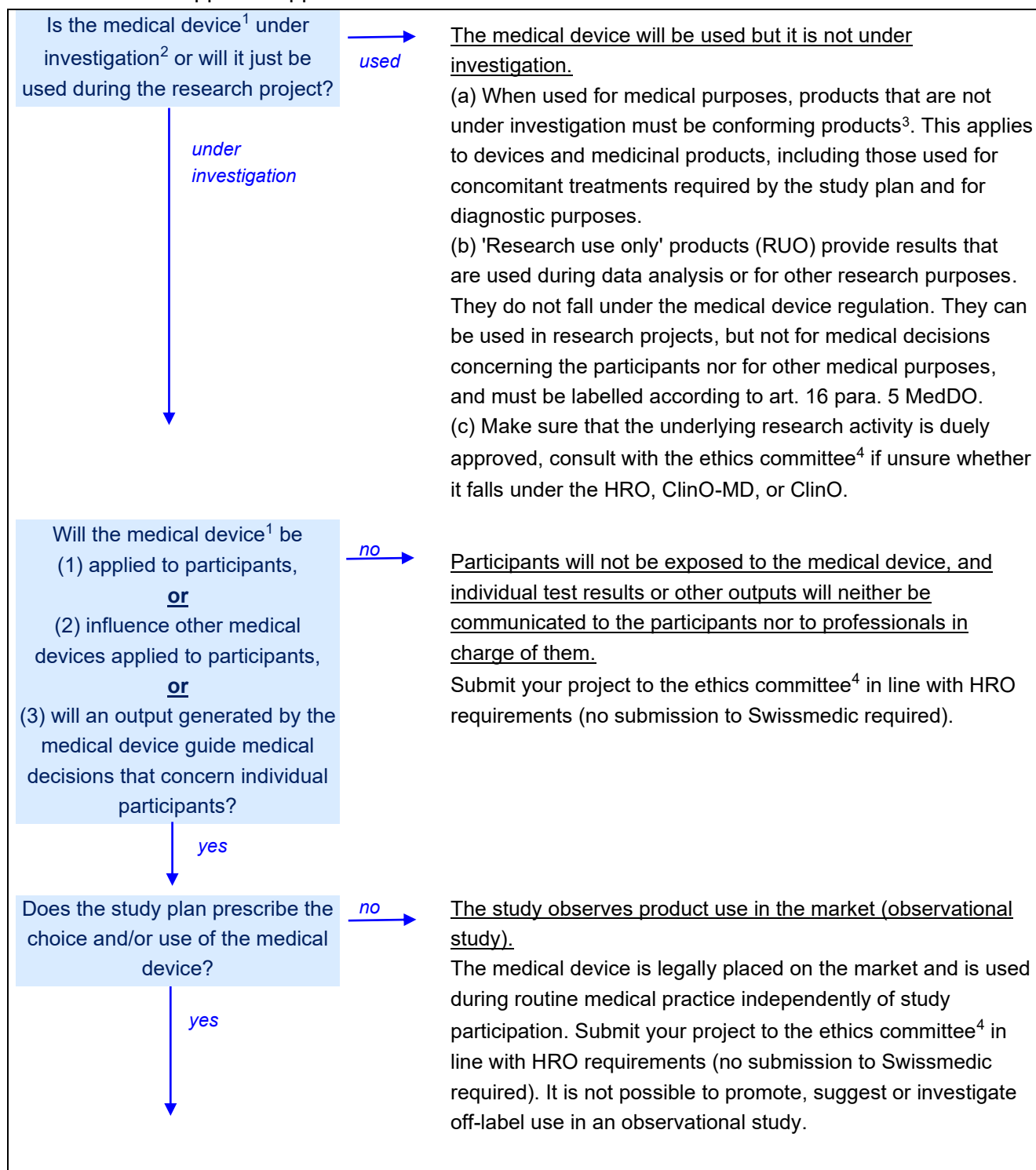
The application procedure for combined studies is described in Information Sheet

