

Please note that, on 6 September 2018, Swissmedic will change its submission practice and forms. Submissions will be switched over as follows:

- Until 5 September 2018 please continue to submit the documents as hard copy. Exception: You can submit tabular summaries of SAE reports and documents with less than 20 pages by e-mail (to clinicaltrials.devices@swissmedic.ch, maximum data volume: 3 MB).
- From 6 September 2018 continue to submit the tabular summaries of SAE reports by e-mail to clinicaltrials.devices@swissmedic.ch. All other submissions will be switched to the new electronic submission route via the Swissmedic Portal (eGov Service eMessage, www.swissmedic.ch/emessage-de). Register as a user on this site. Always take note of the latest information from Swissmedic on www.swissmedic.ch/cj where the forms and eDok folder structure are available.

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1 Objective

This information sheet is intended for sponsors of clinical trials of medical devices, Contract Research Organisations (CROs), and clinical investigators. It provides guidance on the authorisation process, reporting requirements of sponsors, and the surveillance of clinical trials by the Swiss Agency for Therapeutic Products, Swissmedic.

2 Introduction

The Human Research Act (HRA, SR 810.30) regulates biomedical research on human subjects at the Federal level and is based on internationally recognised principles.

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

Medical devices include, for example, implants, therapeutic devices, diagnostic devices for use on patients and other products¹, but not medicinal products and transplant products with living cells. Information on clinical trials with medicinal products and transplant products can be found in separate documents at

- www.swissmedic.ch > Human medicines > Clinical trials
- www.swissmedic.ch > Human medicines > Special categories > Transplant products

3 Legal basis and standards

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

- European Medical Devices Directives – existing regulatory requirements, in particular:
 - European Directive 90/385/EEC relating to active implantable medical devices, Annexes 1, 6 and 7
 - European Directive 93/42/EEC concerning medical devices, Annexes I, VIII and X
 - European Directive 98/79/EC on *in vitro* diagnostic medical devices

European regulations – new regulatory requirements (contains transitional periods), in particular:

- Regulation (EU) 2017/745 on medical devices
- Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices
- National law, and in particular:
 - Federal Act on Research involving Human Beings (Human Research Act, HRA, SR 810.30)
 - Ordinance on Clinical Trials in Human Research (ClinO, SR 810.305)
The ordinance is currently undergoing a revision for adaptation to the European regulations on medical devices and *in vitro* diagnostic medical devices
 - Ordinance on Organisational Aspects of the Human Research Act (HRA Organisation Ordinance, OrgO-HRA, SR 810.308)

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)

- Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA, SR 812.21)
- Swiss Agency for Therapeutic Products Fees Ordinance (GebV-Swissmedic, SR 812.214.5)²
- Standards:
 - EN ISO 14155, Clinical investigation of medical devices for human subjects – Good Clinical Practice
 - Other European harmonised standards that reflect the status of science and technology with regard to the development and manufacturing of medical devices
- International texts
 - Declaration of Helsinki, Biomedicine Convention, Additional Protocol by the Council of Europe to the Biomedicine Convention, CIOMs Guidelines, etc.

4 Compliance with the EN ISO 14155 standard

Art. 5 ClinO; Annex I Section 2 ClinO

- In Switzerland, compliance with this standard is mandatory for clinical trials of medical devices.
- The EN ISO 14155 standard defines internationally recognised terms and describes, for example, the content of the documents necessary and the obligations of involved persons.

For clinical trials involving a particularly low risk, certain deviations are possible, particularly for post-market trials. However, the protection of the participants and data quality and security may not be affected by such deviations. All deviations must be disclosed in the clinical investigation plan (CIP) of the clinical trial. The deviation must be described and the absence of effects of the deviation on the protection of the participants and data quality and security must be justified. A separate, dedicated section in the CIP is recommended for deviations (e.g. "Compliance with the EN ISO 14155 standard").

5 Authorisation of clinical trials of medical devices

5.1 Trial categories and responsible authorities

Arts. 20 and 23-34 ClinO

- Category A trials: For these trials, the investigational devices concerned may be placed on the Swiss market (i.e. the CE mark has been obtained) and the devices will be used in the trial as stated in the CE-marked instructions for use. In particular, for example, the relevant indications, contraindication, device settings and precautions must be observed. Such trials are often termed "post-market trials".
These trials are examined and authorised by the competent Cantonal Ethics Committee. In Switzerland, the Cantonal Ethics Committee also decides alone whether it is acceptable to carry out burdensome additional investigations. For your applications, please follow the instructions of the Cantonal Ethics Committee³.
- Category C clinical trials: For these trials, the medical devices are not CE marked, or will not be used in accordance with the CE-marked instructions for use, or their use is prohibited in Switzerland. Such trials are often termed "pre-market trials".
These trials can begin in Switzerland once the authorisations of both Swissmedic and that of the Cantonal Ethics Committee have been obtained. Applications for authorisation may be sent simultaneously to the two institutions. Before beginning a trial, please ensure that you have

² Until 31.12.2018: Therapeutic Products Fees Ordinance (HGebV, SR 812.214.5).

