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DG Pre/R&D/Clinical investigation

Frequently Asked Questions

- Clinical Investigation Applications –

The following is a list of frequently asked questions (FAQ) regarding clinical investigation applications. This document will be continuously expanded and updated.

The aim of this document is to improve the efficiency and reduce unnecessary delays during the validation, assessment and submission of information regarding clinical investigation applications and focusses on recurring issues.

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General:

1. **Q: Which clinical investigation should be submitted to FAMHP?**

   A: All clinical investigations with medical devices who do not bear the CE marking, must be submitted to FAMHP.
   If you want to conduct a clinical investigation with a CE medical device outside the intended purpose, so outside the instruction for use and/or the CE certificate, you must submit this clinical investigation to FAMHP.

2. **Q:What is the difference between pre-market and post-market clinical investigations?**

   A: A pre-market clinical investigation is a clinical investigation carried out before market approval of the investigational device.

   A post-market clinical investigation is a clinical investigation carried out following market approval, intended to answer specific questions relating to the approved clinical performance, or effectiveness and/or safety of this medical device when used in accordance with its approved labelling, so also strictly following the instruction for use released by the manufacturer. In this case post market clinical investigation is synonymous with post market clinical follow up.

   If marketed products are being investigated for new indications, other than described in the approved labelling and/or instruction for use, pre-market's legislation on clinical investigations must be applied.

3. **Q: What should I do if my intended clinical study includes both an investigational medical device and an investigational medicinal product? What to do when applying for combined Clinical Investigation Applications and Clinical Trial Applications?**

   A: From time to time, studies are applied for that combine an investigational medical device and an investigational medicinal product. In this case, both a Clinical Investigation Application and Clinical Trial Application (CTA) are required. Sponsors are requested to submit both applications at the same time to the FAMHP and refer to the connected clinical investigation/clinical trial application in the respective cover letters, this to enable a combined review of all aspects of the application and thereby allow timely assessment.

4. **Q: Which ethics committee can approve a clinical investigation?**

   A: An ethic committee with a full accreditation; a complete list can be found on our website, here.

5. **Q: Is it acceptable to submit a clinical investigation application before all results of preclinical testing are available?**

   A: The first paragraph of ISO 14155-2011, Annex B (on the contents of the investigator's brochure), section B.3 states "*Summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing justifying its use in human subjects. The summary shall include or, where applicable, refer to the results of […]*". This text implies that all preclinical tests should be completed before it can be decided whether use in human subjects is justified and by consequence, all preclinical tests should be completed before submitting a clinical investigation application.
   Cfr. ISO 14155-2011 Annex B, points B.3

6. **Q: Must a notification be submitted if a clinical investigation will be conducted with a new accessory for the CE-marked device (in the authorised indication for use)?**

   A: If you use an accessory that is not included in the instruction for use of the medical device, a clinical investigation application is mandatory as it is considered outside the scope of CE-certificate.

7. **Q: Must a notification be submitted if a clinical investigation will be conducted with a medical device / accessory (even Class I – non-sterile) if it has no CE-marking?**

   A: Yes, a notification is mandatory whatever the classification of the product.

8. **Q: Must a notification be submitted if a clinical investigation will be conducted with a custom-made medical device or a custom-made accessory?**

   A: A custom made medical device doesn't bear a CE-label, nevertheless a similar methodology must be applied; any medical device must demonstrate its performance and safety for the intended purpose. Meaning that if you investigate a custom made medical device in a clinical study with the objective to finally demonstrate the compliance to essential requirements, you must notify this clinical investigation to FAMHP.

   Once the manufacturer is ready to launch this process of printing medical devices on the market, he notifies it to the competent authority, meaning that the product is considered as put on the market. This notification is considered as the border between pre-market and post-market phase for custom made medical devices for a specific intended purpose. From then, an application for a clinical investigation is not necessary as far as the custom made medical device is used following the statement provided to FAMHP (including the indication).

9. **Q: Must a notification be submitted if a clinical investigation will be conducted with a CE-labelled medical device used in the indication for which it has been accepted but where changes in software or changes in technical aspects of the use are tested?**

A: Yes, if you make modification(s) to a CE-labelled medical device, not foreseen by the manufacturer in the instruction for use, it is not considered as the device approved under this certificate, so a clinical investigation application must be submitted.

