

Swissmedic Symposium Clinical Trials
Bern, 14.06.2017

Medical devices - specificities



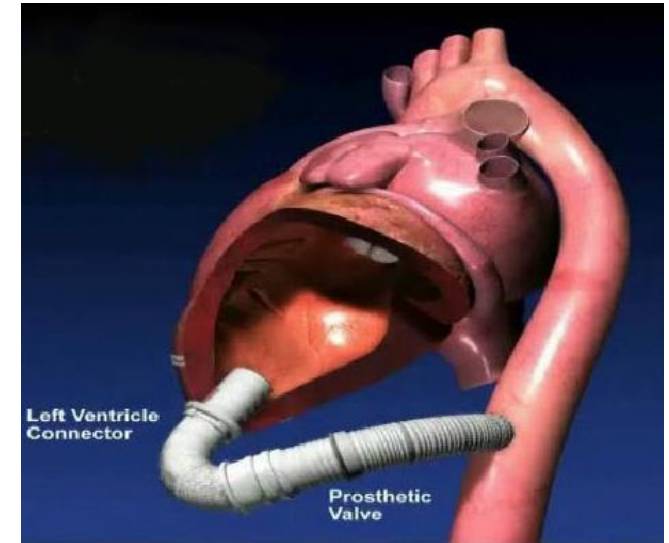
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1. Introduction

Medical devices:
roughly 500'000 products



Tonyliepert, 2011-10-10



Amitchell125 at English Wikipedia, 2009

Clinical trials of medical devices, activities of Swissmedic

- approx. 100 pre-market clinical trials of medical devices currently ongoing
 - ~ 30-40 new applications / year
 - > 700 reports / year
 - ~ 300 general questions / year
- surveillance and inspections of sponsors, CRO's, investigators
 - ~ 10% of approved pre-market clinical investigations
- European harmonisation
 - CIE working group
 - EUDAMED databank
 - Several guidelines (MEDDEV 2.7/1, 2.7/2, 2.7/3.)
 - Revision of the European regulations for medical devices
 - Coordinated review of multinational clinical investigations in future

2. MEDDEV 2.7/2

European guidelines for competent authorities for making a validation / assessment of clinical investigation applications

- MEDDEV contains recommendations for CA reviewers.
- a European training program for CA reviewers started in October 2016: improve skills, train new reviewers, foster confidence building and collaboration, facilitate the future “*Coordinated assessment procedure for clinical investigations*” (art. 78 MDR).
- MEDDEV 2.7/2 was included in the October 2016 European training: mock dossier review and questionnaire. MEDDEV 2.7/2 therefore expected to be applied increasingly over the next few years.
- MEDDEV 2.7/1 is available at http://ec.europa.eu/growth/sectors/medical-devices/guidance_de

Examples of risk management expectations described in MEDDEV 2.7/2:

- management of risks due to the learning curve:
training before use, supervision during first use
- duration of follow-up:
must meet study needs as well as safety needs of subjects
- procedures for patients lost to follow-up
contact persons for mortality/ SAE studies
- retrieval and analysis of used products
- management of first-in-man trials
- etc.

Examples of risk management expectations described in MEDDEV 2.7/2 (1):

- management of risks due to the learning curve: training before use, supervision during first use

A.2: the following information should be considered under Annex A.2 of EN ISO 14155:2011

Consideration: When the handling of the specific device is complex or unfamiliar to the investigator: Have risks associated with learning been properly mitigated (such as training prior to the first use, support during the first cases). In addition, when inadequate handling of a complex or unfamiliar device can cause serious adverse events (SAE): Supervision of every investigator by an experienced person during the first use(s) should be foreseen and properly described in the CIP (or IB)

Examples of risk management expectations described in MEDDEV 2.7/2 (2):

- duration of follow-up:
must meet study needs as well as safety needs of subjects

A.6.1: the following information should be considered under Annex A.6.1 of EN ISO 14155:2011

Consideration: Is the duration of the follow up sufficient?