³ List and information on www.swissethics.ch

received authorisations from both institutions and that they are based on identical versions of the trial documentation. Otherwise, please submit an amendment in order for the documents to be aligned before the trial starts (for amendments, see Section 7.2.1 below).

Comments:

- Devitalised human tissues: According to Swiss law, no conformity marking is available for classical and active implantable medical devices where devitalised human tissue is used for their production or which contain such tissue. These devices may not be placed on the market in Switzerland if they have not yet been released for the market by the manufacturer or if the manufacturer has not yet notified them to Swissmedic⁴. Clinical trials with non-marketable medical devices fall within Category C.
- Custom-made devices: Custom-made devices are not marketable⁵ if the custom manufacturer systematically employs methods that have not been adequately validated from the preclinical or clinical standpoint. Clinical trials with non-marketable custom-made devices fall within Category C.
- Non-conforming medical devices for in-vitro diagnosis (IVD): Medical use is not involved in numerous performance studies of IVD; in particular, individual test results are not reported to investigators, treating doctors, patients or other persons. Such research projects are not clinical trials and are approved solely by the ethics committee.

5.2 Applications to Swissmedic for the authorisation of Category C trials of medical devices

Arts. 33, 36 and Annex 4 ClinO; Art. 54, para. 4, letter b TPA; HGebV

5.2.1 First submission to Swissmedic of an authorisation application

<p>First submission of an authorisation application</p> <p>Via the Swissmedic Portal eGov Service eMessage (http://www.swissmedic.ch/emessage-en) submit the zipped eDok structure enclosing form BW510_00_005e_FO, among others.</p>

The eDok structure, an explanation video, forms, information sheets and information on the eGov Service eMessage are available in various languages at www.swissmedic.ch/cj and www.swissmedic.ch/cj > How to submit.

For category C trials of devices that emit ionising radiation, please also read section 5.4 of this information sheet.

5.2.2 Formal check

Swissmedic will carry out an administrative check within 7 days to ensure that all the required documents have been provided. Incomplete submissions are considered to be incorrect, and may not be processed by Swissmedic. In such cases, Swissmedic requests applicants to submit a complete application, and in the meantime does not process the documents further. Once all the documents are provided, Swissmedic acknowledges the receipt of the formally correct application documents,

⁴ Art. 3 TPA; Art. 2 paragraph 1 MedDO; Art. 6 MedDO.

⁵ In addition to the prescribing doctor, the custom manufacturer influences various aspects of the design and manufacture. However, the custom manufacturer is not free to choose its general custom manufacturing methods. The Essential Requirements for medical devices must be demonstrably fulfilled, incl. the required clinical data. In medical practice, deviations from validated custom manufacturing methods are permitted only to cover the individual needs of a particular patient. The situation is different in research practice. Non-conforming custom manufacturing methods are determined in advance (not individually) and are the subject of investigation in category C clinical trials.

provides the European EUDAMED identification number for the trial (if not already attributed), and informs that the review of the content is starting.

5.2.3 Review and authorisation

Swissmedic can ask for additional information during the review process. If a positive assessment is possible on the basis of the documentation submitted, Swissmedic authorises the trial within 30 days, with restrictions or conditions if appropriate. The review may, in certain cases, be extended to 60 days (for first-in-man trials, manufacturing using a new procedure, or devices that can emit ionising radiation).

5.2.4 Refusal

If a positive assessment is not possible, Swissmedic will first send a preliminary decision, followed by the final decision. The preliminary decision lists the findings, any missing information, as well as references to the current requirements. Based on this information, the sponsor can clear up any misunderstandings, submit any missing information, correct application documents and resubmit these to Swissmedic. Sponsors may contact Swissmedic by phone, if necessary, to ask questions regarding identified shortcomings and discuss required changes. If issues can not be handled in due time, the sponsor can retract the application, a new submission is possible at any later point in time.

