Clinical Data Requirements in the European Union

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Requirements for Clinical Data

Dir. 2007/47/EC
Which medical devices require a clinical evaluation?
- ALL Medical Devices regardless of Classification
A documented and systematic literature review

A detailed discussion covering the benefit/risk ratio of the device when comparing to:

- All current available therapeutic alternatives for the same indication
- Similar products from, for example, competitors for the same indication
Clinical Evaluation
The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.
Which route should you follow for the device under consideration?

Equivalence Route

Clinical Investigation Route
MEDDEV 2.7/4 – What is a clinical investigation?

- A clinical investigation is defined as any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.
MEDDEV 2.7/4 – What is the objective of a clinical investigation?

- The objective of a clinical investigation is to assess the safety and clinical performance of the device in question and evaluate whether the device is suitable for the purpose(s) and the population(s) for which it is intended (EN ISO 14155).
MEDDEV 2.7/4 – When should a clinical investigation be undertaken?

- The Conformity Assessment process for active implantable medical devices as well as for class III and implantable medical devices requires that a clinical investigation is undertaken unless it is duly justified to rely on existing data.

Section 1.2 of Annex 7 of directive 90/385/EEC
Section I.1a of Annex X of directive 93/42/EEC
MEDDEV 2.7/4 – When should a clinical investigation be undertaken?

- Depending on clinical claims, risk management outcome and on the results of the clinical evaluation, clinical investigations may also have to be performed for non-implantable medical devices of classes I, IIa and IIb.

- Additional clinical investigations may be feasible to corroborate the existing clinical evidence with regard to aspects of clinical performance, safety, benefit/risk-ratio or to determine relative effectiveness and safety with suitable comparators.
Clinical Investigation Route

Clinical Investigation – When to start?

- The clinical investigation shall not commence until written approval/favourable opinion from the ethics committee and, if required, the relevant regulatory authorities of the countries where the clinical investigation is taking place has been received.

April 2014
Clinical Investigation Route

Clinical Investigation

- Sponsor
- Favorable opinion of ethics committee
- Investigation site
- Insurance
- CIP Annex A normative
- CIB Annex B normative
- Informed consent form
- Qualified investigators
- Approval of Competent Authority

April 2014
Clinical Investigation Route

Documents evaluated by EU Notified Bodies

- CIP
- Letter of No Objection
- Ethics Committee opinion
- Signed and dated final report

April 2014
Literature Route – Equivalence Approach

- Same intended use
- Technical and biological equivalence
- No clinically significant difference regarding safety and performance
Equivalence Approach

Literature Route
- Define search criteria
- Explore the results
- Look for consistency of results
- Consider evidence levels of the different datasets
- Consider transferability of the data to the device under evaluation
Check the results of the clinical evaluation by asking 5 questions:

<table>
<thead>
<tr>
<th>Question</th>
<th>Color</th>
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<tbody>
<tr>
<td>Is the performance as intended?</td>
<td>Blue</td>
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<tr>
<td>Are there any safety concerns?</td>
<td>Blue</td>
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<tr>
<td>Is the benefit/risk ratio positive?</td>
<td>Blue</td>
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<td>Is non inferiority and similarity to state of the art shown?</td>
<td>Blue</td>
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<tr>
<td>Is the final conclusion critical, objective and transferable?</td>
<td>Light Blue</td>
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Clinical Evaluation Report (CER)

The appropriate CER shall include:

- Scope and context of the evaluation
- Clinical data
- Appraisal and analysis stages
- Conclusions

The appropriate CER must be: Signed and dated by the evaluator(s)

The appropriate CER must include: A justification for the choice of evaluator(s)
The appropriate CER shall be prepared as a stand-alone document to facilitate the assessment of a third independent party

The stand-alone document must comprise:

- Background regarding device technology
- Intended Use
- Claims regarding performance and safety
- Nature and extent of clinical data
- Suitability of the referenced information
- Acceptability of the risk/benefit ratio
Preamble (46) in the proposed regulation

- Demonstration of compliance with the general safety and performance requirements should be based on clinical data.

- Clinical data of Class III medical devices and Implantable medical devices should be, as a general rule, based on clinical investigations to be carried out under the responsibility of a sponsor.

Preamble (47) in the proposed regulation

- Clinical investigations in line with major international guidance in this field, such as the international standard ISO 14155:2011.
Preamble (48) in the proposed regulation

- An electronic system should be set up at Union level to ensure that every clinical investigation is registered in a publicly accessible database.

- No personal data of subjects participating in a clinical investigation should be recorded in the electronic system.

Preamble (51) in the proposed regulation

- This Regulation should only cover clinical investigations which pursue regulatory purposes laid down in this Regulation.
Article 4: Placing on the market and putting into service

- A device shall meet the general safety and performance requirements which apply to it, taking into account its intended purpose.

- Demonstration of conformity with the general safety and performance requirements shall include a clinical evaluation in accordance with Article 49.
Article 49: Clinical Evaluation
Manufacturers shall conduct a clinical evaluation in accordance with the principles set out in this Article and Part A of Annex XIII.

A clinical evaluation shall follow a defined and methodologically sound procedure based on either of the following:

- A critical evaluation of the relevant scientific literature
- A critical evaluation of the results of all clinical investigations
- A critical evaluation of the combined clinical data
At all times and for each conformity assessment procedure and each kind or category of products in relation to which it has been notified, a notified body shall have within its organization the necessary administrative, technical and scientific personnel with technical knowledge and sufficient appropriate experience relating to medical devices and the corresponding technologies to perform the conformity assessment tasks, including the assessment of clinical data.
Notified bodies shall have available personnel with clinical expertise. This personnel shall be integrated in the notified body’s decision-making process in a steady way in order to:

- Identify when specialist input is required
- Appropriately train external clinical experts
- Be able to discuss and challenge the clinical data contained in the CER
- Be able to ascertain the comparability and consistency of the clinical
- Assessments conducted by clinical experts
- Be able to make an objective judgment
Global Clinical Affairs

Europe

Internal

External
Collaboration with your Notified Body

TO AVOID PITFALLS AT A VERY EARLY STAGE

“A Goal without a plan is just a wish.”