10. **Q: What is relevant legislation and which standards or equivalent should be applied for the conduct of a clinical investigation?**

A: At the minimum, the clinical investigation must be in line with the international standard ISO 14155:2011 on Good Clinical Practice for clinical investigations of medical devices for human subjects, the most recent version of the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects, Regulation (EU) 2016/679 (General Data Protection Regulation), the Belgian Royal Decree of 07/05/2004 on human experimentation and one of the two EU Directives: 93/42/EC (on medical devices, Royal Decree of 18/03/1999) or 90/385/EC (on active implantable medical devices, Royal Decree of 15/07/1997). A new EU Regulation on medical devices (MDR 2017/754), however, has entered into force on May 25, 2017, which is when a three year transition period began. Therefore, the MDR will fully apply in EU Member States from May 26, 2020 and will replace the two existing Directives on medical devices.

11. **Q: What is the transitional provision relating to the conduct of a clinical investigation?**

A: Clinical investigations which have started to be conducted in accordance with Article 10 of Directive 90/385/EC or Article 15 of Directive 93/42/EC prior to 26 May 2020 may continue to be conducted. As of 26 May 2020, however, the reporting of serious adverse events and device deficiencies shall be carried out in accordance with MDR 2017/745.

Investigator's Brochure

12. Q: What is an Investigator's Brochure?

A: An Investigator's Brochure (IB) is a compilation of the current clinical and non-clinical information on the investigational medical device(s) relevant to the clinical investigation. The content is technical and scientific. The full details of the content is provided in annex B of ISO 14155.

In summary the content includes, but is not limited to :

- details allowing device(s) to be identified;
- trade name of device(s);
- generic name of device(s);
- model name of device(s) and/or trade name or generic name of the investigational device(s);
- model number(s) including revision number(s), if any (or reference from apparent model number if appropriate);
- copy of device(s) labels and IFU(s) [including version nr and date of issue] including risks, contraindications and warnings (if available);
- A description of the device including a full list of accessories, principles of operation and block or flow diagrams of components, together with a brief description of other devices designed to be used in combination for the purpose of the investigation, if applicable;
- identification of any features of design that are different from a previously similar marketed product (if relevant);
- details of any new or previously untested features of the device including, where applicable, function and principles of operation;
- description of software, functionality and constraints, version (if relevant);
- design drawings, if necessary for the understanding of the functioning of the device;
- identification of any special manufacturing conditions required and if so, how such requirements have been met.
- All preclinical testing (design calculation, in vitro tests or bench testing, mechanical and electrical tests, reliability tests, any performance tests, biological evaluation, …)
- Summary of existing clinical data (summary of each studies and their results but add also a global summary regarding all the clinical data collected highlighting the current uncertainties and which gaps have still to be fulfilled)
- Description of risk management, including a detail of risk analysis.

13. **Q: Is it allowed to not include all required information (cfr ISO 14155) in the IB and protocol but instead refer to annexes?**

A: We prefer for all information to be included in the IB and protocol. However, if it is decided to move part of the information to annexes (or other referenced documents), than these should be submitted with the IB and protocol as part of the initial data package accompanying the clinical investigation application.

14. **Q: What information should be provided regarding the material composition of the medical device?**

A: A clear overview of materials used in the device should be provided. For more complicated devices, this can be accompanied by an annotated drawing or photograph of the device. Especially for all human (patient, clinician, …) contacting materials, sufficient detail should be provided, even if contact is only brief or occasional. The information provided should be sufficiently specific and should include the supplier, supplier product code, generic name, brand name and if applicable, the grade, quality, specification or standard adhered to. Preferably, the information is provided in a tabular format.
Cfr. ISO 14155-2011 Annex B, point B.2 c)
Cfr. MedDev 2.7.2 rev2, p. 15

15. **Q: What information should be provided regarding the sterilization of the medical device?**

A: The sterilization method used should be stated and a sterilization validation report should be provided. Compatibility of the sterilization method and the device materials should be discussed, if applicable. In case ethylene oxide is used as sterilizing agent, please specify whether testing for residuals is performed and provide the results of these tests, this in compliance with ISO 10993-7:2008
Cfr. MedDev 2.7.2 rev2, p. 47

16. **Q: What information should be provided regarding the manufacturing process and quality control?**

A: A summary of relevant manufacturing processes and related validation processes should be presented, in line with ISO 14155-2011. This can be done by means of a manufacturing flowchart. In-process controls should be described and acceptance criteria for these tests should be clearly defined. Preclinical quality tests (e.g. mechanical and electrical tests, performance tests, reliability tests) should be described and acceptance criteria for these tests should be clearly defined.
Cfr. ISO 14155-2011 Annex B, points B.2 d) and B.3.