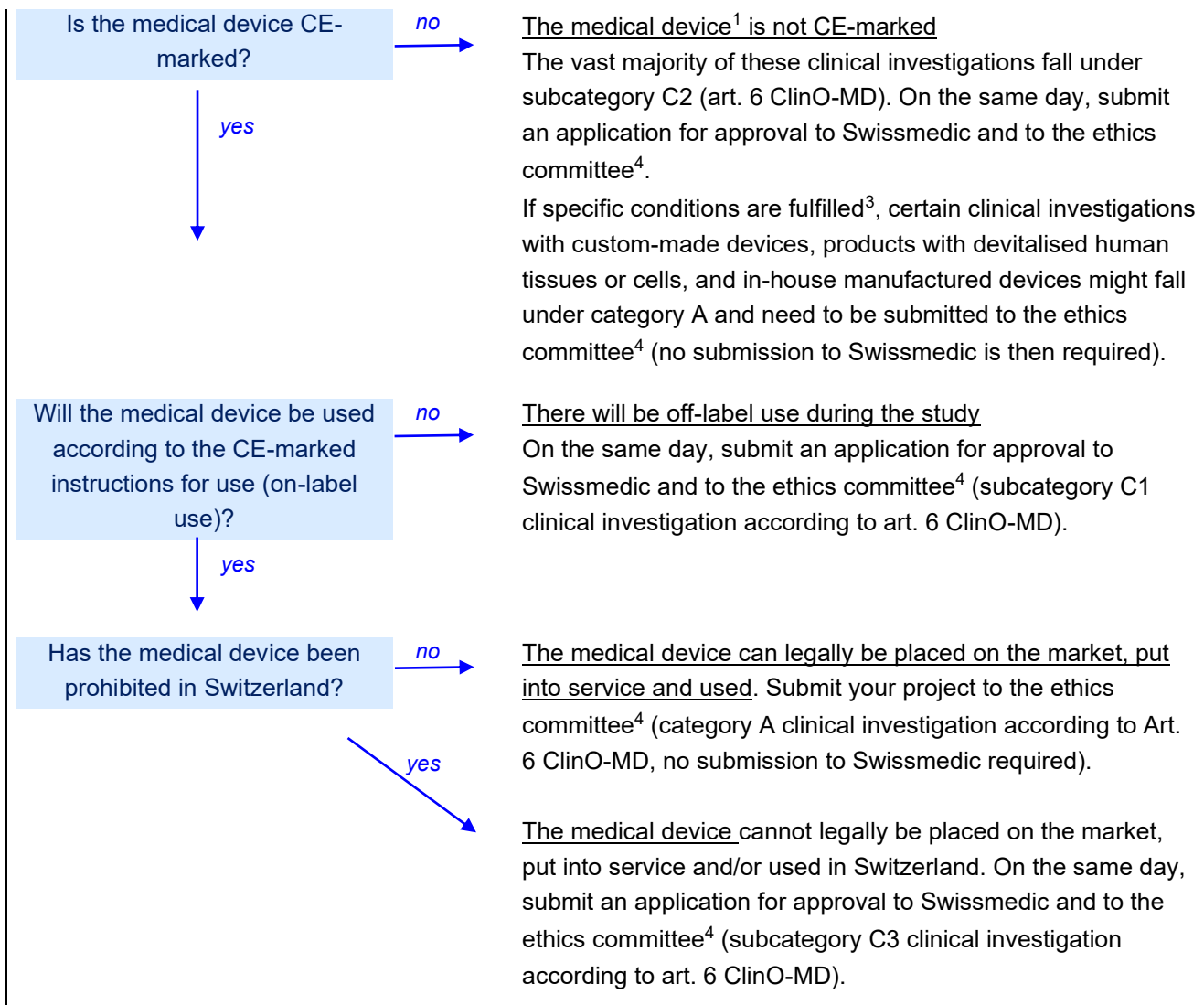
⁵ Information available at www.swissethics.ch/en/ethikkommissionen

[BW600 00 017e MB](#)

Below, you can find a decision tree showing the type of research and to which institution you have to file an approval application. In case of doubt, contact the cantonal ethics committee, which in Switzerland is the responsible entity for the delimitation and categorisation of research projects.

