

How to perform a medical device clinical trial

Considerations from an operational point of view

Basic thoughts

What is the purpose of your trial?

- Feasibility / proof of concept
- CE mark
- Post marketing surveillance
- Combination of CE and PMS
- Pure Marketing
- Scientific data

Basic thoughts

Regulatory needs?

- ISO 14155 / GCP
- MDD / US regulations
- Local regulations (data protections & radiation protection)

Basic thoughts

What resources do I need?

- Regulatory specialist
- QA
- Project Management
- CRAs
- Data management
- Statistician
- Medical writer / technical writer
- Safety specialist
- Admin support

Basic thoughts

What documents are needed to submit?

- Clinical Investigation Plan (protocol)
- Patient informed Consent
- Investigator Brochure, additional technical documentation
- Instructions for use
- Draft Case report forms, and other information to be provided to subjects (patient questionnaires, diaries)
- Insurance Certificates
- Contracts for sites/investigators
- copy of the curriculum vitae (CV) of the principal investigator(s)
- Training material
- Device technical feedback forms
- Forms and logs for investigator file

Basic thoughts

What else to be considered?

- Timing – duration of trial
- Which countries, How many sites
- „Good“ sites
- Lead Investigator – KOL?
- Proper Investigators
- Enough devices in time - manufacturing
- Training material
- Investigator technical training
- Core lab needed?
- Patient – device ID cards

CIP - Protocol

- The content of the CIP is specified in the Annex A of ISO 14155:
 - Rationale
 - Objectives: What do i want to achieve – endpoints
 - Study Design justification, methodology
 - Description of the investigational device
 - Data needed to get there
 - Interim analysis ?
 - Patient population, Inclusion and exclusion criteria
 - Follow up frequency and duration
 - Examinations needed – what is standard for indication
 - Monitoring plan
 - Statistical considerations
 - Safety / Risk and benefits
 - Data management

Patient informed consent

- Standards to be followed (ISO 14155 section 4.7)
 - Description and purpose of the trial
 - Easy to understand background and device explanations
 - Local adaptations/translation needed
 - Needed in early stage, since requested by insurances in some countries
 - Process of obtaining informed consent to be followed

Investigator Brochure



The purpose of the IB is to provide the principal investigator with sufficient safety or performance data from pre-clinical investigations or clinical investigations to justify human exposure to the Investigational device specified in the CIP.

- Standards to be followed (ISO 14155, Annex B)
- Contains Investigational device information, Preclinical testing data; Clinical data; Risk management
- The principal investigator(s) shall acknowledge the receipt of the IB
- Local authorities request additional documents (test results, sterilisation certificates, separate conformity statement)

Case report forms

- Described in ISO14155 **Annex C**
- Paper or electronic?
- Keep as simple and short as possible
- Just focus on data that is really needed!
- Electronic CRF might be used for safety reporting
- Consider to collect device handling feedback / evaluation CRF for investigator

Insurance

- Be aware of local country requirements
- Standard at 500k euro per patient
- No insurance (besides general liability) needed for non interventional post marketing studies
- Insurance certificates needed for submission

Special forms

- Device accountability on site
- Device technical feedback/complaint; Device deficiency forms
 - Forms may or may not be part of the CRFs.

Site selection/qualification



Besides “classic” site qualification parameters (resources, experience, patient population etc.) consider as well, that:

- Site needs to have the adequate technical equipment
- Be qualified by education, training and experience (updated CV)
- The investigator is experienced in the procedure for implanting your device (and in clinical research)
- Disclose potential conflicts of interest
- Site can perform planned follow ups (ultrasound, echo, x-ray, MRI etc.)
- Adequate storage area and conditions, separated from potentially similar devices
- A qualified investigation site team and adequate facilities

Submissions

- Consider roughly 3 months for approvals if all goes well.
- Submission to **ethics committee** : national and/or regional EC (according to countries); (EC meeting date important for submission timelines)
- Submission to **regulatory authority**: define if a notification or approval is needed (according to CE mark status, interventional or not (in France); private or public hospital (in Italy)...))
- Often parallel process (EC/CA) possible, but no CA approval without positive EC vote
- Potentially additional **radiation approval** needed
- Some countries request special **data protection submission** or contract approvals

Technical training

- Cadaver / animal training of implant procedure to be considered

Training of investigators and other applicable research staff on

- Implant accessories / instruments
- Software / programming of device
- additional technical equipment (programmers)
- Emergency handling

Proper documentation!!

Initiation

- Proper training of site in ISO/GCP, patient population, study procedures and documentation
- Safety aspects and reporting
- Device storage, handling and accountability
- Device technical feedback/complaint

Enrollment/Baseline



- Basic patient data recording after informed consent
- QoL, VAS scores, other questionnaires
- Basic Imaging if applicable, other exams like holter ECG, HF tests etc.

Procedure

- Essential event in device trials

Procedural related data to be recorded (could be tricky, when unusual data is requested in CRF) like:

- Timings
- Fluoroscopy time
- Technical / handling feedback
- Measurements during procedure
- Anatomical details
- Issues, adverse events

Discharge

- Potential first check of performance, proper placement etc. + safety check

Follow up phase

- Regular follow ups for device performance, efficacy and safety check, whenever possible in same timing as standard follow up for indication.
- QoL, VAS scores, other questionnaires
- A standard could be 3 Mo, 6 Mo, 12 Mo and yearly thereafter (up to 5 years or even more)

Reporting: Safety

- In device trials in EU all SAEs have to be reported to CA and EC (changed in 2010)
- Reporting Timelines
- In post marketing trials, where device falls under Meddev, just SADEs need reporting (serious adverse device effects = SAEs that are related to procedure or device)
- Regarding study data – device safety it is crucial whether an event was caused by device or not.
- Device deficiencies should be reported as well if they could have led to a serious adverse device effect

Classic Issues

- Enrollment lower than promised
- Technical issues with device
- Site not adhering to protocol or standards
- Inconsistent / incomplete source data
- Safety, Safety, Safety – underreporting of SAEs
- Improper device implant, handling, programming
- Incomplete follow ups, imaging not done as requested by protocol
- Incompliant patients
- Lack of investigators time

Summary of Regulations

- ISO 14155: Clinical investigation of medical devices for human subjects
- MEDDEV 2.12-1 rev 6: GUIDELINES
ON A MEDICAL DEVICES VIGILANCE SYSTEM
- MEDDEV 2.12-2, May 2004, Guidelines on Post Market Clinical Follow-up
- Medical Devices Directive (EU Directive 2007/47/EC): covers the regulatory requirements of the European Union for Medical Devices