17. **Q: What information should be provided regarding the biological evaluation (ISO 10993)? What is an appropriate level of detail regarding the biocompatibility data?**

A: A (justified) classification in line with ISO 10993-1 should be provided. A brief summary of each evaluation required by ISO 10993-1, Annex A should be provided. It should be clear from this summary whether actual testing or an evaluation based on literature data was performed and where applicable, test results should be provided (e.g. for cytotoxicity testing, it is recommended to report the specific assay used and the % cell viability observed, rather than simply stating "passed").

For investigational devices with extensive clinical data or for devices that differ only little (in their material composition, design and anatomical target site) from devices with extensive clinical experience, the section on biocompatibility evaluation can be kept brief and may be limited to an overview table.

If a device is CE marked but investigated for an non-CE marked indication and if the classification according to Annex A of ISO 10993-1 does not change, no further information on biocompatibility evaluation is required (other than the justified classification of the medical device in line with ISO 10993-1, Annex A in view of the new indication).

Cfr. ISO 14155-2011 Annex B, points B.3 h

18. **Q: What information should be provided regarding preclinical (animal, cadaver) testing of the device?**

A: Animal study summaries should be included in the Investigator's Brochure (a reference to external documents is not sufficient) and should contain sufficient information, including: species, breed, number of animals, age of animals, GLP status, version of the device used (also see below) and an overview of the analyses performed. Any notable finding should be mentioned and discussed.

Study design choices including species used, study duration and choice or absence of comparator should be explicitly justified.

In case of non-GLP studies, applicants are recommended to follow the ARRIVE guidelines (to the extent that this is possible) in the preparation of the study report cfr. [https://www.nc3rs.org.uk/sites/default/files/documents/Guidelines/NC3Rs%20ARRIVE%20Guidelines%202013.pdf]. During assessment of the clinical investigation application, the full study report may be requested; to reduce the overall time to clinical investigation approval, the applicant may consider submitting the full study reports of pivotal non-clinical studies at the time of the initial application (however, this does not negate the obligation to include a summary of pivotal preclinical studies in the Investigator's Brochure).

Device version used in preclinical testing: In the summaries of the non-clinical studies, the applicant should either confirm that the device used was identical to the device for clinical use (including e.g. sterilization) or detail any differences between the device used preclinically (e.g. animal studies, biocompatibility studies) and clinically. If the device that will be used in the clinic differs from the device used in animal studies, a justification for not using the final, clinical design of the device should be provided.

An overview of the design history of the medical device (e.g. in table form) is recommended and appreciated. Preferably, this contains for each iteration the version number, a photograph/drawing and a brief overview of changes with regards to the previous iteration.

Clinical Investigation Plan

19. Q: What information should be included in the protocol?

A: A protocol, also called clinical investigation plan (CIP), is a document which gather several information regarding the study ;background information, the rationale, objectives, outcomes, design, pre-specified analysis, methodology, monitoring conduct, safety and follow-up and record-keeping of the clinical investigation data.

Below, an example of standard protocol content for a clinical investigation:

1. Identification and description of the investigational device
a) Summary description of the investigational device and its intended purpose.
b) Details concerning the manufacturer of the investigational device.
c) Name or number of the model/type, including software version and accessories, if any, to permit full identification.
d) Description as to how traceability shall be achieved during and after the clinical investigation, for example by assignment of lot numbers, batch numbers or serial numbers.
e) Intended purpose of the investigational device in the proposed clinical investigation.
f) The populations and indications for which the investigational device is intended.
g) Description of the investigational device including any materials that will be in contact with tissues or body fluids. This shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.
h) Summary of the necessary training and experience needed to use the investigational device based on risk management.
i) Description of the specific medical or surgical procedures involved in the use of the investigational device.

