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MEDICAL DEVICE

Clinical Investigation and Clinical Evaluation

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1. Regulation of medical devices in the EU: right before change

To market a medical device (MD) in the EU, a manufacturer must demonstrate that the device is safe, that it performs as intended, and that the risks associated with the use of the device are acceptable when weighed against the benefits to patients. Clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device to verify its clinical safety and performance. It may be based on a literature review and/or clinical experience and/or clinical investigations. While some medical devices do require data generated from a clinical investigation, it is often possible, for low- to medium-risk devices (Class I, IIa, and IIb), to rely on a literature review and/or clinical experience to support the device's intended use.

The Medical Devices Directives (MDDs) form the foundation of Europe's regulatory framework for medical devices. The relevant EU legislation addressing the clinical evaluation of medical devices is the Medical Device Directive 93/42/EEC, as amended (March 2010) and the Active Implantable Medical Device Directive 90/385/EEC, as amended (March 2010). This legislation was transposed into national law in all concerned countries.

2. European regulation of medical devices is undergoing significant revision

On 26 September 2012, the European Commission published a proposal for regulation of medical devices and a separate proposed regulation of In-vitro devices (IVD) (which will not be discussed here). On 22 October 2013, the European Parliament voted to accept 347 amendments to the Commission's Medical Devices Regulation Proposal. The formal legislative vote was held on 2 April 2014, which resulted in the Parliament's adoption of the amended Proposal. This action closed the first reading of the ordinary legislature procedure. On 5 November 2014, the Committee on the Environment, Public Health and Food Security of the European Parliament mandated the rapporteurs to enter into negotiations with the Council of the EU, aiming to reach an agreement on these proposals. The Trilogue on the new regulation stared in October 2015 and aiming to be completed by June 2016, including special attention to genetic testing, companion diagnostics, chemicals, reprocessing, insurance, scrutiny/special notified bodies, transitional measures and the validity of certificates, classification (MD 6, 19, 21; IVD 1, 4, 5), and clinical investigations/performance studies IVD.

A significant aspect of The Medical Devices Regulation Proposal is that it represents a bid to raise the regulatory bar on clinical evidence requirements, exposed as inadequate by the scandal of defective breast implants produced by the French Poly Implant Prothese (PIP).

Increased demands placed on medical device notified body performance are leading to more rigorous inspections of manufacturers' clinical evaluation documentation ahead of the implementation of new regulations.

3. Clinical Investigation of Medical Device

The Good Clinical Practice (GCP) standard for medical device investigation is laid down in EN ISO 14155 (2011). European legislation also explicitly requires adherence to the Declaration of Helsinki, which defines the ethical principles to be respected when performing investigations on human subjects.

As a rule, all clinical investigations need to obtain positive opinion from designated Ethics Committee and approval by the Competent Authorities of involved countries. Other regulatory institutions may need to be involved in the regulatory process depending on national law.
The essential documents for a medical device investigation are similar to the ones required for a pharmaceutical study. The term Clinical Investigation Plan is generally used to refer to the study protocol in the case of a clinical investigation of a medical device. There is a requirement to include a section on risk management in the Clinical Investigation Plan.

Regulatory requirements for clinical investigations of medical devices are different to pharmaceuticals and this has an impact on the design of their clinical investigations. There is no legal requirement to demonstrate the efficacy of the device to obtain CE marking. The objective of the clinical investigation is to demonstrate the safety and performance (conformity with claims) of a medical device. In a pharmaceutical study the objective is to demonstrate the safety and efficacy of the medicinal product. One consequence is that case numbers in a medical device investigation are usually lower than in pharmaceutical studies. The stage of a clinical investigation which needs to be satisfactorily completed for CE marking may therefore be likened to Phase II in drug development, where evidence of clinical activity of a drug is sought, rather than Phase III. Since efficacy does not need to be demonstrated, randomized controlled trial designs for medical devices are rarely necessary and therefore proof of statistical significance may not be necessary. Interim analysis of study data may be feasible, provided it has been written into the investigation plan.