5.2.5 Fees

From 01.01.2019 the flat rate fee for handling an application for the authorisation of a clinical trial with a medical device amounts to CHF 5,000.- (GebV-Swissmedic) and is invoiced by Swissmedic. Relevant additional workload caused by shortcomings regarding the documentation and corrections will also be invoiced at a rate of CHF 200.- per hour.⁶

In case of withdrawal of a new authorisation application before review completion the flat rate fee is inapplicable. In this particular case, the work provided up until that point in time will be invoiced at an hourly rate of CHF 200.-.

5.3 Applications to Swissmedic for the authorisation of combined trials

- In combined trials, both medical devices and medicinal products (or transplant products) are the subject of investigation.
- The requirements for trials with medicinal products (or transplant products) and those for trials of medical devices must both be met.
- In such cases, please complete both forms and submit a full documentation for trials of medical devices plus a full documentation for trials with medicinal products or transplant products to Swissmedic, each according to the corresponding requirements.

Switzerland takes into account the current European demarcation criteria between medicinal products and medical devices. Information and criteria for demarcation issues can be found in the "Guide to the Regulation of Medical Devices" at www.swissmedic.ch/md.

⁶ Until 31.12.2018, the flat rate fee for handling an application for the authorisation of a clinical trial with a medical device amounted to CHF 1,000.- (HGebV). Relevant additional workload caused by shortcomings regarding the documentation and corrections was additionally invoiced at a rate of CHF 200.-/h.

Box 1: Examples of combined trials

- Example 1: A new parenteral hormone product (medicinal product) and a new pen injector (medical device) are to be tested in a clinical trial. This is a combined trial involving a medicinal product and a medical device.
- Example 2: Drug-eluting coronary stents are considered to be medical devices in accordance with European regulations. Clinical trials of these products are medical device trials and need not be handled as combined trials.

During a combined trial please send reports about adverse events as follows:

- Send reports relating to medicinal products to SUSAR@swissmedic.ch, please observe the Information sheet "Safety relating to clinical trials - Compulsory notification".
- Reports relating to medical devices:
The forms can be found at www.swissmedic.ch/ci > Reporting during ongoing clinical trials.
 - Send tabular SAE reports according to MEDDEV 2.7/3 by e-mail to clinicaltrials.devices@swissmedic.ch.
 - From 6 September 2018, all other reports will be sent in the eDok structure via the Swissmedic Portal (eGov Service eMessage, www.swissmedic.ch/emessage-en).

5.4 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. 1, Art. 2 para. b section 6, Art. 28, Art. 36, Art. 44 and Annex 4 section 5 ClinO and Art. 28 of the Radiation Protection Ordinance (SR 814.501)*. These documents must be submitted to the Cantonal Ethics Committee and, if required, to the Swiss Federal Office for Public Health and to Swissmedic.

For Category C trials with therapeutic products that can emit ionising radiation, Swissmedic will forward a complete copy of the application to the Swiss Federal Office of Public Health.

6 Review and surveillance activities by Swissmedic

Art. 54 TPA; Art. 32 para. 3 ClinO; Arts. 46-48 ClinO

6.1 Frequent objections

In order to authorise Category C trials, Swissmedic checks the status of the fulfilment of Essential Requirements (device requirements according to EU legislation), if the product risks are duly considered in the clinical trial and the product data is in line with current scientific knowledge and correctly indicated in the protocol.

In category C clinical trials the following aspects that have recurrently led to objections by Swissmedic. Additional information regarding each of these aspects can be found in the annex:

- Recording 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 trials 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 a trial dependent on additional conditions.

7 Submissions to Swissmedic during clinical trials (notification duties and authorisations)

The following sections describe duties of the sponsor in regard to Swissmedic. Requirements in regard to Cantonal Ethics Committees must also be followed. These are not addressed in this information sheet; please follow the instructions of the Cantonal Ethics Committees.

In accordance with the EN ISO 14155 standard and according to the law, it is mandatory for sponsors of clinical trials to operate an appropriate quality assurance system and all duties must be assigned to an individual. The sponsor should check the following:

- Whether written procedures are available and up to date,
- whether the notification duties and authorisation requirements for Switzerland are correctly implemented,
- whether the job descriptions of personnel are complete and up to date,
- any contracts with external parties,
- the appropriateness of the basic and advanced training of involved personnel.

7.1 Category A trials

Art. 42 ClinO and Art. 15 MedDO

In these trials, only serious incidents with the devices need to be reported to Swissmedic (materiovigilance). In the clinical trial the sponsor must submit the report to Swissmedic.

The definition of the term "serious incidents" and the organisation of the reporting process are regulated in Switzerland in the same way as in the EU. Further details can be found at www.swissmedic.ch/md > Materiovigilance. If necessary, please consult the materiovigilance contact person at your hospital and send the materiovigilance reports to materiovigilance@swissmedic.ch.

