

Guidance to Notification form
Clinical investigation of medical devices

(Version 2014-03-26)

This guidance is intended as a general explanation of some requirements relating to clinical investigations of medical devices and should not be regarded as an authoritative statement of the law nor as having any legal consequence.

The Notification form is intended for clinical investigation of non-CE marked medical devices, or medical devices CE-marked for a different purpose than intended in the clinical investigation.

Send the completed form to each National Competent Authority (NCA) for medical devices in the states where the investigation is planned to be conducted. Follow national instructions, usually the form is required both electronically in a docx-format and as a signed version (e.g. scanned in pdf-format).

The content of sections or separate fields with blue label, filled in by the manufacturer, will be uploaded by the NCA into the Eudamed. It is a secure web-based portal acting as a central repository for information exchange between National Competent Authorities and the European Commission. Eudamed is not publicly accessible. The Competent Authorities of the EU, EFTA Member States and Turkey are responsible for entering information about Clinical Investigations of medical devices into Eudamed.

For further information on the Eudamed database and clinical investigations of medical devices, please refer to the EU commission's web sites:

http://ec.europa.eu/health/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm

and

http://ec.europa.eu/health/medical-devices/dialogue-parties/working-groups/cie_wg_index_en.htm

The medical device's directives, Council Directive 90/385/EEC relating to active implantable medical devices and Council Directive 93/42/EEC concerning medical devices, can be found at the EU commission's web site:

http://ec.europa.eu/health/medical-devices/documents/index_en.htm

Note that the directives are implemented as national legislation in the member states. Always consult the national legislation regarding clinical investigations since there may be some differences in requirements.

The MEDDEV guidelines on medical devices can be found at the EU commission's web site:

http://ec.europa.eu/health/medical-devices/documents/guidelines/index_en.htm

Fill in the requested information in the designated fields of the form. Please see further information below.

Section 1 Clinical investigation identification and status

Submission type

Select one of the three options,

- First submission
- Resubmission after refusal/halt
- Significant amendments.

Consult national guidelines concerning what is regarded as a significant amendment that needs to be notified.

NCA registration number

Fill in, if applicable, the registration or reference number previously obtained from the National Competent Authority (NCA) for the same clinical investigation.

Submission date

This is the date when the sponsor submits the notification to the NCA. Select the date from pop-up calendar.

Eudamed identification number

Eudamed assigns an identification number - CIV ID - to each clinical investigation registered in the database by a Competent Authority (CA). The CA must communicate this CIV ID to the manufacturer.

The manufacturer must use this CIV ID in all communications related to the same clinical investigation in all concerned states. The manufacturer can only have a Eudamed CIV ID if the manufacturer has previously notified the same clinical investigation to a CA.

Is there a Clinical trial of a medicinal product with a EudraCT number linked to this notified clinical investigation of a medical device?

Fill in if applicable

Title of the clinical investigation

Fill in the title. It is important that the title remains unchanged if the same clinical investigation is notified to more than one CA.

Clinical investigation plan (CIP) code

The CIP code must remain unchanged throughout a clinical investigation and notification procedures in different member states. The CIP code and the Manufacturer's name are used to search for and generate a Eudamed CIV ID.

Version and date of the CIP

Use version and date of the CIP to indicate any changes/amendments/updates to the CIP throughout the notification procedure and conduct of the CI.

Section 2 Manufacturer

Fill in the indicated fields.

Section 3 Authorised Representative within the EEA if applicable

Fill in the indicated fields if applicable.

Authorised representative means any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter's obligations under the medical device directives. The requirement to have an authorised representative is applicable to all medical devices placed on the Community market, when the manufacturer is based outside of the EU.

The requirement to have an authorised representative is also applicable to devices intended for clinical investigation (MDD, AIMDD) or performance evaluation (IVDD) within the Community market, where the manufacturer is based outside of the EU. For guidance, please see the MEDDEV 2.5/10 Guideline for Authorised Representatives, January 2012.

