

Definition of terms in the notification form

The numbers refer to the corresponding positions in the notification form.

1. Sponsor

Natural or legal person (usually the manufacturer) who takes the initiative and plans a clinical investigation and of which the proper conduct he is liable to. The sponsor is also responsible for reaching an agreement with the principal of the concerned healthcare provider concerning the carrying out of the investigation. If the clinical investigator and/or his principal take the initiative and plan the investigation, they assume the role of the sponsor.

2. Authorised representative

Natural or legal person authorised by the sponsor/manufacturer to represent him within the EEC.

3. Contract Research Organisation, CRO

Natural or legal person engaged by the sponsor to assist him in regulatory and other matters in connection with clinical investigations.

4. Monitor

Person appointed by the sponsor to verify source data and monitor the proper conduct of the investigation. Reports to sponsor.

5. Clinical Investigator

Person with the required qualifications to carry out the clinical investigation and with whom the sponsor has made an agreement to do so. Along with his principal responsible for the well-being and safety of participating subjects during the investigation. In case of more than one clinical investigator at an investigation site, the sponsor may assign one of them to principal investigator.

6. Co-ordinating Investigator

The clinical investigator in a multi-centre investigation who the sponsor has appointed to co-ordinate the conduct of the investigation.

8.3, 9.3 GMDN code

Internationally approved five-digit number code dividing up medical devices into groups with similar function/purpose. Beside the number code each group is defined by a generic denomination. GMDN = Global Medical Device Nomenclature.

8.8 Investigation of medical devices involving medicinal products

When a clinical investigation of a medical device involves a medicinal product or a substance perceived as a medicinal product, one of the following alternatives applies:

1. If the medicinal product/substance is an integrated part of the device and its intended effect is merely ancillary to that of the device, a notification of clinical investigation of a medical device shall be submitted to the MPA (Example: heparin-coated catheter).
2. If the medicinal product/substance has an effect other than ancillary to the effect or properties of the device but is intended to be exclusively used together with the device and where the combination is not to be reused, an application for clinical investigation of a medicinal product shall be submitted to the MPA (Example: pre-filled syringe).

To both alternatives apply that the documentation concerning the medicinal product/substance (alt. 1) and the medical device (alt. 2), respectively, shall allow for a complete evaluation of favourable and unfavourable effects of the product/substance/device when used for the purpose intended in the investigation.

3. 3. If neither alternative 1 nor 2 is applicable, a notification of clinical investigation of a medical device as well as an application for clinical investigation of a medicinal product shall be submitted to the MPA. The reviews will be co-ordinated.

In case of uncertainty which alternative applies, the MPA may be consulted.

8.9 Investigation of medical products containing tissues of human or animal origin or when such tissues have been part in the manufacturing process

When a clinical investigation of a product containing tissues of human or animal origin or when such tissues have been part in the manufacture of the product, one of the following alternatives applies:

1. If the product is a medical device and (a) as an integrated part contains a component originating from human blood or plasma or (b) entirely or partly is made of non-viable animal tissue, a notification of clinical investigation of a medical device shall be submitted to the MPA.

To both alternatives apply that the documentation on the component/tissue shall allow for a complete evaluation of favourable and unfavourable effects when used for the purpose intended in the investigation. Cf. LVFS 2001:11 and LVFS 2003:11, bilaga 11.

2. If neither alternative 1a nor 1b is applicable, the MPA shall be consulted for information on the regulatory requirements for the investigation.

11.11 Plan for post market clinical follow up

The long-term performance and safety of a novel medical device may be difficult to assess merely from observations made during a clinical investigation. The manufacturer is therefore obliged to set up a system for post market surveillance in accordance to Annex ("Bilaga") 2, point 3 in LVFS 2001:5 and LVFS 2003:11, respectively (the Swedish implementations of Directives 90/385/EEC and 93/42/EEC).

In line with this obligation, manufacturers/sponsors may decide to follow up the performance and safety in a more active way than through the regular vigilance system by a continued systematic collection of clinical data after the device has been CE-marked and placed on the market, i.e. a post market clinical follow up. The design and extent of such a follow up shall be described in the CIP.