*Antoine de Saint-Exupery*
Prior to starting the clinical evaluation, the following aspects must be at least defined:

- Are there any design features of the device and/or target treatment populations that require specific attention?
- Can data from equivalent devices be used?
- What is the type and source of available data?
- Is the justification for not performing a clinical investigation reasonable?
- Is the PMCF Plan acceptable?
Post-market clinical follow-up Plan

The documented, proactive, organized methods and procedures set up by the manufacturer to collect clinical data based on the use of a CE-marked device.

Post-market clinical follow-up Studies

A study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance of a device when used in accordance with its approved labelling.
EUROPEAN COMMISSION
DIRECTORATE GENERAL for HEALTH and CONSUMERS
Consumer Affairs
Health technology and Cosmetics

MEDDEV 2.12/2 rev2
January 2012

GUIDELINES ON MEDICAL DEVICES

POST MARKET CLINICAL FOLLOW-UP STUDIES
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

Why PMCF?

Rare complications or problems become apparent after wide-spread or long term use of the device.

An appropriate PMS Plan is key to identifying and investigating residual risks associated with the use of medical devices placed on the market.
Why PMCF?

To confirm the safety and performance throughout the expected lifetime of the device, the continued acceptability of identified risks and to detect emerging risks on the basis of factual evidence.
Why PMCF?

There may be limitations to the clinical data available in the pre-market phase:

- Duration
- Number of subjects
- Investigators involved (Heterogenicity?)
- Subjects (Heterogenicity?)
- The controlled setting of a clinical investigation vs. the full range of clinical conditions encountered in general medical practice
Can PMCF be used to demonstrate conformity and place a product on the market?
Data obtained from PMS and PMCF are **not** intended to replace the pre-market data necessary to demonstrate conformity with the provisions of the legislation.
When to do a PMCF?

The decision to conduct PMCF studies must be based on the identification of possible residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio.
PMCF is mandatory per example, for:

- Innovative Products
- Significant changes
- High product related risks
- High risk anatomical locations/target populations
- Emergence of new information on safety or performance
- Where CE marking was based on equivalence
- Unanswered questions of long-term safety and performance
PMCF Methodologies

- Extended follow-up of patients enrolled in premarket investigations
- A new clinical investigation
- A review of data derived from a device registry
- A review of relevant retrospective data from patients previously exposed to the device
When not to do a PMCF?

PMCF studies may not be required when the medium/long-term safety and clinical performance are already known from previous use of the device or where other appropriate post-market surveillance activities would provide sufficient data to address the risks.
Structure of a PMCF Plan?

PMCF Plan must include:

- Clearly stated research question(s)
- Clearly stated objective(s)
- Related endpoints
- Scientifically sound design with an appropriate rationale
- Statistical analysis
- A plan for conduct according to the appropriate standard(s)
- A plan for an analysis of the data and for drawing appropriate conclusion
The study plan should identify and where needed justify at minimum:

Study population (corresponding to the CE-mark scope)
- Inclusion/exclusion criteria
- Rational and justification of the chosen study design including use of control groups
- Selection of sites and investigators
- Study objectives and related study endpoints and statistical considerations
- Number of subjects involved
- Duration of patient follow-up
- Data to be collected
- Analysis plan
- Procedures/criteria for early study termination
- Ethical considerations
- Methods of quality control of data where appropriate
ISO 14155 – GCP

The EN ISO 14155:2011 addressess good clinical practice (GCP) for the design, conduct, recording, and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.
Implementation of the PMCF study, analysis of data and conclusions

The study should:

- Be executed with adequate control measure to assure compliance with the plan
- Include data analysis with conclusions drawn by an expert according to plan
- Have a final report relating back to the original plan (Objectives/Hypotheses)
The Notified Body shall

- Review the appropriateness of the manufacturer’s general PMS procedures and plans
- Verify that PMCF is conducted by or on behalf of the manufacturer by appropriately competent assessors
- Verify that Clinical Investigations were conducted in accordance with relevant provisions of the directive(s), related guidance and standards
- Verify the need for PMCF and/or appropriateness of any justification
- Assess the appropriateness of the proposed PMCF plan
Responsibilities of your Notified Body

The Notified Body shall

- Verify if the gathered PMCF Data were used to update the clinical evaluation report
- Consider whether based on the specific device assessment, data obtained from PMCF should be transmitted between scheduled assessment activities
- Consider an appropriate period for certification of the product in order to set a particular time point at which PMCF data will be assessed
- Set conditions to submit interim reports between certification reviews
Scrutiny Procedure

**Proposal Commission**

1. NB informs COM, submits IFU
2. COM informs MDCG
3. NB submits prel. report to MDCG
4. MDCG may involve subgroups
5. MDCG may ask for more
6. MDCG comments on prel. report
7. NB takes into consideration
8. COM may define more device groups

**Proposal Parliament**

1. SNB informs COM
2. COM informs MDCG
3. MDCG may involve ACMD
4. ACMD: clinical assessment
5. MDCG may ask for more
6. MDCG decides
7. SNB needs to follow MDCG decision
8. COM may organise meetings