Section 4 Sponsor

Fill in the indicated fields if applicable.

Definition of sponsor as stated in the EN ISO 14155:2011 (Clinical investigation of medical devices for human subjects – Good clinical practice):

Sponsor - individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation

NOTE When an investigator initiates, implements and takes full responsibility for the clinical investigation, the investigator also assumes the role of the sponsor and is identified as the sponsor-investigator.

Section 5 and 6 Medical device to be investigated

Fill in the indicated fields.

If more than one medical device is subject for the investigation, please use additional notification forms and fill in sections 1, 5 and 6.

GMDN = Global Medical Device Nomenclature

A GMDN code is a five-digit number, each group of devices is also defined by a generic denomination. Example: GMDN code – 35176, generic denomination - Anesthesia mask. The purpose of GMDN codes is to standardize device identification of medical devices for reasons of safe data exchange between competent authorities and others, exchange of post-market vigilance information, research, medical record keeping, e-commerce and inventory purposes.

It is recommended, but not mandatory, that the manufacturer provides a GMDN code to their investigational device.

For further information, please see:

<http://www.gmdnagency.com/>

Section 7 Comparator medical device

Fill in the indicated fields if a medical device is used as a comparator.

A comparator refers to a medical device, therapy (e.g. active control) or placebo used in the reference group in the clinical investigation.

Section 8 Clinical investigation

Fill in the indicated fields. Fill in the checkboxes for the states where the clinical investigation is planned to be conducted. It may occur, after you have completed one or more checkboxes that the form freezes and the other fields cannot be filled in. If this happens, save the file, close it and open again to clear the lock.

Section 9 Clinical investigation – Design and additional information

Fill in the indicated fields. The *summary of clinical investigation plan* is expected to be a very short overview in a few sentences. An overall synopsis and further details of the clinical investigation is expected to be found in the Clinical Investigation Plan.

Section 10 Mandatory attachments

The 60-day review process starts only when all the mandatory attachments are submitted with the notification form. The mandatory attachments are those listed in section 10 of the notification form. If a document is missing, this has to be motivated. Select Yes/No in the Notification form to indicate the submitted documents.

Clinical Investigation Plan (CIP)

For guidance regarding the content of the CIP, see Annex A in EN ISO 14155:2011. The CIP should cover the following topics:

- General information
 - Identification of the clinical investigation plan
 - Sponsor
 - Principal investigator, coordinating investigator and investigation site(s)
 - Overall synopsis of the clinical investigation
- Identification and description of the investigational device
- Justification for the design of the clinical investigation
- Risks and benefits of the investigational device and clinical investigation
- Objectives and hypotheses of the clinical investigation
- Design of the clinical investigation
 - General descriptions
 - Investigational device(s) and comparator(s)
 - Subjects
 - Procedures
 - Monitoring plan
- Statistical considerations
- Data management
- Amendments to the CIP
- Deviations from clinical investigation plan
- Device accountability
- Statements of compliance
- Informed consent process

- Adverse events, adverse device effects and device deficiencies
- Vulnerable population
- Suspension or premature termination of the clinical investigation
- Publication policy
- Bibliography

The CIP should be dated and signed by the sponsor and the principal investigator or the national coordinating investigator if it is a multicentre clinical investigation.

Investigator's brochure (IB)

For guidance regarding the content of the IB, see Annex B in EN ISO 14155:2011. The IB may be provided as a separate document or inserted as a section of the CIP. The IB should cover the following topics:

- Identification of the IB
- Sponsor/manufacturer
- Investigational device information (including description, components, materials, standards, mechanism of action, literature survey with reference list etc.)
- Preclinical testing
- Existing clinical data
- Risk management
- Regulatory and other references

If the investigational device will be in direct contact with body tissues or will be in contact with some other device/product that will be in direct contact with body tissues, the documentation on the material of the device as well as products and substances in the manufacturing process shall allow for an assessment of risks for unfavourable biological effects.

