Review Article

Medical Device Clinical Trials in Europe

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ABSTRACT

Medical devices are the machine, tool, instrument, apparatus, implant, calibrator in vitro, or software intended for use in the healthcare sector to diagnose, control, prevent or treat an illness. The safety of the population is the priority to launch new medical devices for the treatment and diagnostic of several diseases. Innovation in industries and regulations work together to supply devices for the various world market and to enhance the quality and safety of existing devices in the market. The main key for devices is to classify the determination of actual regulatory pathway which ensures the security standards and other regulatory requirements in a specific country. Medical device trials are quite different from the clinical trials. For any high-risk devices, the new EU law states that the manufacturer has to prepare an entire summary for their evidence. Complete transparency is necessary for the maximum possibility of informed decisions to use new medical devices. This article provides an overview regarding the study of medical device trials, classification of medical devices in Europe, the regulatory framework for the approval of medical devices and clinical investigation of medical devices in the European Union.

Keywords: Medical device, medical device regulation, clinical investigations of medical devices, post-marketing clinical follow-up, healthcare, calibrator.

INTRODUCTION

By definition, a medical device is any "article, instrument, apparatus or machine that utilised in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for few health purpose" (World Health Organization). Medical devices are classified on their basis of intended use, invasiveness, duration of use, and therefore the risks and potential harms related to their use [1].

Preclinical Research

Preclinical testing may involve the following:

Bench testing – To assess the performance and safety of the device and confirm that it performs as designed for.

Technical testing – For accuracy and reliability of the device. The prototype is usually rebuilt using different materials.

Computer simulations – Computer simulations can provide accurate predictions about the device effects in humans and identify potential risks or unwanted effects that may be improved by redesigning the device.

Animal studies – If appropriate, the device will be tested in animals to assess its bio-compatibility, toxicology and other safety concerns. Efficacy could also be performed in animals but isn't always possible due to anatomical and biological differences, particularly if the device is meant for complex or rare human diseases [2].

Medical device clinical trials are different from drug trials in which only patients with the condition in which the device is designed to treat are involved. They are traditionally of three different types of studies.

Exploratory or Feasibility Study

Exploratory studies (also known as feasibility studies) are conducted in the early stages of device development. They are used to establish preliminary safety and effectiveness of the device and style the next stage of the trial, the pivotal study [3].

Pivotal Study

Pivotal studies are performed to demonstrate the device is safe and effective for a selected use within an outlined patient population. The results of this study is for the market approval of device from regulatory.

Post market Study

Run either as a condition of approval to meet a business objective, post-market studies are similar to Phase IV of clinical drug trials since the goal is to understand long-term effectiveness of the device and potential adverse events related to utilization of the device.

From Idea to Clinical Trials to Market

Comparison of Pharmaceutical Trails and Medical Device Trials[6]

Pharmaceutical Trials	Medical Device Trials
○ Controlled studies ○ ex: drug vs no drug ○ Or, vs commonly used drug or standard care ○ Placebos used ○ ex: sugar pills, saline injection ○ Randomization ○ Blinding (single / double-blinded) ○ Crossover studies	○ Controlled studies ○ ex: device vs no device ○ Or, vs another device, standard care or physical therapy ○ Placebos rare ○ ex: sham surgery, inactive device ○ Sometimes randomized ○ Blinding is rare / difficult ○ Crossover studies sometimes possible

Study Design

Randomized controlled trial is the gold standard of study design, preferably with blinding and a placebo as the control 4.

Controlled means that group of participants who receive no treatment, a placebo, or other treatment (comparison study).

Randomized means that trial participants are randomly assigned to either the treatment group or the control group.

Specific barriers to conduct trials on medical devices by randomization

The major barrier identified for randomized clinical trial on medical devices [4,5].

- Randomization including timing of assessment, acceptability, blinding, choice of comparators groups & consideration on the learning curve.
- Difficulties in determine appropriate outcome.
- **Blinding** means that participants don't know which treatment they are receiving (single-blinded), and in some studies, neither do the doctor(s)/study coordinated (double-blinded).

This study design is far more difficult or impossible to implement for medical devices, however. A well-controlled study design is generally acceptable.

Aims of Clinical Investigations[7]

Reach the intended purpose planned in its design and work are expected.

- Provided the expected clinical benefits.
- Acceptable risk/benefits ratio.

European Device Trials

EU directive MEDDEV 2.1/3 rev 3(21 march 2010), national legislation has revision of medical devices definition [8].

Medical device is an instrument, apparatus, appliance, software, materials or other article whether used alone or together, including the software intended by its manufactures to use specifically for diagnostic and therapeutic purpose.

- ❖ Diagnosis, prevention, monitoring, treatment of disease/injury.
- ❖ Investigator, replacements or modification of the anatomy of a physiological process.
- ❖ Control conception.