7.2 Category C trials

7.2.1 Changes (amendments)

Art. 34 ClinO

Amendments require Swissmedic authorisation/notification as well as Ethics Committee authorisation/notification. Before submitting an amendment, please check which documents and what information has already been provided to Swissmedic, and which of them are affected by the amendment. Changed documents only need to be submitted.

For amendments, the sponsor needs to submit the following documents to Swissmedic:

- A cover letter explaining the reason for the amendment
- Documents affected by the amendment, with all changes compared to the earlier version highlighted in the text. Please only submit the versions with the changes highlighted in the text, and not the clean versions.

a) Amendments that are submitted to authorisation

The following amendments must be authorised by Swissmedic before being implemented; requests are reviewed by Swissmedic within 30 days:

- Changes to the therapeutic product, or to its administration or use.

- Changes based on new preclinical or clinical data which may affect product safety. In this case, the sponsor must also decide whether there is a need to suspend the use of the device temporarily in order for the situation and the consequences to be analysed (*see also Art. 37 ClinO*).
- Changes concerning the production of the device(s) which may affect product safety.

Submission of amendments requiring authorisation

Via the Swissmedic Portal eGov Service eMessage (http://www.swissmedic.ch/emessage-en) submit the zipped eDok structure enclosing form BW510_00_004e_FO, among others.

- b) Change of sponsor, issuing of an authorisation for the new sponsor
Submit documents at least 30 days before the scheduled amendment date.

Submission of a change of sponsor
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Via the Swissmedic Portal eGov Service eMessage (http://www.swissmedic.ch/emessage-en) submit the zipped eDok structure enclosing form BW510_00_004e_FO, among others.

The following attachments should be submitted:

- Cover letter from the previous sponsor with details about when its activities in the trial end and any explanations about the changes.
- From 6 September 2018, the completed form BW510_00_005d_FO, with all the details of the new sponsor.
- Amended trial documents in “Track changes” mode.

- c) Amendments requiring notification

All other amendments must be notified to Swissmedic. Please note that authorisation from the Cantonal Ethics Committee may be required for these amendments. The list of amendments that require authorisation from the Cantonal Ethics Committee can be found in *Art. 29 ClinO*.

Submission of amendments requiring notification
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Via the Swissmedic Portal eGov Service eMessage (http://www.swissmedic.ch/emessage-en) submit the zipped eDok structure enclosing form BW510_00_004e_FO, among others.

The form is available at www.swissmedic.ch/ci in various languages.

Art. 34 ClinO — Fees

From 01.01.2019 the flat rate fee for handling amendments that are submitted to authorisation amounts CHF 1,000.- (GebV-Swissmedic) and is invoiced by Swissmedic. Relevant additional workload caused by shortcomings regarding the documentation and corrections will additionally be invoiced at an hourly rate of CHF 200.-.⁷

In case of withdrawal of an amendment requiring authorisation before review completion, the flat rate fee is inapplicable. In this particular case, the work provided up until that point in time will be invoiced at a rate of CHF 200.- per hour. Likewise in case of change of sponsor requiring authorization the provided work will be charged according to the hourly rate of CHF 200.-.

⁷ Until 31.12.2018 the handling of amendments submitted to authorisation was invoiced at a rate of CHF 200.-/h (HGebV).

7.2.2 Safety (risks and safety measures)

Arts. 12 and 15 HRA; Art. 34 and 37 ClinO

The sponsor and the investigator themselves take all necessary measures without delay in order to protect the trial subjects from immediate danger (*Art. 34 ClinO*).

In the course of the clinical trial, new circumstances that could threaten the safety of the trial subjects and the corresponding safety and protective measures must be notified to Swissmedic within 2 days. The following situations in particular must be reported:

- device deficiencies requiring measures
- previously underestimated risks
- safety-related measures or amendments of the Clinical Investigation Plans agreed upon with foreign authorities or Ethics Committees or imposed by them.

Notification of new circumstances that could threaten the safety of the trial subjects, and the corresponding safety and protective measures

Via the Swissmedic Portal eGov Service eMessage (<http://www.swissmedic.ch/emessage-en>) submit the zipped eDok structure enclosing form BW510_00_004e_FO, among others.

The form is available at www.swissmedic.ch/ci in various languages.