The chapters of preclinical testing (e.g. laboratory tests, animal studies) and existing clinical data (from use in humans) shall contain previous experience of the device or similar devices including any possible or confirmed unfavourable effects. The documentation shall also include possible or confirmed interactions with other devices, medicinal products or agents.

Copy of clinical investigation insurance policy covering the participating subjects

Patients and healthy volunteers participating as subjects in clinical investigations of medical devices in Sweden are covered by the Patient Injury Act (SFS 1996:799). The Act requires those responsible for the subjects' safety and well-being, i.e. the clinical investigator and his principal, to hold a patient injury insurance policy. A copy of the policy or a document of similar signification shall be amended to the notification documents.

The sponsor is advised to acquire an insurance policy covering for possible reclaims raised by the patient injury insurance provider as well as claims raised in accordance with the Swedish Product Liability Act.

Subject information and consent form (in national language)

A copy of the information in the national language (Swedish in Sweden) explaining the aim, nature and possible risks of the proposed investigation to the subjects and a copy of the form used to obtain a written informed consent of subjects to participate in the investigation must be enclosed with the notification. Also include a form intended to obtain consent to disclosure of the subject's medical records to the sponsor's representatives, regulatory authorities and the Ethics committee. (See EN ISO 14155:2011.)

Copy of the opinion of the Ethics Committee if available

Research in the form of clinical investigations of medical devices needs approval by an Ethical Review Board (ERB) prior to initiation.

In Sweden this is regulated by the Ethical Review Act SFS 2003:460. For further information regarding procedures and forms, please see:

<http://www.epn.se/sv/start/startside/>

The application for an ethical review shall be submitted to the ERB by the clinical investigator (on behalf of his principal) on the stipulated form. In case of a multi-centre investigation the application for review shall be submitted by the coordinating investigator.

Submit to the MPA (Swedish Medical Products Agency) a copy of the application to the Ethical Review Board along with the decision and statement by the ERB. If the Board's decision and statement are missing at the time of submission, they may be submitted when available.

List of National investigations site(s), Clinical Investigator (s)

If not included in the CIP, provide separately the list of the principal investigator(s) including the national coordinating investigator in case of a multicentre investigation.

Note the following definitions according to SS-EN ISO 14155:2011:

- Investigation site - institution or site where the clinical investigation is carried out.
- Principal investigator - qualified person responsible for conducting the clinical investigation at an investigation site.

NOTE 1. If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

- Investigator - individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical investigation-related decisions.
- Coordinating investigator - investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation.

Qualifications of the principal investigator(s) (one per site) including the national coordinating investigator if applicable

It is recommended that a *Curriculum vita* include the following information:

- Name
- Date of birth
- Education

- Earlier employment
- Present employment
- Academic qualifications (e.g. publications)
- Education in GCP (good clinical practice)
- Participation in earlier clinical studies (role, type of study)
- Date and signatur

Declaration of conformity with Essential Requirements

All notifications must contain a statement (Active Implantable Medical Devices Directive 90/385/EEC: Annex 6,2.2; Medical Devices Directive 93/42/EEC: Annex VIII, 2.2) that the device in question conforms to the Essential Requirements except with regard to those aspects of the device that are to be investigated and that in respect of those aspects, every precaution has been taken to protect the health and safety of the patient.

The statement must be dated and signed by the managing director or regulatory affairs manager or manager responsible for compliance with the essential requirements. By signing this statement the manufacturer is declaring that the device *actually meets* all of the relevant Essential Requirements, other than those subject to the investigation. Manufacturers must therefore ensure that, at the time a notification is submitted to the Competent Authority, all documentation required to demonstrate conformity with the relevant parts of the Essential Requirements are available for submission.

Section 11 Attachments, if not included in the IB, as applicable

Results of risk analysis

If not included in the IB, submit the risk management report of the investigational device. The Competent Authority may request further documents from the risk management process such as a formal risk analysis, including any code keys, where device-related hazards to subjects and users are identified and assessed. Measures taken to mitigate the risks and to secure the safe use of the device shall be documented (EN ISO 14971) and verified/validated. The justification of the investigation shall be evident from the risk assessment.