Decision tree for approval applications





¹ The medical device can be a stand-alone product, or a product that is used as part of a system, including software (e.g. an app or an MRI sequence). Refer to art. 1 to 3 MedDO for definitions and exceptions. Consult the information sheet BW630_30_007e_MB (Medical Device Software) and the European guidance document MDCG 2019-11 in order to determine whether a software is a medical device.

² Investigation for assessment of the safety or performance of the device.

³ See annex A7 of this information sheet (BW600_00_015e_MB) for guidance on clinical investigations with custom made devices, with therapeutic products that contain devitalised human tissues or cells, or with certain medical devices manufactured and used in the same healthcare institution.

⁴ The application for the clinical trial is submitted to the ethics committee responsible for the investigator. In a multicentric clinical trial the application is submitted to the lead ethics committee responsible for the coordinating investigator. The coordinating investigator is the individual with responsibility in Switzerland for coordinating the investigators responsible for the various trial sites in Switzerland. The list of ethics commissions that details the cantons for which they are responsible can be found here: www.swissethics.ch/en/ethikkommissionen

5.2 Applications to Swissmedic for the approval 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 approval application

First submission of an approval 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 approval 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:

1. 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 MedDO⁶.
2. The use of the investigational device is, at most, associated with minimal risks to the subjects.
3. 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).
4. 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 completion 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

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

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 [MDCG 2021-8](#) under 'Checklist of general safety and performance requirements, standards, common specifications and scientific advice'.
- 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 emitting ionising radiation, please also submit documents according to section 5.4 and annex A7 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 approval

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 approve a clinical investigation after ethics committee approval.

5.2.4 Shortcomings

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, conditions or charges, 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 approval procedure, you will receive letters of decision.

5.2.5 Fees

The flat rate fee for handling an application for the approval of a clinical investigation of a medical device is CHF 5000.- for a regular review, CHF 1500.- for a simplified review and CHF 1000.- for a substantial modification (FeeO-Swissmedic). The fee will be invoiced by Swissmedic. Relevant additional workload will be invoiced at a rate of CHF 200.- per hour, for example in case of shortcomings and corrections.

Academic sponsors may apply for an 80% reduction of the flat rate fee. To be eligible for the fee reduction, the sponsor must confirm that it does not receive financial support for the conduct of the clinical trial (or parts thereof) from commercial "for profit" sources. Sponsors who receive financial support from non-commercial funding sources, such as university funds, the Swiss National Science Foundation, foundations or Innosuisse, may still apply for a fee reduction.

To apply for the reduction please complete the following documents:

- [BW610_10_029e FO Application fee reduction.pdf](#) and
- [BW610_10_030e VL Appliation fee reduction selfdeclaration.docx](#)

Place both documents in folder 00.00_Swissmedic_forms of your submission eDok as described in Annex A6.

5.2.6 Submission in case of confidentiality restrictions

If the sponsor does not have access to certain documents needed for the submission for reasons of confidentiality, they can be submitted separately in a second submission. In this case, please follow the steps below:

1. Describe the situation in the cover letter of your main submission and list the affected documents. State how many additional submissions are foreseen together with the anticipated submission date.
2. Select the appropriate tick box indicating that the submission is affected by confidentiality restrictions in the form [BW610_10_021e FO](#).
3. Upload the main eDok and wait for the acceptance of delivery confirmation.
4. Instruct the person / entity who will submit confidential documents to perform the following steps:
 - a. Fill in the form [BW610_10_028e FO](#) using the delivery ID which you can find on the acceptance of delivery confirmation that you received for the main submission.
 - b. Prepare an eDok as described in Annex A6, place the form [BW610_10_028e FO](#) and all confidential documents in the eDok.
 - c. Submit the eDok as described in Annex A6.

Note that the formal check of your submission will only start once all parts of the submission have been received by Swissmedic and the documentation is complete. If deficiencies or questions arise that concern the documents affected by confidentiality restrictions, Swissmedic will directly contact the

person / entity listed on the form [BW610 10 028e FO](#) as the holder of the confidential documents. All other communication will be sent to the sponsor or to its representative.