7.2.3 Serious adverse events (SAEs) and device deficiencies

Art. 42 ClinO; MEDDEV 2.7/3; Art. 5 and annex I.2.2 ClinO together with points 6.4, 8.2.5 and 9.8 of standard EN ISO 14155

General information

- All AEs and device deficiencies must be recorded correctly by the investigator on the Case Report Forms (CRFs). An example can be found in Annex 1.
- For pre-market trials with relevant risks in particular, the information must be monitored continuously by the sponsor. It is mandatory for sponsors to identify excessive risks rapidly and to prevent them. For unexpected SAEs (with regard to type, severity or frequency), it may be necessary to suspend interventions temporarily in order to carry out further investigations or to check the design of the device, the basis of the trial or trial procedures. See also Section 7.2.2.

The following issues must be reported to Swissmedic

- all serious adverse events in Switzerland and abroad must be reported in cases where it cannot be excluded that they are caused by the investigational device or a procedure carried out within the framework of the clinical trial (i.e. serious and not obviously unrelated);
- all device deficiencies noted during the trial in Switzerland and abroad that have a potential for causing serious adverse events.

A device deficiency is a shortcoming of a medical device with regard to its identity, quality, durability, reliability, safety or performance. Deficiencies include malfunctions, user errors, misuse, inadequate labelling and instructions.

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

Is the case serious⁸?

Criteria for device deficiencies

⁸ According to Annex 1 ClinO and the MEDDEV Guideline 2.7/3 of May 2015

- Device deficiencies that might have led to a medical occurrence
 - a) if either suitable action had not been taken,
 - b) if intervention had not been made, or
 - c) if circumstances had been less fortunate.

Criteria for adverse events

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

A planned hospitalization for a pre-existing condition or a procedure required by the Clinical Investigation Plan without a serious deterioration in health is not considered to be a serious adverse event.

When using the term "serious", please use only the criteria listed here. These are more stringent than criteria sometimes used in daily clinical practice or those used in clinical trials with medicinal products.

Can a causal link between the event and the investigational device or the intervention/procedure be ruled out?

Causality cannot be ruled out if

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

Timelines for notification, forms for sponsors:

- Events must be reported to Swissmedic within 7 days. Reporting is the responsibility of the sponsor.
- For multi-centre studies, the table in accordance with the MEDDEV Guideline 2.7/3 must be submitted to Swissmedic by eMail (to clinicaltrials.devices@swissmedic.ch). This Excel table is completed cumulatively over the course of the trial, and changes compared with the last version are highlighted.
- For all studies (multi-centre and mono-centre): If an event takes place in a Swiss center, is serious, and is not obviously unrelated, please:

Notification of serious adverse events and device deficiencies

Via the Swissmedic Portal eGov Service eMessage (http://www.swissmedic.ch/emessage-en) submit the zipped eDok structure enclosing form BW510_00_006e_FO, among others.

The forms are available at www.swissmedic.ch/ci in various languages.

7.2.4 Annual safety report on the safety of participants

Art. 43 ClinO

From the date of approval of the trial by Swissmedic, a report must be submitted annually. A typical report includes the following information:

- Data cut-off date of the report: Date up to which study data should be considered in the report.
- Status of recruitments: Current number of trial subjects worldwide and in Switzerland, duration of the currently existing follow-up observations
- Expected serious adverse events: Description, occurrence in the trial arm versus control arm and medical literature, evaluation by the sponsor
- Serious unexpected adverse events, including device deficiencies: causality with the investigational device or a procedure, possible causes, problems related to the use of the medical devices at the trial centres
- Safety-relevant measures taken by the sponsor or imposed by Ethics Committees or authorities anywhere in the world
- Results from other clinical trials with the investigational device (if available)
- Sponsor's conclusions regarding the safety of the trial subjects and the continuation of the trial
- Annex with the list of the serious adverse events for which reporting is mandatory (SAEs and serious device deficiencies) and which was taken into account for the content of the report at the cut-off date

The report must be up to date. Sponsors may submit the report to Swissmedic before the specified deadline, which in multinational trials allows to write and submit a joint annual report for all authorities involved.

Notification of Annual safety reports
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Via the Swissmedic Portal eGov Service eMessage (http://www.swissmedic.ch/emessage-en) submit the zipped eDok structure enclosing form BW510_00_004e_FO, among others.

The form is available at www.swissmedic.ch/cj in various languages.

7.2.5 Completion, discontinuation, interruption of the trial

Art. 38 ClinO

- The sponsor must notify Swissmedic of the completion of a clinical trial within 90 days (as of last patient, last visit).
- A discontinuation or an interruption of the trial, and the reasons for this, must be notified within 15 days.
- The final report, with contents in accordance with EN ISO 14155, must generally be submitted within one year of completion.