List of applied standards

Submit, if not included in the IB, a list of standards applied in full and description and justification of any deviations from applicable harmonised European standards. It is recommended to use the following format or similar to provide this information.

Standard (identifier and title)	Version/ Year	Compliance (with the exception of clinical requirements that will be assessed during clinical investigation)		
		Full	Partial	Description of all deviations and of the alternative solutions adopted to meet the essential requirements of directive 93/42/EEC or 90/385/EEC (as applicable)
		<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	

		<input type="checkbox"/>	<input type="checkbox"/>
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Documentation on tissues of animal origin in the investigational device

See COMMISSION REGULATION (EU) No 722/2012 of 8 August 2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin:

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:212:0003:0012:EN:PDF>

This regulation has entered into force from 29 August 2013. Where applicable a copy of the TSE certificate of suitability issued by the European Directorate for the Quality of Medicines (EDQM), or the evaluation by a Notified Body according to regulation 722/2012, is expected to be submitted with the Notification of a clinical investigation.

Documentation on human blood derivate or on medicinal substances in the investigational device

Submit a copy of the scientific opinion obtained by the Notified Body from a Competent Authority designated by European Medicines Agency (EMA), or a copy of the evaluation from the Notified Body (after having received such scientific opinion) regarding the incorporation of a human blood derivate or a medicinal substance in the investigational device.

Regulatory background:

The investigational device in question must conform to the relevant essential requirements apart from the aspects covered by the clinical investigations.

One of the essential requirements states that where a device incorporates, as an integral part, a human blood derivative, the notified body shall, seek a scientific opinion from the European Medicines Agency on the quality and safety of the substance including the clinical benefit/risk profile of the incorporation of the human blood derivative into the device.

If a medicinal product/substance is an integrated part of the device, and its intended effect is merely ancillary to that of the device, the quality, safety and usefulness of the substance must be verified by analogy with the methods specified in Annex I to Directive 2001/83/EC.

Reference: The medical device directives 90/385/EEC (ANNEX 1 Essential requirements, section 10) or 93/42/EEC (ANNEX 1 Essential requirements, section 7.4)

For guidance see MEDDEV 2. 1/3 rev 3, Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative, Section C.

For guidance see also the EMA guideline (2009/10/WC500004337) on the procedural aspects and dossier requirements for the consultation to the EMA by a notified body on

an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device:

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004337.pdf

Documentation of products/drugs/substances which the device under investigation will be used together / co-act / be compared with

Submit information if not included in the CIP

Intended device labelling

The proposal shall demonstrate how the investigational device will be labelled.

The device shall not carry the CE-mark but be labelled with the inscription "Exclusively for clinical investigation" ("Uteslutande för klinisk prövning"). The labelling must comply with applicable essential requirements of the medical device directives 90/385/EEC (ANNEX 1, section 14) and 93/42/EEC (ANNEX 1, section 13) as implemented in national laws.

It shall be possible to connect a specific device to the identity of a subject, while maintaining confidentiality.

In general, the text should be in the national language (Swedish). English texts may be used if risks for misinterpretation can be excluded. In cases where the device cannot be labelled, the sponsor must show how equivalent information can be linked to the device in a safe and durable manner.

Instructions for use to subjects (in national language) or professional users

Submit the instructions for use if not included in the CIP. The instructions for use shall include if appropriate: instructions for installation, maintenance, cleaning and sterilisation of the device as well as necessary training needed for its use.

Case Report Form (CRF)

If not included in the CIP

Evaluation forms to be filled in by subjects or staff (in national language)

If not included in the CIP

Copy of the application to the Ethics Committee

This document is mandatory if there is no opinion yet available from the Ethics Committee.

Section 12 Signature

The Notification form needs to be submitted in electronic form (.docx) and in a dated and signed version, preferably scanned in pdf format. The notification form should be signed by the person having the sponsor's role.

Follow national instructions regarding submission procedures.