5.3 Submissions to Swissmedic for combined studies

You can find detailed information for your submissions in Information Sheet [BW600 00 017e MB](#).

5.4 Devices emitting 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 approval procure. See annex A7 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 approve 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 reporting duties, notification duties and approval 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 approval that has been granted, or make the continuation of an investigation dependent on additional conditions.

7 Submissions during clinical investigations (reporting duties, notification duties, approvals)

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).

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/en/ethikkommissionen 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 relationship between the event and the test procedure used in the clinical trial has been ascertained. Use the form [BW610 20 023e FO](#).
- For Annual reports and the final report (clinical investigation report), refer to art. 35 to 37 and Art. 39 ClinO-MD.

7.2 Category C clinical investigations

Table: Overview of submissions after initial approval of a clinical investigation.

Type of submission	Deadlines
<p>Modifications (Art. 15 and 20 ClinO-MD)</p> <ul style="list-style-type: none"> - requiring approval - requiring notification 	<p>Substantial modifications can be submitted anytime.</p> <p>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.</p> <p>Submit non-substantial modifications to Swissmedic as soon as possible.</p> <p>Submit to the ethics committee either together with the next annual report or as soon as possible according to the document '<i>Substantial modifications to clinical investigations of medical devices</i>'¹</p>
<p>Reportable SAE and device deficiencies (Art. 33 ClinO-MD)</p>	<p>7 days</p>
<p>Safety and protective measures (Art 34, 36 and 38 ClinO-MD)</p> <ul style="list-style-type: none"> - temporary halt or premature termination on safety grounds (Art. 36 and 38 ClinO-MD) - other measures (Art. 34 ClinO-MD) 	<p>24 hours</p> <p>2 days</p>
<p>Annual report (Art. 35 and 38 ClinO-MD)</p>	<p>No later than 1 year after the date of approval / the last annual report</p>
<p>Interruption and premature termination (Art. 36 and 38 ClinO-MD)</p> <ul style="list-style-type: none"> - on safety grounds - not on safety grounds 	<p>24 hours²</p> <p>15 days²</p>
<p>Completion of the clinical investigation in Switzerland³ (Art. 36 ClinO-MD)</p>	<p>15 days</p>
<p>Final report (clinical investigation report) and summary for lay persons (Art. 37 and 38 ClinO-MD)</p> <ul style="list-style-type: none"> - after regular study completion - after interruption or premature termination 	<p>Within 1 year, exceptions are possible if motivated by scientific reasons⁴</p> <p>Within 3 months</p>

Radiation incident (Art. 39 ClinO-MD, the permissible dose guide value has been exceeded in a subject)	7 days
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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.

7.2.1 Modifications (amendments)

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

Modifications require Swissmedic approval/notification as well as ethics committee approval/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(s) 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 approval (substantial modifications)

Submission of modifications requiring approval

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 approved 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 inclusion criteria, exclusion 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 [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 approval 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.

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 will find two automatic acknowledgements in eMessage (for successful upload and technical validation). Check whether the technical validation was successful, the message serves as proof of your submission. See annex A6 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 approval. 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 and comply with legal obligations.

Fees: The flat rate fee for handling modifications that are subject to approval amounts to CHF 1000.-⁷ 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 approval 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 premature 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 premature 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

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 para 2 ClinO-MDat any time.

⁷ Reduced fees are available for certain academic clinical trials, see section 5.2.5.

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 potential⁸, 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 A1 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 the 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, adequateness of investigation procedures, and if necessary prepare and file amendments. See also section 7.2.2 (measures for safety reasons) and 7.2.1 (amendments).

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 a SAE, a report for the device deficiency and a report for the SAE need to be sent to Swissmedic. If a device deficiency causes several SAE, each SAE needs to be reported and followed-up 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 that

- adverse event CRF contain checkboxes with the different seriousness criteria for medical devices,
- 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.

⁸ 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

- 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 device.