In comparative pharmaceutical studies the most robust comparator is a placebo control, which is often applied and generally required by authorities. In a medical device investigation, a placebo control is usually not feasible. This is particularly the case with implantable devices, where placebo control groups (involving sham surgery) are not possible. However, studies comparing a medical device with standard therapy are possible, although in some cases there may be no standard therapy available which is similar enough to warrant comparison, especially for novel devices. In addition the user (usually a healthcare professional) often cannot be blinded to study intervention.

A specific feature of medical device investigations is that product performance may be influenced by user. Furthermore, the use of a medical device may sometimes be associated with a learning curve for the user, where the outcomes improve with experience.

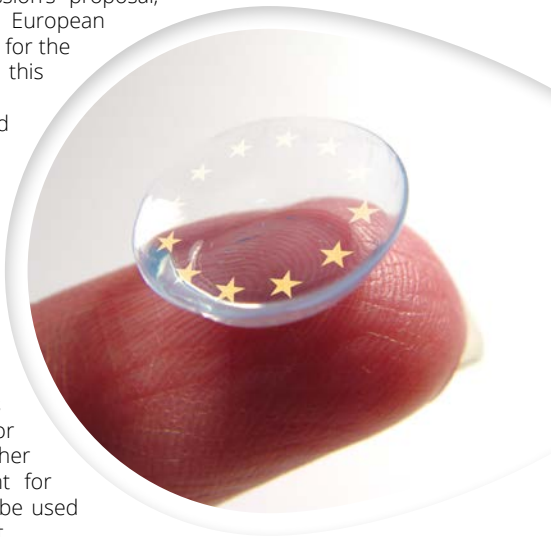
Another feature is that adverse events, in particular adverse device effects, may not only concern the investigation subjects but also third parties, such as users of the device. In contrast, adverse events in pharmaceutical studies are only monitored for the clinical study subjects.

Due to the wide range of types of device, testing methodologies vary widely. Some performance data might simply require user handling feedback; other data might be more analytical. Medical devices often create large amounts of data that are transmitted, processed and stored via specific software interfaces. For such data sets, specific monitoring rules have to be established focusing on supervising data processing rather than individual data points.

Moreover, medical devices are subject to frequent incremental innovation. Results from long-term clinical studies with predicate devices may no longer be relevant to improved products and medical procedures.

4. Proposal adopted by the European Parliament introduces new requirements

With EU action pending, the European Commission's proposal, including the proposed amendments from the European Parliament, outlines new clinical data requirements for the regulations for medical devices. Key initiatives in this area will be highlighted in this section.



The reach of the regulation is also being extended to manufacturers of products, until now not considered to be medical devices. The Proposal states (Article 2, paragraph 1, point 1): "The implantable or other invasive products, as well as products using external physical agents, intended to be used for human beings, which are listed on a non-exhaustive basis in Annex XV, shall be considered medical devices for the purposes of this Regulation regardless of whether or not they are intended by the manufacturer to be used for a medical purpose". The following types of products are listed in Annex XV: contact lenses; implants for modification or fixation of body parts; facial or other dermal or mucous membrane fillers; equipment for liposuction; invasive laser equipment intended to be used on the human body; intense pulsed light equipment.

4.1. Introduction of new concept: clinical benefits

The amended Proposal introduces the concept of "clinical benefit" of medical devices. It will no longer be sufficient to demonstrate safety and claimed performance; medical devices will need to show actual clinical benefit for patients. Failure to do so using available clinical data may require a clinical investigation to be performed.

4.2. Failure to prove equivalence may necessitate a clinical investigation

In Annex XIII "Clinical evaluation and post-market clinical follow-up" the Proposal states that existing clinical evidence with comparable devices can be used for the clinical evaluation, provided device equivalence can be demonstrated. This instruction is similar to the current medical device directive; however, the criteria will be stricter and it will be more difficult to convincingly prove equivalence. Without clinical evidence to demonstrate performance and safety, a clinical investigation will be needed.