The follow up does not need to be restricted to subjects originally included in the investigation. See also MEDDEV 2.12-2.

12. Instructions for preparing the notification documents

If relevant documentation has been submitted in connection with a previous notification of the current investigation, reference may be made to this documentation (please quote the MPA reference number).

12.1 Clinical Investigator's Brochure, CIB

In the CIB (sometimes denoted Product documentation) the device shall be documented as far as possible and in all aspects necessary to allow for the clinical investigator to make a thorough evaluation of the device and its properties. The CIB shall include (cf SS-EN ISO 14155-1):

1. Identification and description of the device and its components (construction, function, materials, manufacturing process, necessary software etc).
2. The claimed performance and clinical benefit of the device as well as the type of patients it is intended for.
3. Standards met by the device
4. Instructions for use and, as appropriate, instructions for installation, maintenance, cleaning and sterilisation of the device as well as necessary training needed for its use.
5. Previous experience including possible or confirmed unfavourable effects of the device or similar devices obtained from laboratory tests, animal studies and use in humans.
6. Possible or confirmed interactions with other devices, medicinal products or agents.
7. A formal risk analysis 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 (cf SS-EN ISO 14971). The justification of the investigation should be evident from the risk assessment.

If the 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. See “Investigation of devices where medicinal products are involved” and “Investigation of products containing tissues of human or animal origin...”.

The CIB may be provided as a separate document or inserted as a section of the Clinical Investigation Plan (see below).

12.2 Clinical Investigation Plan, CIP

The CIP (sometimes denoted the Protocol) shall provide information clarifying the background to and justification for the investigation and how it will be conducted. Detailed guidance on the development of the CIP is available in SS-EN ISO 14155-2. In summary the CIP shall include as applicable:

1. Title and code designation of the investigation, version and date of the CIP
2. Name and address of sponsor, authorised representative, monitor, investigation site(s), clinical investigator(s), co-ordinating investigator and other persons involved in the investigation as well as their function and qualifications
3. Background with literature survey (with reference list) outlining the basis for the clinical investigation
4. Similar or the same information as provided in the CIB. If the CIB is appended as a separate document, it may be referred to.
5. Primary and where applicable secondary objectives
6. Measurable and defined primary and where applicable secondary variables that correspond to the objectives
7. Details of the design and the type of investigation, including where necessary randomization methods, masking methods and proposed dates of commencement and conclusion of the investigation
8. How the device and any device or agent for comparison are to be handled during the investigation, with indications of the times of

- recording performance and safety variables and where appropriate anticipated adverse device effects – survey to be included
9. Relevant identification and documentation concerning any device or agent with which the device under investigation is intended to be used with or compared against (relevant documentation must be included as an attachment)
 10. Criteria determining which subjects should be included in the investigation, criteria for withdrawing subjects from the investigation and the procedure for enrolling subjects into the investigation.
 11. How the conditions during the investigation are to be standardized, treatment that is permitted and not permitted.
 12. Definitions of adverse events and adverse device effects and instructions for recording and reporting these.
 13. Methods used to quantify performance, evaluate safety and record possible adverse device effects and by whom measurements will be performed.
 14. How the investigation will be concluded, any follow-up period, plans for any continued use of the device after completed investigation. If a post market clinical follow up is planned it shall be described. See MEDDEV 2.12-2.
 15. Specified criteria for early termination or suspension of the investigation as derived from the risk analysis.
 16. Statistical assessment of the investigation's probability to reach a conclusion based on the number of subjects, number of devices, method errors, variability, clinically significant differences in the performance/safety variables and any withdrawal of subjects.
 17. An account for which comparisons (including interim analyses), statistical methods (including definition of the population to be analysed and handling of subject withdrawals) that are intended and by whom the results are to be analysed.

18. Instructions for evaluation, installation, use, maintenance and cleaning of the devices intended for use by clinical staff or subjects (in Swedish).
19. Forms intended to be used to record data (Case Report Forms).
20. Approval of the CIP by means of dated signatures of the sponsor, authorised representative and clinical investigator(s).