Seriousness criteria for adverse events⁹ 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,

⁹ See also [MDCG 2020-10 rev. 1](#)

- 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 the reporting of sponsors to Swissmedic

- For multi-center studies, reportable SAEs and device deficiencies with an SAE potential must be reported to Swissmedic within 7 days:

Tabular summary reporting of serious adverse events and device deficiencies that occur in all centres (worldwide)

Use the Excel table [MDCG 2020-10/2](#), fill in the data as described in the guidance [MDCG 2020-10/1](#) and send the table via eMail to clinicaltrials.devices@swissmedic.ch.

Please make sure you have implemented the latest revision of MDCG 2020-10/1 and /2. The Excel table is filled in cumulatively over the course of the investigation, highlighting all changes compared with the previous version. Always submit the Excel file to Swissmedic (not a pdf file), Swissmedic must be able to search and edit the table.

- If a reportable SAE or a device deficiency with an SAE potential occurs in a Swiss site, please also fill in and submit the following form that contains more detailed information:

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

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 report

Art. 35 and 38 ClinO-MD

Submission of the annual report

Use the form [BW610 20 021e FO](#). See annex A6 for instructions on how to create an eDok and submit the report.

From the date of approval of the clinical investigation, a report must be submitted annually to the cantonal ethics committee and Swissmedic.

A template is available on the swissethics website:

www.swissethics.ch/templates > EN > Annual Safety and General Progress Trial Report > ClinO-MD

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 and product use, worldwide and in Switzerland: Current number of subjects, number of products used, duration of the currently existing follow-up observations
- Status of the clinical investigation abroad (countries involved, any study interruptions or premature 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
 - 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 of the investigational device (if applicable), new safety information from the literature and other sources, findings and recommendations of the DMC/DSMB
 - 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, with a comparison to expected incidences

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, premature termination, interruption of the investigation

Art. 36 to 39 ClinO-MD

Notification of completion, premature 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 completion of a clinical investigation within 15 days (as of last patient, last visit). A premature termination 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 (clinical investigation report) including a summary presented in generally understandable terms must generally be submitted within one year of completion. Include contents according to Annex XV chapter III of the MDR and Commission Guidance 2023/C 163/06¹⁰. You can also find information in the annex of ISO 14155. In case of a temporary halt or premature termination, the report is due within 3 months.

For clinical investigations of devices emitting ionising radiation, 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 Radiation Protection Division of the Swiss Federal Office of Public Health.

¹⁰ https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en

8 Data retention requirements

Art. 40 ClinO-MD

An archiving period of at least 10 years after the completion 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

Art. 8 ClinO-MD

For submissions to Swissmedic, use the eGovernment portal 'eMessage'. In annex A6 you can find information explaining how to make a submission to Swissmedic. BASEC must be used for submissions to cantonal ethics committees.

EUDAMED2 permits the identification of multinational clinical investigations and the coordination among national surveillance authorities in Europe. EUDAMED2 is currently a depository for basic data on clinical trials of medical devices and any modifications and national measures and is only available to competent authorities. Pre-market clinical investigations are assigned a EUDAMED identification number (the so-called EUDAMED 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 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

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*).

ANNEXES

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

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
- none of the above

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:

[Version number]

[pagination]

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. For additional information, see also information on risk mitigation in guidance MDCG 2024-3.

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 subjects/ while using the devices for the first time.
- c) Enroll a narrow study population with more favorable benefit-risk profile. If issues with catheter systems may lead to rescue surgery or conversion to surgery, do not enroll patients at high or extreme surgical risk in the early phase of use.
- d) 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 meets expectations. If necessary, carry out additional product tests, improve product design, the IFU, inclusion criteria, exclusion criteria, other aspects as needed.
- e) 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.
- f) 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 for any missing data or for implausible contents or combinations of data. 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.
- g) Monitoring: Foresee frequent visits to the sites and ensure compliance with the CIP, accurate recording of AE and DD, as well as compliance with reporting deadlines.
- h) 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 needs to be assessed periodically. The committees oversee seriousness and causality attributions made by investigators, recognise unexpected types, severities and frequencies of harm, 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 the European seriousness criteria and causality assessment criteria that are applicable specifically to investigations of medical devices (latest revision of guidance [MDCG 2020-10](#)).