4.3. Extended range of devices requiring clinical investigations

Under the amended Proposal, the range of high-risk devices that will require clinical evidence collected via a clinical investigation is being extended to include: Class IIb devices intended to administer and/or remove a medicinal product and devices manufactured utilizing tissues or cells of human or animal origin, or their derivatives, which are non-viable or are rendered non-viable. These devices are listed in Article 43a(1) along with: implantable devices; devices incorporating a substance; and all other class III devices. Special notified bodies will be involved in the conformity assessment procedures of these devices.

4.4. Efficacy, not performance, will need to be verified in a clinical investigation

Chapter VI (which has been amended to Chapter V) and Annex XIV "Clinical Investigations" of the Proposal introduces the requirement for the demonstration of "efficacy" of the device in a clinical investigation. It should be noted that objections have been raised to this requirement by Eucomed on the basis that, unlike pharmaceuticals, the efficacy of devices often relies on the skills and experience of the healthcare professional, the quality of the hospital, and many other factors.

4.5. Aim: randomized controlled clinical trials with well-chosen controls

Early on in the Proposal is stated the requirement for clinical investigations to be appropriately targeted and controlled. Annex XIV to the Proposal "Clinical Investigations" dictates the use of randomized controlled investigations and states that the use of any other design would need to be justified. The amendment specifically references the control therapy and the involvement of independent experts in relation to randomized controlled investigations. As pointed out by Eucomed, it is not clear how randomized controlled designs will be implemented in cases where it would be hard to randomize devices due to strong ethical and practical issues in the choice of the "comparator" (for example, it would be impossible to use a comparator for an implantable cardiac defibrillator). Furthermore, standards of care and therefore the control therapies differ depending on a specific country and healthcare expert.

5. Clinical Evaluation and the Clinical Evaluation Report

Clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device to verify its clinical safety and performance. The evaluation is based on comprehensive analysis of pre- and post-market clinical data relevant to the intended use. This includes data specific to the device as well as any data relating to devices claimed as equivalent by the manufacturer. The whole process is documented in the Clinical Evaluation Report (CER).

Clinical data sources for a clinical evaluation:

Clinical Data Source	Manufacturer's Device	Equivalent devices*
Published Data	X	X
Clinical Investigation	X	/
Post-Market Surveillance Data	X	/
Public Adverse Effect Databases e.g. MAUDE	X	X
Compassionate use Data	X	/
Internal Corrective and Preventive Actions (CAPAs)	X	/

** Devices that are demonstrated by the manufacturer to be equivalent in some or all aspects to the manufacturer's own device*

Once pertinent data is assembled and summarized, it is reviewed to ascertain whether it supports the safety and performance of the device sufficiently to meet the relevant Essential Requirements set out in the EU Medical Device Directives.

The clinical evaluation needs to cover: any design features that pose special performance or safety concerns; the intended purpose and application of the device; and the specific claims made about the clinical performance and safety of the device. It is important to describe the merit and limitations of any data cited or included in the evaluation. The manufacturer's risk assessment documentation is included in the review process to ensure that all risks identified are discussed and addressed/mitigated in it. The

instructions for use (IFU) for the device are reviewed during the process to ensure that data is gathered from the same population using the device in the same way for the same indications, as described in the IFU. Finally, conclusions are drawn about whether the Essential Requirements relevant to clinical safety and performance are met.

Clinical evaluation is an ongoing process conducted throughout the life cycle of a medical device. It is undertaken with an initial conformity assessment that is used to obtain the marketing license or CE mark of the device in the EU, and then repeated periodically as new clinical information becomes available (e.g. from ongoing and/or published studies) or changes are made to the device's design or intended use. These evaluations are also used to update the risk analysis of the device, identifying potential areas of concern, which if applicable are then noted via changes made to the design, materials, manufacturing, or instructions for use. If there are no issues, the device is approved for continued marketing in the EU.