For clinical trials with radioactive sources, and in accordance with Art. 44 ClinO, the investigator provides all relevant information concerning radiation protection within one year to the Federal Office of Public Health, and including – in particular – a retrospective radiation estimation for the trial subjects. Exemptions to the reporting requirement may be granted on request.

Notification of trial completion, discontinuation, interruption
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Via the Swissmedic Portal eGov Service eMessage (http://www.swissmedic.ch/emessage-en) submit the zipped eDok structure enclosing form BW510_00_004e_FO, among others.

The form is available at www.swissmedic.ch/cj in various languages.

8 Data retention requirements

Art. 45 ClinO

- An archiving period of at least 10 years after the end of the trial is generally required (for sponsors, investigators, manufacturers of investigational devices);
- the period is at least 15 years for implants.

9 EUDAMED databank and public registry

Art. 64 TPA; EUDAMED Decision 2010/227/EU; Arts. 64-67 ClinO; Annex X Section 2.2 of Directive 93/42/EEC on medical devices or Annex 7 Section 2.2 of Directive 90/385/EEC on active implantable medical devices

- A databank for the EU and EFTA Member States (EUDAMED) permits the identification of multinational clinical trials and the co-ordination among national surveillance authorities in Europe. EUDAMED is a depository for basic data on clinical trials with medical devices and any amendments and national measures.
- Pre-market clinical trials 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 within Europe, and is communicated to the sponsor.
- If a EUDAMED CIV-ID has already been assigned to your trial, when submitting an application for authorisation in other countries you need to inform the competent authorities accordingly.

The EUDAMED databank is not public. Registration in EUDAMED therefore does not replace the entry in a public registry that is mandatory according to *Art. 64-67 ClinO* and also required by the Declaration of Helsinki. Public registries include e.g. www.clinicaltrials.gov or a primary registry for clinical trials recognised by the WHO. The registration must be carried out by the sponsor before the clinical trial takes place. For information on national registration, please consult www.kofam.ch. The data must be recorded there in the version that has been authorised by the competent Ethics Committee (*Art. 64 para. 3 ClinO*).

10 Sponsors with registered offices abroad

Art. 2 letter c ClinO

- Sponsors headquartered in another country must specify a representative domiciled/headquartered in Switzerland to act as the direct contact for Swissmedic. Preliminary decisions, official decisions and invoices from Swissmedic are sent to the representative.
- Legal and natural persons domiciled or headquartered in Switzerland can be specified as representatives, e.g. distribution companies, a lawyer or the clinical investigator.
- Additional information can be found at www.swissmedic.ch/cj > Authorisation procedure, in the document "*Interpretation guide: Obligations of representatives of foreign sponsors*".

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

- In Switzerland, the fulfilment of the liability and coverage obligations is subject to review and approval by the Cantonal Ethics Committee. Taking out insurance coverage with an insurance company headquartered in Switzerland or with a branch office in Switzerland is acceptable. This ensures that the trial subjects are able to assert both their right of direct claim and associated legal enforcement claims in Switzerland.
- Further information on insurance can be found at www.swissmedic.ch/md_ci_bw in the document "*Interpretation guide: Obligations of representatives of foreign sponsors*". Information of Cantonal

Ethics Committees regarding the requirements for insurance policies can be found at www.swissethics.ch > templates.

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 - Frequent objections

A1: Recording of adverse events and device deficiencies

Art. 12 and 15 HRA; Annex I ClinO and statement of the manufacturer according to Annex 6 of Directive 90/385/EEC or Annex VIII of Directive 93/42/EEC; EN ISO 14155 sections 3.5, 8.2.5, 9.8, A.14, C.2.4.h and C.2.4.i.; Art. 42 ClinO with Annex I ClinO and MEDDEV 2.7/3, Version Dec. 2010

The sponsor has a duty of care and must satisfy reporting requirements in respect of adverse events and device deficiencies. In category C trials, as a rule, the sponsor must receive and check information from the investigators continuously throughout the trial. Suitable forms are required (Case Report Forms, CRF) and to be completed by the investigators. Box 2 to 4 show typical examples suited to category C trials of medical devices.

Box 2: Example showing systematic documentation of occurrence of adverse events and device deficiencies (the texts are integrated in CRF for procedures, follow-up 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 an "Device deficiency" form. No

Box 3, example: Content of a typical form for detailed documentation of "Adverse events"

Study title

Name of sponsor

Site Number:

Patient ID:

Age of the patient / Year of birth:

Date the center became aware of event:

Date of implantation / procedure:

Date of event / date of onset of symptoms:

Criteria for seriousness

- death
- life-threatening illness or injury
- permanent impairment to a body structure or a body function
- led to in-patient hospitalization or prolongation of existing hospitalization
- 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 foetal distress, foetal death or a congenital abnormality or birth defect

Description of event, measures taken, outcome:

[blank space for extensive descriptions]

.....