- i) Stopping criteria: Define the type and number of incidents that will lead to the suspension of further use.
- j) 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.
- k) Systematic return and examination of devices in case of problems or explantation, if applicable evaluation of excised tissues.
- l) 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.
- m) 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 A3.
- n) 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.

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

- a) 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.
- b) 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).
- c) Reports: The number of *patients lost to follow-up* and the results of the sensitivity analyses should be included in the final report (clinical investigation report) and publications.

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

- a) Clinical investigation plans that describe no measures for patients lost to follow-up.
- b) 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. 6, 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, . Investigations with own employees are considered as problematic due to financial dependence. Note that pregnancy may cause an increased risk of complications if, for example, reanimation, unplanned open surgery, revision surgery would become necessary. Therefore, pregnant women and other patients with increased risks may need to be excluded from clinical investigations involving relevant risks on safety grounds, particularly in the early phases of medical device development.

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 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 on 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*).

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/en).
- 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/cj and www.swissmedic.ch/clinical-investigations-en > [How to submit](#)
- Step by step video: [eGov Service eMessage – Clinical trials with medical devices, submission of applications and notifications](#)

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:

1. 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/clinical-investigations-en > How to submit > "eDok electronic folder structure (ZIP)", and download the standardised folder structure.

2. 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, or in case of confidentiality issues, you can split the documents (two eDoks for one submission). Explain the split in your cover letter.

3. 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 account, 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 successful ('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: (a) Do not add, delete or rename any folders in the standardised folder structure. In particular, ensure that you do not drag and drop any of your folders into the standardised folder structure. (b) 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, 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: Special groups of products

- a) **Personalised medical devices** (patient-matched medical devices, patient-adapted medical devices, custom-made medical devices): Consult the European guidance [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.

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 Swissmedic information sheet [BW630 30 007d MB](#) (Medical Device Software) and the European guidance [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 approval 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) **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.

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 are transitional periods for legacy products that depend of different conditions. For additional information, see information sheet MU600_00_016_MB; it is permissible to import (and for manufacturer to deliver) products for category A clinical trials until the end of the applicable transition period. Swissmedic approval 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 approval is required for the conduct of category C clinical trials.

- d) **Devices emitting ionising radiation, radiation protection**

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 devices emitting 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) **Devices according to Annex XVI of the MDR (listed devices without a medical purpose):**

The list of products concerned is published in Annex XVI to the MDR and in the MedDO, please regularly check if the list has been updated. 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.

Requirements applicable to the devices themselves are described in EU implementing regulation 2022/2346, please regularly check for newest updates.

Requirements applicable to the planning, approval and conduct of clinical investigations are identical for Annex XVI devices as for other medical devices.

f) **In-house devices:** Manufacture and use of non CE-marked medical devices in healthcare institutions

Art. 9 MedDO together with art. 5(5) of the MDR describe the conditions allowing a healthcare institution to manufacture and use certain medical devices within its own premises and without the need of a notified body and CE-marking in order to address the specific needs of target patient groups which cannot be met, or cannot be met at the appropriate level of performance, by an equivalent CE-marked device available on the market.

For information on the conditions that must be fulfilled, please consult the Swissmedic guidance [BW630_30_829d_WL](#) and Swissmedic information available at www.swissmedic.ch > EN > Medical devices > Frequently asked questions > Devices manufactured and used in healthcare institutions.

Swiss healthcare institutions must notify the devices to Swissmedic before they are put into service. Notification forms are available at www.swissmedic.ch > EN > Medical devices > Market access > Notification of medical devices.

It is acceptable to use these medical devices in monocentric category A clinical investigations in the same healthcare institution. In the CIP, lay open that the device is not CE-marked and describe fulfilment of the General Safety and Performance Requirements and of each condition listed in art. 5(5) of the MDR. These cases are rare.