2. Justification for the design of the clinical investigation
Justification for the design of the clinical investigation, which shall be based on the conclusions of the evaluation and shall comprise :
a) an evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations carried out to justify the use of the investigational device in human subjects, and
b) an evaluation of clinical data that are relevant to the proposed clinical investigation.

c) if appropriate, a description of the clinical development stage see Annex I

3. Risks and benefits of the investigational device and clinical investigation
a) Anticipated clinical benefits.
b) Anticipated adverse device effects.
c) Residual risks associated with the investigational device, as identified in the risk analysis report.
d) Risks associated with participation in the clinical investigation.
e) Possible interactions with concomitant medical treatments.
f) Steps that will be taken to control or mitigate the risks.
g) Risk-to-benefit rationale and justification of the selection of clinical endpoint(s).
The primary endpoint shall be appropriate for the investigational device and clinically relevant.
h) Scientific justification of relevant effect size or non-inferiority margin, as applicable.

4. Objectives and hypotheses of the clinical investigation
The objective must serve the purpose of the clinical investigation and must relate to the hypotheses (where applicable) and corresponding endpoints relevant to the target population.
a) The purpose of the clinical investigation, claims for clinical performance or effectiveness and safety of the investigational device that are to be verified (if applicable).
b) Objectives, primary and secondary, described as 'superiority', 'non-inferiority', or 'equivalence'.
c) Effect sizes and equivalence limits, where applicable,
d) Hypotheses, primary and secondary (if applicable).
e) Risks and anticipated adverse device effects that are to be assessed.

5. Design of the clinical investigation
5.1 General
a) Description of the design type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale for the choice.
b) Description of the measures to be taken to minimize or avoid bias, including randomization, concealment of allocation, blinding/masking, assessment of blinding plan and management of potential confounding factors.
c) Primary and secondary endpoints, with rationale for their selection and measurement.
d) Methods and timing for assessing, recording, and analyzing variables.
e) Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.
f) Any procedures for the replacement of subjects (not applicable to randomized clinical investigations).
g) Clinical investigation sites: number, location and if appropriate differences in clinical investigation site characteristics.

5.2 Investigational device(s) and comparator(s)

a) Description of the exposure to the investigational device(s) or comparator(s), if used.

b) Justification of the choice of comparator(s).

c) List of any other medical device or medication to be used during the clinical investigation.

d) Number of investigational devices to be used, together with a justification.

5.3 Subjects

a) Inclusion criteria for subject selection.

b) Exclusion criteria for subject selection.

c) Criteria and procedures for subject withdrawal or lost to follow up

1) When and how to withdraw a subject from the clinical investigation or stop the use of the investigational device.

2) Documentation of efforts to be made to trace subjects that are lost to follow up and possible reasons

3) Whether and how subjects are to be replaced.

d) Point of enrolment.

e) Point of randomization (if applicable)

f) Total expected duration of the clinical investigation.

g) Expected duration of each subject's participation.

h) Number of subjects required to be included in the clinical investigation, and where needed anticipated distribution of enrolment among the participating clinical sites.

i) Estimated time needed to select this number (i.e. enrolment period).

j) Relationship of investigation population to target population

k) Information on vulnerable, pregnant and breastfeeding population, if applicable.

5.4 Procedures

a) Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice.

b) Description of those activities performed by sponsor representatives (excluding monitoring).

c) Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results.

The methods for addressing these factors in the clinical investigation, for example by subject selection, clinical investigation design (such as stratified randomization) or by statistical analysis shall be described.

The follow-up period during the clinical investigation shall permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the investigational device and allow any risks associated with adverse device effects over that period to be identified and assessed.

The CIP shall specifically address what medical care, if any, will be provided for the subjects after the clinical investigation has been completed (if applicable).

5.5 Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned.

6. Statistical considerations

With reference to section 4 and 5, the description of and justification for statistical design and analysis of the clinical investigation should cover the following :

a) analysis population and procedures that take into account all the data,

b) descriptive statistics of baseline data, treatments, secondary endpoints and safety data,

c) analytical procedures including measures of precision such as confidence intervals and stratification, if applicable,

d) sample size justification taking into account expected drop out rates,

Describe how many procedures, if any, should be performed by a single user as part of the learning curve and how these data are to be analyzed.

e) the significance level and the power of the clinical investigation,

f) pass/fail criteria to be applied to the results of the clinical investigation,

g) the provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable,

h) adjustment of error probabilities for multiple statistical tests,

i) the specification of subgroups for analysis,

j) exploratory analysis and sensitivity analysis, if applicable,

k) procedures for reporting any deviation(s) from the original statistical analysis plan,

l) the treatment of missing, unused or spurious data, including drop-outs and withdrawals,

m) in multicentre clinical investigations, the maximum number of subjects to be included for each centre.