Generally, from a clinical perspective, the manufacturer is required to demonstrate that the device achieves its intended performance during normal conditions of use and that the known and foreseeable risks, and any adverse events, are minimized and acceptable when weighed against the benefits of the intended performance, and that any claims made about the device's performance and safety are evidence-based.

The MEDDEV 2.7.1 Rev. 3 guidelines provide manufacturers with guidance regarding how to evaluate the clinical safety and performance of their devices. According to these guidelines, prior to undertaking a clinical evaluation, the manufacturer must define its scope based on the Essential Requirements that need to be supported by clinical data.

Having first identified the Essential Requirements, a manufacturer must:

- identify available clinical data relevant to the device and its intended use;
- evaluate data in terms of its suitability for establishing the safety and performance of the device;
- generate any clinical data needed to address outstanding issues;
- bring all the clinical data together to reach conclusions about the clinical safety and performance of the device;
- document the results of this process in a CER.

6. Preparation of Fully Compliant CERs Will Be More Demanding

The increased demands placed on notified body performance will have consequences for manufacturers of medical devices. They can expect increasingly intense scrutiny over compliance with clinical data requirements, and in particular of the CER since the CER provides key evidence in terms of non-compliance. Notified bodies may want to examine the clinical evaluation and CER to assess the compliance of products, including lower risk products, not just during regular audits, but during the unannounced audits.

Thorough review by notified bodies means that manufacturers will need to pay rigorous attention to factors such as: justification of their choice of the author to prepare the CER; provision of rigorous proof of equivalence of additional devices included in the clinical evaluation; and inclusion of a plan for Post Market Clinical Follow-up (PMCF) studies.

The author of the CER should be appropriately qualified and experienced. If equivalence to a marketed product cannot be demonstrated and documented in a CER, clinical investigations will be required; if PMCF studies are not planned, a robust justification will need to be provided. In the stricter environment, companies need to check rigorously their clinical data and clinical evaluation. Questions every company producing medical devices need to ask themselves include:

- Is my company keeping up with the regulatory developments?
- Do all our products (all categories) have CERs?
- Have all our CERs been updated to the current MEDDEV requirements?
- Are all our CERs fully compliant?
- What action do we need to take to avoid the issuance of non-conformities by notified bodies?
- If non-conformities have already been issued by notified bodies, how should they be rectified?

7. Conclusion

The amended Medical Devices Regulation Proposal aims to ensure more solid clinical data to support medical device CE marking applications. Clinical evaluation requirements will be more stringent, and there will be a requirement to demonstrate clinical benefits of the device and provide a rigorous proof of equivalence, if the evaluation is based on comparable devices.

In a move that is likely to have the greatest impact on manufacturers of medical devices, the amended Proposal has introduced a requirement for efficacy into the European medical device regulatory system, which, since its inception, has been based upon essential requirements for safety and performance. Demonstration of efficacy is best achieved with a randomized controlled investigation. Although a randomized controlled study design may not be feasible or ethical with some implantable devices, such a study design provides clear potential advantages. Large, multi-center randomized controlled clinical investigations allow reliable general conclusions to be drawn from results while enabling the detection of small, clinically significant effects that smaller trials might miss. This evidence is currently lacking for most medical devices.

The proposal, as amended, would result in an increased need for randomized controlled clinical investigations to gain and maintain CE approval for high-risk devices, a classification which has been extended and now includes some class IIb devices. In addition, the requirement for demonstrating clinical benefit will bring more randomized study designs regardless the classification. For lower risk devices, clinical investigations would have to be performed to achieve CE approval, if relying on existing clinical data could not be justified. Also, independent experts would be needed to provide justification for the choice of the control intervention or to justify clinical study design for studies other than randomized, controlled investigations.

A Progress Report prepared by the Italian Presidency of the Council of the EU and published on 25 November 2014 stated that the discussion of the Working Party on Pharmaceuticals and Medical Devices is moving in the direction of further aligning the provisions on ethical and methodological principles to those for clinical trials of medicinal product. As the regulatory stakes are being raised for clinical investigations of medical devices manufactures will need to acknowledge that quality standards will need to be increased in order to approach those expected for clinical trials of pharmaceutical products.