If an applicable General Safety and Performance Requirement (Annex I of the MDR) is not fulfilled, or if a condition listed in art. 5(5) of the MDR is not fulfilled: An approval application for category C2 clinical investigation must be submitted to Swissmedic and to the ethics committee. Example: There is a CE-marked device with an appropriate performance on the market, the conditions are therefore not fulfilled.

g) Products that are a combination

A product that combines a device with a medicinal product / ATMP¹¹ is considered either a medical device (with an ancillary medicinal substance), or a medicinal product / ATMP (that includes a medical device component). The corresponding regulation is applicable to trials with these products. 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 for combined studies vs products that are a combination

- Example 1: A new injectable hormone (medicinal product) and a new reusable pen injector (medical device) will both be tested in a clinical trial. This is a combined study. Both requirements apply, requirements for clinical trials of medicinal products and requirements for clinical investigations of medical devices. For your submissions to Swissmedic, refer to Information Sheet [BW600_00_017e MB](#).
- Example 2: A drug-eluting coronary stent is considered a medical device. Clinical trials of these products are clinical investigations of medical devices. They are not combined studies, requirements for trials of medicinal products do not apply.
- Example 3: A single-use infusion device prefilled with a drug is considered a medicinal product. Clinical trials are medicinal product trials. They are not combined studies, requirements for clinical investigations of medical devices do not apply.

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 of medical devices can be found on the Internet: www.swissmedic.ch/ci

¹¹ Advanced therapy medicinal products (ATMP) include, for example, gene therapy products, somatic cell therapy products, tissue engineered products, RNA products.

Change history

Version	Change	sig
6.2	The phone number in the footer of the title page has been updated. Wording has been adjusted in sections 5.2.4 and Annexes A1 and A2. A new section (5.2.6) has been added on submission in case of confidentiality restrictions. More detailed instructions were added to section 7.2.1c). A link to the Swissethics template was added to section 7.2.4 on annual reports. Section 9 on databanks used in Switzerland has been updated. More guidance on pregnancy has been added to Annex A4. New information has been included under 'Troubleshooting' in Annex A6 for submissions via the eMessage portal. In section f) of Annex A7, a link has been added to Swissmedic guidance on in-house devices. Links, typos, formatting have been checked and updated.	sci
6.1	Box 4 in Annex A2: Information added on enrolling a narrow study population with more favorable benefit-risk profile. The federal revision of Human research act ordinances resulted in some updated terminology (authorisation/approval, clinical trial with/clinical trial of, etc.). Reference added to the Swissmedic information sheet MU600_00_016_MB.	sci
6.0	Combined studies: A new information sheet dedicated to submissions for combined studies has been published by Swissmedic. Corresponding contents in sections 1, 5.1.2, 5.3 and Annex A7 have been replaced by references to the new information sheet. Section 7.2.5: Updated references for the final clinical investigation report and summary.	sci
5.0	New contents available in section 5.2.5 concerning reduced fees for academic sponsors.	sci
4.4	Annex A2 has been updated according to MDCG 2024-3.	sci
4.3	New layout. Appendix A7, in-house manufacturing in healthcare institutions: New references added (link to new Swissmedic information available on the topic, link to the notification form for in-house manufactured devices). Appendix A7, combined trials: Update on sending CIOMS forms for SUSAR to Swissmedic.	nay/sci
4.2	Updated contents available in annex 7 concerning combined trials (submissions for combined trials in Switzerland, submissions when non conforming products are added to previously authorised trials)	sci
4.1	Updated contents available in section 5.1 (updated decision tree for authorisation applications), section 5.1.5 (flat fee for simplified reviews), section 5.1.a (EU implementing regulation 2022/2346 on devices without a medical purpose), section 7.2 (revision of MDCG 2020-10), section 5.1.a and annex A7 (devices without an intended medical purpose), annex A7 (fees for combined trials; notification of SUSAR during combined trials; combined trials submissions when non conforming products are added to previously authorised trials; reference to MDCG 2023-1 on in-house devices).	sci
4.0	New contents available in section 5.1.b (decision tree for submissions to Swissmedic), section 5.2 and annex A7 (combined trials of medicinal products and devices) annex A6 (eMessage submissions, link to new video tutorial), and annex A7 letter g (medical devices manufactured and used in the same healthcare institution).	sci