Primary purpose of medical devices is employed for health care. The aim of medical devices is to guage the safety of one or more human subjects & also to analyze the performance of medical devices. Clinical trials on medical devices are step before equipment enters the market by requesting registration. Medical devices range from relatively simple devices like patches & wheelchairs .to complex devices as pacemakers & MRI-scanners.

How many Classifications does exist[9,10]?

The EUMDR 2017/745 has 4 main categories for medical devices. They are:

Class I: low risk, safety standards. It is approved by regulatory authority & the manufacturers themselves can

issues the CE mark. It is further divided into 3 subcategories. They are as follow

Class IS: product that is delivered sterile.

Class IM: with measuring function.

Class IR: new sub class for product that are reprocessed and validated.

***Class IIA*:** medium risk, general standards, quality system & special controls for supporting documentation including clinical and non clinical by manufacturers.

Ex: ultrasonic diagnostic equipment, wheelchair, hearing aids, suction equipment.

Class IIB: medium to high risk.

Ex: infusion pumps, ventilators, implants.

Class III: high risk, Clinical trials are recommended. Most are non randomized and single arm. Pnre market reviews include clinical trial & animal studies providing proof of safety and effectiveness.

Ex: replacement of heart valves, breast implants, defibrillators, pacemakers.

Conduct of Clinical Investigations[11]

Sponsor and investigator collect information data according to **EN ISO 14155** list excellent analytic practice for clinical testing medical devices.

Advice for Sponsor Conducting Medical Devices Trial Under New Regulations:

- Consider a full service approach with a CRO that has considerable experience in medical device studies for the European market
- Consult expert bio-statisticians in order guarantee successful protocol and study design
- Consider a SAS programming team that can comply with data base one specialized vendor to increase efficiencies and reduce cost
- Incorporate a centralized monitoring solution in order to monitor the quality site and site data remotely and more accurately.

Clinical Safety Reporting

Safety reporting requirements for devices differ from those for drugs for devices manufacturer are required to report all SAE'S, even if it is directly not related to devices or procedures of devices used SAE'S in clinical trial investigation of medical devices commenced prior to efficient data of new act medical devices not completed this data shall be reported to institute in compliance with existing legal regulations both to sponsor and investigator. SAE is reported to sponsor in the form of documents like written description of event to institute through letter, fax, email. The form is a part of recommendation by MEDDEV 2.7/3. This requirements are applies to implants, invitro devices and diagnostic. If a participant in an invitro devices trial experience a health condition that is not related to device but that condition must be reported [12].

Regulatory Requirements

Medical devices trials are not required to submit IND application they are subject to 21CFR part 812 [investigational device exemption]. On may5 2017 European parliament publish new regulation for medical devices & invitro diagnostic which introduce [13].

An expanded definition of medical devices related to prediction & prognosis of disease.

Stricter rules & requirement for clinical evaluation & clinical investigation.

LIFE cycle of all product available EU market.

A new device identification system for easy to trace [unique device identifier].

An implant card contains name, serial number, UDI, device mode, relevant warning and precautions

An EU wide coordinated procedure in multi center clinical studies on medical devices

Reinforced requirements for manufacturer to collect data.

Improved coordination post marketing surveillance and vigilance.

Process for Registering Medical Devices in Europe[14]

Determination of MDD that applies to the devices.

Determine the class using annex ix.

Choose conformity assessment procedures.

Appoint an authorized representative located in Europe

Audit of QMS &.technical documents by notified body.

Register devices with competent authority of medical member.

Prepare declaration of conformity stating medical device complies with applicable devices.

Affix CE marks

Place in market.

List of Guidance MEDDEV'S

The European commission provides a range of guidance documents to assist stakeholders in implementing directives related to medical devices [15].

2.1 scope, field of application, definition

- MEDDEV 2.1/1 definition of Medical devices, Accessory" and Manufacturer" April 1994.
- MEDDEV 2.1/2 rev 2 Field of application of directive "active implantable medical devices" April 1994
- MEDDEV 2.1/2.1 Treatment of computer used to program implantable pulse generators February 1998

- MEDDEV 2.1/3 rev 3 Borderline products, drug delivery products, & medical devices on incorporating, as integral part, an ancillary medical substance December 2009
- MEDDEV 2.1/4 Interface with other directive
- Medical devices directive 89/336/EEC concerning to electromagnetic compatibility and directive 89/686/EEC concerning to personal protective equipment March 1994
- MEDDEV 2.1/5 medical devices with a measuring function. June 1998
- MEDDEV 2.1/6 qualification & classification of standalone software July 1998

2.2 Essential requirements

- MEDDEV 2.2 /1 rev 1 EMC requirements February 1998
- MEDDEV2.2/3 rev 3 " Use by"- date June 1998MEDDEV 2.2/ rev 4 Conformity assessment of invitro fertilization and assisted reproduction technologies products January 2012

2.5 Conformity assessment procedures

- MEDDEV 2.5/3 rev 2 Sub contracting quality systems related June 1998
- MEDDEV 2.5/6 rev 1 homogenous batches(verification of manufacturers products) Conformity assessment for particular group of products
- MEDDEV 2.5/7 rev 1 Conformity assessment of breast implants July 1998
- MEEDEV 2.5/10 Guideline for authorized representatives January 2012

2.10 Notified bodies:

- The documents on designation of notified bodies under new regulations are in the sections above (MDCG Documents)
- MEDDEV 2.10/2 rev 1 Designation & monitoring of notified bodies within the framework of EC directives on medical devices. Annex I, II, III, IV April 2001.