.....
.....
.....

Causality with the intervention/procedure

- not related
- unlikely
- possible / not known
- probable
- causal

Causality with the device

- not related
- unlikely
- possible / not known
- probable
- causal

Expectedness

- Expected Unexpected

Study arm [for open-label comparative studies only]

- Verum Control

Outcome

- resolved without sequels
- ongoing, medical condition is not stable, please provide updates on a regular basis
- resolved with sequels, medical condition is stable

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Box 4, example: Content of a typical form for detailed documentation of "Device deficiencies (i.e. . malfunctions, use errors, and inadequate labelling)

Study title

Name of sponsor

Site Number:

Patient ID:

Date of event / of the observation:

Nature of the problem

- Malfunction*
- Use error Benutzungsfehler*
- Inadequate labelling*
- Other:*

Criteria for seriousness

Is a Device deficiency that did not lead to an adverse event but could have led to a medical occurrence

- a) if a suitable action had not been taken*
- b) if intervention had not been made*
- c) circumstances had been less fortunate*

Description of the deficiency (occurrence, measures taken, outcome):

[blank space for extensive descriptions]

.....
.....
.....
.....
.....
.....
.....

Impact on person

- led to an adverse event. Please complete the „Adverse event“ CRF.*
- None*

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A2: Risk-reduction measures

The sponsor is obliged to implement risk reduction measures depending on the status of clinical development, the degree of innovation and the risk potential. Box 5 shows safety measures that need to be considered and, where necessary, included in the clinical investigation plan for pre-market clinical trials. The aim is to avoid problems, or identify them at an early stage, so that the trial subjects are not exposed to unnecessary risk.

Box 5: Safety measures for pre-market clinical trials

- a. Prior training of every user: *Possibly with models, animals, cadavers.*
- b. On-site supervision of every user: *Supervision while using the devices for the first time.*
- c. Individual releases: *The sponsor analyses the data after each use (or each trial subject) and clarifies any questions with the investigator. Depending on the data, the sponsor either releases the next use or evaluates the need for a change to the investigational device or its applications. The data needed for the releases has to be defined (on AE, SAE, device deficiencies, other information), incl. the minimum required follow-up of the previous use / trial subject.*
- d. Risk-adapted recruitment of trial subjects: *Do not expose an unnecessarily large number of trial subjects. Define phases, e.g. First-in-man Phase / Feasibility Phase. Before recruiting further trial subjects, carry out an interim analysis, define the data needed for the interim analysis, incl. the minimum required follow-up of trial subjects who have already been treated. For interim analysis, 100% source data verification and resolution of queries (AE, SAE, device deficiencies, missing data) often needs to be foreseen.*
- e. Short deadlines for the investigators to submit reports to the sponsor, monitoring of centres: *Particularly for observations relating to device deficiencies, SAE, AE. Foresee rapid checks for the CRF, including attributions (not serious/serious, expected/unexpected, device deficiencies with/without a potential for serious harm). If necessary, retrain centres, in case of unexpected issues temporarily suspend device use and/or foresee other measures.*
- f. Committees: *Data monitoring committee (DMC), e.g. data safety monitoring board (DSMB) or data safety monitoring committee (DSMC). In double-blind randomised trials, unblinded data need to be assessed, investigators should not be part of the group.*
- g. Stopping criteria: *Define type and number of incidents that will lead directly to the suspension of further uses.*
- h. Implant card for trial subjects: *In addition to standard information the card also needs to include information on participation in the research project, title of the trial, contact details of the investigator.*
- i. Return and examination of used devices: *i.e. in the event of problems during the use of the device, device deficiencies, explantations (possibly with surrounding tissue).*
- j. Follow-up of trial subjects: *While feasibility studies generate data for further product development steps, information that ensure the safety of the trial subjects and their adequate further management also need to be collected. Problems should be readily identified (e.g. by close observation of the entire healing process, any subsequent procedures and adaptations to the device intended by the manufacturer, the short, medium, long-term outcomes), unforeseen issues need to be analysed centrally and communicated to the investigators.*
- k. Contact persons for information on serious incidents: *Investigations concerning trial subjects who are lost to follow-up should be planned in a risk-based approach, for details see Annex 3.*
- l. Restrictions for diagnostic results: *While non-conforming diagnostic devices are considered unreliable, incorrect test results can cause wrong decisions on patient care. Do not report individual results unnecessarily to investigators, treating doctors, patients or other individuals. Justify exceptions, define communication in case of alarming results and incidental findings.*
- m. Other measures: *Depending on the specific project.*

A3: Handling of mortality, disabilities, patients lost to follow-up

Annex 1 ClinO and the statement of the manufacturer in accordance with Annex 6 of Directive 90/385/EEC or Annex VIII of Directive 93/42/EEC; Arts. 12 and 15 HRA

The course of various diseases and different interventions are linked to mortality and to physical or mental disability. Such events can therefore be foreseen as endpoints. The trials must be planned in such a way that the endpoints foreseen by the sponsor can be recorded correctly.