12.3 Statement of conformity with Essential Requirements (12.3)

The sponsor shall assure that the device fulfils the Essential Requirements as stated in LVFS 2001:5 (the Swedish implementation of Directive 90/385/EEC) or LVFS 2003:11 (the Swedish implementation of Directive 93/42/EEC) apart from those parts which have given rise to the proposed investigation, and that all necessary measures have been taken to protect the health of the subjects and the staff (see Annex ("Bilaga") 7 of LVFS 2001:5 or Annex ("Bilaga") 10 of 2003:11).

12.4 Intended labelling of the device

The proposal shall demonstrate how the device will be labelled. The labelling shall comply with the instructions stated in Annex ("Bilaga ") 1 of LVFS 2001:5 or Annex ("Bilaga") 1 of LVFS 2003:11 (the Swedish implementations of Directives 90/385/EEC, Annex I and 93/42/EEC, Annex I, respectively). The device shall not carry the CE-mark but be labelled with the inscription "Uteslutande för klinisk prövning" ("Exclusively for clinical investigation"). It shall be possible to connect a specific device to the identity of a subject, while maintaining confidentiality (in accordance with Section 7 of the Confidentiality Act, SFS 1980:100).

In general, the text must be in 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.

12.5 Application for Ethical Review

Research in the form of clinical investigations of medical devices need approval by an Ethics Review Board prior to initiation. The Board's review is carried out in accordance with the Swedish Act (SFS 2003:460) and Ordinances (SFS 2003:615 and 616) on Ethical Review as well as the

statutes of the Swedish Research Council (VRFS 2004: 1) on Ethical Review. Application for ethical review shall be submitted by the clinical investigator (on behalf of his principal) on the stipulated form which may be downloaded from <http://www.forskningsetikprovning.se/eng/index.htm>

The application shall be sent to the regional Ethics Review Board within whose region the investigation site is located. Application for review of a multi-centre investigation shall be submitted by the co-ordinating investigator in Sweden and sent to the regional Ethics Review Board within whose region he has his investigation site.

A copy of the application along with the decision and statement by the Board shall be appended to the notification to the MPA. If the Board's decision and statement are missing at the time of submission, they may be sent in later.

During an investigation in progress, the sponsor and the clinical investigator(s) shall inform the Ethics Review Board in accordance with existing regulations and the Board's requirements.

12.6 Insurance policy covering 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 significance shall be appended 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.

12.7, 12.8. Information to subjects and their informed consent

A copy of the information in Swedish 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 application. See EN ISO 14155-1, pp 6.7 and 6.10.

12.9. Subjects consent to disclose their medical records (12.9)

Forms with information in Swedish used to obtain a written consent from subjects to disclose medical records to the sponsor or a foreign control

authority must be provided (in accordance with Section 7 of the Swedish Confidentiality Act, 1980:100).

12.10 Qualifications of the clinical investigator

Clinical investigators holding a physician's specialist certificate issued by the Swedish National Board of Health and Welfare shall provide a copy of the certificate. Other investigators shall provide a Curriculum Vitae (CV).

The CV shall give name, date/place of birth, address and place of work, and shall show the training, appointments and any other information that will confirm the suitability of the clinical investigator to be responsible for the investigation. The CV is to be signed and dated by the clinical investigator and attested by two persons with no connection to the proposed investigation.

12.11 Documentation concerning devices/agents/medicinal products with which the device under investigation is intended to be used

This documentation shall specify all devices, medicinal products or agents intended to be used in combination with the device under investigation. The documentation shall include the identity of the device(s), agent(s) or medicinal product(s) and of the manufacturer(s). All the information required in order to understand the intended interaction with the device under investigation and any possible risks of adverse device effects/interactions shall be provided.

12.11 Documentation pertaining to devices or medicines with which the device under investigation is intended to be compared

The documentation shall include the identity of the device or medicine and of the manufacturer and certify that the comparative in all aspects will be used as intended by its manufacturer. The choice of comparative shall be justified and the CIP must ensure an equitable comparison. All information which is required to assess the appropriateness of the comparative device or medicine for comparison in the proposed investigation and the possible risk of adverse device effects and interactions shall be provided.