20. Q: What information should be provided on the design of the clinical investigation?

A: The design should be sufficiently detailed with evidence of its robustness and validity. Information is required on study type (e.g.; exploratory, confirmatory), phase of device development, subject number, endpoints, selection criteria, representativeness of the investigation population in relation to the target population, vulnerable subjects involved (if applicable), clinical procedures and diagnostic tests used in the course of the clinical investigation, any deviation from normal clinical practice, the investigational device, any comparator or other device or medication used, and thus any concomitant treatments permitted or prohibited, number of medical devices and comparators (if applicable) used per subject, symptoms, parameters and/or results to be studied, details of measures taken to minimise bias, follow-up provided, and expected (total and per subject) duration of the investigation. Where possible, a schematic overview of study assessments and visits is included.

Justification of follow-up duration is recommended. The extent and nature of monitoring activities for the proper conduct of the investigation in accordance with the clinical investigation plan should be described and, conform article 72 of MDR 2017/745, be based on objective(s) and methodology and degree of deviation of the intervention from normal clinical practice. Use of either single arm or (choice of) comparator or other (historically) controlled design and the concept of blinding and unblinding, or running open label need to be covered, with rationale and justification. Overall, the investigation has to be designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects. For that, a rationale in relation to the available preclinical data and results of clinical evaluation may be recommended.

21. Q: What information should be provided regarding data collection and management in the framework of a clinical investigation?

A: In the clinical investigation plan, a description should be provided of the procedures implemented which can guarantee that the data generated in the clinical investigation is reliable and robust. For that, arrangements for data collection, protection, monitoring (accounting for data accuracy, data completeness, resolving of queries, and the presence or absence of a data safety monitoring board) and retention but also statistical approaches with sample size determination require careful consideration. Conform article 72 of MDR 2017/745, all clinical investigation information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection. In addition, appropriate technical and organisational measures should be installed to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves transmission over a network.

22. Q: What information should be provided regarding device accountability and traceability?

A: Attention should be given to incorporate adequate procedures for the accountability and traceability of the investigational device, in particular control of access to and adequate storage of the device, follow-up in relation to the device used in the clinical investigation and the return of unused, expired or malfunctioning devices. Further, conform article 72 of MDR 2017/745, the sponsor should establish a procedure for emergency situations which enables the immediate identification and, where necessary, an immediate recall of the devices used in the investigation.

23. Q: What information should be provided on safety reporting?

A: The clinical investigation plan should provide the definitions of adverse events (AE) and serious adverse events (SAE), device deficiencies (DD), and the procedures for the recording and timely reporting of (S)AE that occur during the clinical investigation. Reportable events must be evident from the study protocol. In this regard, it is reminded that DD that might have led to a SAE where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are handled under the SAE reporting system. Information on event recording and reporting can be found in Meddev 2.7/3 rev3 for guidance under Annex 7 and Annex X of Directives 90/385/EEC and 93/42/EEC, respectively, and article 80 of MDR 2017/745.

24. Q: What information should be provided on protocol amendments?

A: It should be clear from the clinical investigation plan that, once approved, the competent authority shall be notified of all proposed changes to the approved clinical investigation 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 by the investigation, and that the response of no objection will be awaited, in accordance with ISO 14155:2011 and the procedure as laid down in article 75 of MDR 2017/745.

25. Q: What information should be provided in view of the benefit/risk profile of this clinical investigation and investigational medical device?

A: At **first**, a description is required of (1) all incremental risks to which subjects will be exposed to by participating in the clinical investigation (i.e.; risk characterization) and (2) of the manner(s) used to minimize these risks (i.e.; risk mitigation). It is not necessary to include specific mitigations for hypothetical risks that are not supported by scientific evidence or risks that are determined to be negligible due to a low probability of occurrence and low severity of harm. It is, however, recommended to identify all possible risks.

In particular, for risk characterization, the following factors should be considered, individually and in aggregate: types of risk (taking account of the study design as well), their likelihood and duration along with the severity. Also consider the risk factors for HCPs, family members or caregivers, if any, and the risks related to the interpretation of the study data. In specific, the risk of drawing a false conclusion based on clinical data obtained, and the risk of data which are inconclusive or difficult to interpret.