2.11 IVD:

- MEDDEV 2.14/1 rev 2 Borderline & classification issues: A guide for manufacturers and notified bodies
- MEDDEV 2.14/3rev 1 Supply of instruction for use & other information for in vitro diagnostic medical devices. January 2007

Directives and Regulations[16, 17]

The European medical devices industry accounts for around a third of world population. Current regulation on medical devices were adoptive on 5th April 2017.this replace actual directive. Germany, France, UK, Italy, & Spain are top 5 countries to contributes invitro diagnostic equipment in Europe.

Council directive 93/42/EEC of 14june 1993 is concerning medical devices (amended in the year 2010)

Directive 93/68/EEC CE marketing

Directive 2000/70/EC of European parliament and of council of 16th November 2000.(amending council directive 93/42/EEC as regard medical devices incorporating stable devices of human blood or human plasma (amended in the year 2010)

Medical devices directive (93/42/EEC & 2007/47/EEC) for invitro diagnosis and other human or animal product origin (in the year 1993-MDD)

General medical equipment has a simple bandage for high technique radioscopy apparatus

Active implantable medical devices directive (AIMDD in the year 1990) which encompasses all the electronic medical devices in human body are like

A. Implantable defibrillators

B. pacemakers

C. implanted infusion pumps

D. bladder simulator

E. neuromuscular stimulation devices

In vitro diagnostic directive (98/79/EEC) in the year 1998 in which medical devices and strips are used to avoid the patient to diagnose the patient's conditions

As a result, European council enacted the new comprehensive directive (MDR) that come into force in the year 2017 may, because of great need of law. The MDR came into effect soon, but after 3 years of transition period.

New Contents of MDR[20]

A procedure comparable with annex vi of MDD is no longer available.

Requirements for reprocessing of disposable products have increased.

The retention period of the technical documentation was double from 5years of MDD to 10 years for the MDD.

Note: ON SEP 26 2012. The European commission published a proposal for regulation of medical devices and a separate proposal regulation of IVD devices.

On OCT 22, 2013 European parliament voted to accept 347 amendments for medical devices regulation proposed.

Annexes: Annexes are used to market medical devices in Europe; each devices must receive European mark of conformity (CE). CE indicates manufacturing approval and 3 previous directives (MDD, AIMDD, and IVDMDD) are the EUMDD guideline classification. Annex xvi is a new product as medical devices for the first time[19].

High Level Summary of EU MDD Annexes [21,22]

Annexes	Contents	Common guide
ANNEX I	General recruitment	Patient safety & actions
ANNEX II	European commission declaration of conformity	Broad quality system registration. {ISO 9000, EN 46000} mark conformity annex xii technical file for class ii(iia iib) class-iii
ANNEX V	Declaration of conformity	Product quality boldness EN ISO 13485.

EU Approved Device but US FDA had Rejected[23,]

❖ **Covidien Pleura Seal Lung Sealant System**

This device went on EU market in NOV 2007 and is used electric pulmonary resection as on adjusting to standard closure techniques for visceral pleural air leaks. It is rejected in FDA [USA] used on Dura & spine.

❖ **Medtronic Devices**

It is implanted device system designated to measure & record hemodynamic variable continuously. FDA rejected in March 2007 "due to lack of clinical effectiveness".

❖ **PIP Breast Implants**

It is a breast implants manufactured by poly implant prosthesis [PIP]. These was received a CE mark for its silicone breast implants but in 2001 they changed the gel 50, that it was different from the one described in the CE marketing file.

Note: Currently there are 76 notified bodies in Europe and in UK, including BSI, SGS and inter tacks. For the highest risk devices [class-III], the manufacturer must conduct human clinical trial or evaluate effectiveness.

CONCLUSION

- The new regulation seeks to extend medical device effectiveness within the EU market.
- In European union, CE marketing or certification is mandatory for any device to be marketed.
- All medical devices are regulated through notified bodies. These notified bodies ensure compliance to quality & safety standards and approves devices for CE marketing.
- Medical devices directive, minimize the patient risk, by limiting the marketing of novel high-risk devices with minimal clinical data to physicians with necessary training & expertise.
- The new European legislation should require pre-mask demonstration of clinical efficiency & safety by using randomized controlled trial if possible and transparent clinical review.

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