Correctly recorded endpoints are relevant for the correct estimation of the efficacy and safety of the medical devices investigated and for determining the safety for the trial subjects. During pre-market trials 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 trial planning and missing data can moreover threaten the validity of the results.

Corresponding important aspects can be found in Boxes 6 and 7.

Box 6: Organisational aspects for trials with endpoints linked to death or with endpoints that lead to the loss of independence

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

Box 7: Examples of inadequate trial planning in the case of trials with endpoints linked to death or with endpoints that lead to the 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 trial subject with regard to obtaining health information from third parties.
 - in the data analysis, failure to take into consideration the possibility that more trials subjects 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; Point A13 EN ISO 14155

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, children, adolescents, adults lacking the capacity in the consent procedure, patients in emergency situations, pregnant women or embryos / foetuses. Trials with own employees are also considered as problematic due to financial dependence.

For that reason, please check the formulation of the inclusion and exclusion criteria. If particularly vulnerable groups of persons are not explicitly excluded from the trial, the necessary justifications must be in the documentation. Information texts and consent forms are needed for all persons taking part in the trial, 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 trial and, if necessary, to obtain a correct post hoc consent.

In practice, trials under mixed conditions present particular difficulties, and especially if both vulnerable and non-vulnerable trial subjects are to be enrolled or if a temporary, particular vulnerability exists. In such cases, please pay particular attention to correct trial planning. Considerations and examples can be found in Box 8.

Box 8: Considerations regarding trial planning in mixed conditions

Example 1, mixed populations: A trial of a coronary stent is to be conducted. These devices can in principle be used both for elective interventions and for emergency patients with acute myocardial infarction. In a clinical trial, emergency patients are not excluded from the trial based on the inclusion and exclusion criteria: Are you sure the trial should involve emergency patients? Does the documentation state which issues can only be investigated using the emergency patients, and why? How was the necessary number of emergency patients calculated that is needed to investigate these particular issues? For enrolment, how do you make sure that the correct number of emergency patients will be included (stratification)?

Example 2, emergency situation at the beginning of a trial: A coronary stent is used on an emergency patient with a myocardial infarction, and the trial is then continued under regular clinical conditions, with further examinations and enquiries. Who clarifies the emergency patient's capacity to consent, and how? When and how are the patients themselves and / or their entitled 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 trial take place (now with the appropriate reflection period)? Is the written description of this procedure available? Are the necessary documents for the various steps available?

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

A5: Reflection period when consenting for invasive procedures

Art. 16 HRA; Annex 1 ClinO; Point 6.7.2.d EN ISO 14155

The trial subject must be given an appropriate reflection period. For procedures that can be planned, the question of the time required arises, and 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“ (publiziert auf 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 trials.

Box 9: Consent to invasive procedures: the following procedures are not appropriate for elective invasive interventions and will be classified by Swissmedic as critical findings when carrying out inspections of clinical trials

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

Contact in case of questions

General questions: questions.devices@swissmedic.ch

Case related questions: clinicaltrials.devices@swissmedic.ch

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+41 58 462 02 11 (case related questions concerning an application or an approved clinical trial)

Further information from Swissmedic on medical devices can be found on the Internet at
www.swissmedic.ch/md

Change history

Version	Valid and binding as of:	Description, comments	Author's initials
2.2	31.12.2018	<ul style="list-style-type: none"> New content relative to fees: HGebV is replaced by the GebV-Swissmedic Addition of missing Box 4 	dsa
02	01.08.2018	<ul style="list-style-type: none"> New contents: <ul style="list-style-type: none"> - Electronic submissions to Swissmedic and new forms from 6 September 2018 - Chapter 5.1, clinical trials with custom made devices and <i>in vitro</i> diagnostic devices - Annex A1, separation of the terms “adverse event” and “device deficiency” (KlinV amendment of 1.1.2018) - Annex, frequent objections of Swissmedic: New section A2 regarding risk reduction measures in pre-market clinical trials of medical devices Various updated links and references 	sci