Manner(s) in which risks will be minimized may include:

- Protective measures, e.g.; physical protective measures; staged enrolment and interim pre-specified subject safety assessment; pre-specified stopping rules; narrow study population with more favourable benefit-risk profile; performance of study at trained/specialized sites or investigators meeting certain criteria; study oversight (monitoring committees); frequent reporting of SAEs; accurate recording of AEs, including the timing and clinical context and a description of any medical interventions provided and the associated outcomes.
- Communication of safety information and residual risks, e.g.; through labelling or informed consent, training of investigational staff, optimizing communication among sites, communicating safety data and residual risks with ethics committee(s) and competent authority to determine if any additional subject protection measures are needed.

A list of anticipated A(D)E, SA(D)E, DD, including those considered critical, must be prepared.

Secondly, a description should be provided of the anticipated benefits of the proposed clinical investigation. This concerns the direct benefit(s) to the study subjects, but may also cover the benefit(s) to others.

In particular, regarding the direct benefit(s) to the study subject, the following factors should be considered, individually and in aggregate: (a) type of benefit(s) and magnitude of the benefit(s); (b) if possible, probability evaluation of the participant experiencing one or more benefits, or identification of subgroups more likely to experience a benefit; (c) duration of the benefit(s), i.e.; how long the benefit can be expected to last for the participant; (d) medical necessity, if a medical device provides benefits or addresses needs unmet by other medical devices or therapies. Benefit considerations should also include an assessment of whether another medical device or therapy could be used in substitution, and the availability of that other medical device or therapy.

Benefit(s) to others include(s) benefits to caregivers or family members and HCPs, and societal benefit.

Other information providing useful context is appreciated and may include: consideration of patient preference information (when available) characterizing the subjects' perspective on benefit, i.e.; the value that patients place on the use of the medical device, as well as information characterizing subjects' tolerance for risk.

26. Q: What information should be provided on temporary halting or ending of a clinical investigation (participation)?

A: The clinical investigation plan should consider appropriate subject and study stopping criteria as well as procedures for the follow-up (care) of subjects following the end or temporary halt of the investigation, for follow-up of subjects who have withdrawn their consent and for subjects lost to follow-up.
Further, it must be clear from the clinical investigation plan that the competent authority shall be notified of the end of the clinical investigation, and that a justification shall be provided in case of a temporary study halt or early termination, in accordance with articles 10 and 15 of Directives 90/385/EEC and 93/42/EEC, respectively. As laid down in article 77 of MDR 2017/745, study end reporting shall become mandatory within 15 days (but 24 hours if based on safety grounds). In addition, a clinical investigation report will need to be submitted within one year of the end of the clinical investigation or within three months of the early termination or temporary halt. The end of a clinical investigation shall be deemed to coincide with the last visit of the last subject unless another point in time for such end was set out in the clinical investigation plan.

Ongoing Clinical investigation

27. Q: Which events do I have to report?

A: Point 2.3.5, annex X from 93/42 directive: All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.

28. Q: What is an adverse event?

A: An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Meaning that this includes adverse events with the comparator or related to the procedure.

29. Q: What is a serious adverse event (SAE)?

A: A serious adverse event is defined as an adverse event that:

- Led to a death, injury or permanent impairment to a body structure or a body function.
- Led to a serious deterioration in health of the subject, that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient hospitalization or prolongation of existing hospitalization, or
    - in medical or surgical intervention to prevent life threatening illness
    - led to foetal distress, foetal death or a congenital abnormality or birth defect.

30. Q: How and when do I report a serious adverse event?

A: Point 2.3.5, annex X from 93/42 directive: All serious adverse events must be fully recorded and **immediately** notified to all competent authorities of the Member States in which the clinical investigation is being performed.

Closed clinical investigation

31. Q: Do I have to notify the end of a clinical investigation?

A: Yes, the date of the last visit of the last patient participating in the clinical investigation is considered as the end of the study. We ask to send an official signed letter notifying the end of the study. This can be done by email through ct.rd@famhp.be with the following subject "end of clinical investigation – 80M0XXX".

There is no other need to inform the minister of the end of the clinical investigation.

32. Q: Do I have to submit the results of the clinical investigation?

A: Yes, as requested on the approval letter of the clinical investigation and as stated in annex X section 2.3.7 of the Royal Decree 18/03/1999 regarding medical devices. We kindly ask to send the final report, signed by the principle investigator, as soon as available.