- a) long enough to gather data necessary for ensuring the safety of participating subjects and take remedial action if necessary, under consideration of the specific standards, to the type of studies and to the shelf life of the medical device;*
- b) long enough to fully achieve study objectives;*
- c) observations should cover at least entire duration of clinical healing phase/ recovery phase connected to use of investigational devices. Longer observations are necessary if required by a or b (e.g. for implants if long term side-effects can be expected).*

Examples of risk management expectations described in MEDDEV 2.7/2 (3):

- procedures for patients lost to follow-up
contact persons for mortality/ SAE studies

A.7: the following information should be considered under Annex A.7 of EN ISO 14155:2011

Consideration: Patients lost to follow-up

- a) there should be clear procedures on how patients lost to follow-up are handled.*
- b) if study endpoints include death or outcomes that can cause disability / loss of autonomy:*
 - if a study subject cannot be contacted, the procedure should foresee that the center should contact other persons or institutions (in certain countries the family doctor). Such contacts should take place rapidly, especially in FIM studies of devices with relevant risks, in order to enable the sponsor to promptly identify undue risks and take measures that are necessary for preserving the health and safety of study subjects (i.e. temporary stop of recruitment in order to review the design of the device);*
 - the consent form should name the persons or institutions to be contacted and clearly state that the subject allows exchange of medical information*

3. In-vitro diagnostic medical devices



Amitchell125 at Wikipedia, 2009

3.1. Performance evaluation of IVD versus pre-market clinical trials (1)

Current situation: in general no premarket clinical trials

- “performance evaluation” mostly limited to testing characterised samples
 - panels, study specific samples, certain IVD may necessitate prospective studies with multiple retrieval of donor samples and donor data
 - status of investigational IVD?
 - unreliable, not for medical use, risks of error and misinterpretation must be managed, sponsors therefore not allowed to disclose individual test results to donors/ doctors/ therapists/ nurses; no transfer of data to patient files
- clinical trials (outcome, benefits, etc.) not required for CE-marking
- CE-marked IVD are considered reliable as far as stated in IFU
 - for the market
 - for clinical trials (subject specific decisions incl. inclusion/ exclusion, drug selection and dosing, individual monitoring and management)

3.1. Performance evaluation of IVD versus pre-market clinical trials (2)

New European IVD regulation (IVDR): premarket clinical trials of IVD

- introduces new requirements and terminology for IVD: “clinical evidence”, “clinical performance”, “clinical benefit”, “clinical evaluation”, “interventional clinical performance study”
- for some IVD, CE-marking will necessitate clinical trials, clinical aspects (such as patient outcome) may need to be investigated
- clinical investigation rules for medical devices will apply, incl. EN ISO 14155, (EN ISO 14155 is currently being updated)

3.1. Performance evaluation of IVD versus pre-market clinical trials (3)

Situation in Switzerland

- Swiss legislation already allows these studies since 2012
HRA and OClin are applicable to all medical devices (IVD not excluded!) ⇒ category C clinical trials of medical devices, dual authorisation by Cantonal ethics committee and Swissmedic
- HRA and OClin will be updated due to MDR and IVDR

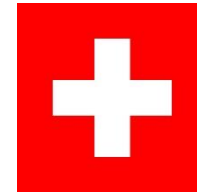
3.2. Clinical trials of various products: Use of lab kits

- medical use, patient specific decisions: **only with CE-marked IVD**
 - e.g. tests for inclusion/exclusion criteria, drug selection and dosage, individual patient monitoring and management

- other purposes: **other lab kits also acceptable**
 - “research only” data, standardisation of study results (e.g. non-CE-marked lab kits used in core labs)
 - make sure scientific soundness of project is not endangered by lab kits of unknown quality
 - risks due to lack of CE-marking must be managed, no disclosure of individual test results to subjects/ doctors/ therapists/ nurses, no transfer of results into patient files

- what in case of dual goals?
 - double analysis of samples, CE-marked IVD for the medical purpose, other test kit for study objectives

4. Developments



- Swissmedic will implement electronic document management and introduce electronic submissions for medical device trials in 2017, additional information will follow in late summer or autumn
- New European regulations for devices were published on 5.5.2017 (MDR, IVDR); Swiss legal framework now being checked and adapted in two consecutive steps (MedDO first, then TPA/ MedDO/ HRA/ OClin), international agreements now also being checked (MRA,...)

Take home message

1. for new pre-market device trials, **check and update risk management solutions and CIP procedures according to MEDDEV 2.7/2** (*user training, supervision during first use, minimal duration of follow-up, first-in-man patients, patients lost to follow-up, retrieval and analysis of devices, ...*)
2. for pre-market **clinical trials of IVD**, **submit** authorisation applications to the ethics committee and **to Swissmedic**
3. **use CE-marked lab kits** for all medical purposes, except in authorised pre-market clinical trials of IVD (*for subject specific activities such as inclusion/ exclusion criteria, drug selection and dosage, monitoring and management of patients, etc.*)
4. there will be changes for device trials: electronic submissions to Swissmedic, implementation of new EU device regulations
⇒ regularly visit **www.swissmedic.ch/ci**



Thank you for your attention