8. Solution: Work with an Experienced CRO

We can help you decide if a clinical investigation will be required and assist you with the setting up and execution of the trial. We can help you ensure that no source of clinical data is overlooked and that the clinical evaluation is carried out in line with current regulations. We can supply a suitably qualified and experienced author to prepare a systematic literature review or a complete CER. We can also review your existing CERs and identify all areas that may be labelled as non-conformities by a notified body.

We will also ensure objectivity, transparency, reproducibility, and consistency, when preparing a CER. All the conclusions must be based on scientific clinical data, and both favorable and unfavorable data need to be included in the dataset that is assessed.

The manufacturer's risk management documents are expected to identify the risks associated with the device and to document that such risks have been addressed. The clinical evaluation is expected to address the significance of any risks that remain after design risk mitigation strategies have been employed by the manufacturer. Therefore the scope of the clinical evaluation will need to be informed by and cross referenced to the manufacturer's risk management documents.

It should be determined whether the clinical evaluation will be based on a literature review (recommended in most cases), clinical experience (recommended whenever possible) and clinical investigations (required in specific circumstances).

Clinical evaluation of medical devices that are based on existing, well established technologies and intended for an established use of the technology, is most likely to rely on compliance with recognized standards and/or literature review and/or clinical experience of equivalent devices.

For devices already on the market with no design changes since the time of the last CER it may be possible to exclude equivalent devices and only use clinical data with the device of interest and to set restrictions on the type of data used (e.g. use only high-quality clinical trials). If relevant changes (design, intended population) have occurred since the last CER, it may still be possible to include only data with the device of interest, but supplementary rationale and/or clinical data will also be needed to explain why design change will potentially bring increased benefit and not lead to increased risk to patient. Devices already on the market which have limited clinical data surrounding their use will require the inclusion of data pertaining to equivalent devices.

High risk devices, those based on technologies where there is little or no experience, and those that extend the current clinical use of an existing technology are most likely to require clinical investigation data. Therefore, for implantable or class III devices, clinical investigations will be required unless it can be duly justified to rely on existing clinical data alone, as stated in the annex X of Directives 93/42/EEC and annex 7 of 90/385/EEC as amended.

The process of receiving approval for new medical devices (in particular high risk devices) will become more complex. Manufacturers of medical devices should begin implementing the necessary systems

for compliance as soon as possible to ensure full compliance when the regulations come into force. Resources need to be committed by manufacturers to clinical evaluation of devices including high quality clinical investigations and steps taken to secure input from individuals with good understanding of the regulatory requirements as well as individuals qualified in GCP procedures.

Many medical device manufacturers, especially those of medical devices in lower risk classes have neither sufficient resources nor expertise to perform high quality clinical investigations in-house. Also, the new legislation will require a wider range of products to be classified as medical devices and regulated as such; therefore, companies who did not deal in devices previously may find that they will do so under the new laws. All these companies, as well as some established large medical device companies with overstretched resources may need to consider outsourcing clinical investigations.

By outsourcing clinical investigations to a full-service CRO device manufacturers can access external regulatory, clinical, and statistical expertise and realize significant efficiency gains, saving time and money. Potential benefits include avoiding the need to hire additional in-house staff or purchase expensive data management software.

8.1. ADAX can assist you!

ADAX will ensure that the clinical investigation will be performed to the most recent regulatory requirements, and that you are made aware of important areas undergoing regulatory changes. Full service outsourcing services encompass the entire trial process but you may only require specialized services such as regulatory consulting, clinical monitoring or data management support.

An important first step is the preparation of a Clinical Evaluation Report to determine if a clinical investigation will be required. If a clinical investigation is deemed to be necessary, we can prepare or assist in the preparation of the necessary documentation, including the Investigator's Brochure and the Clinical Investigation Plan.

With randomized controlled investigations, establishing statistical significance will be necessary. ADAX is experienced in clinical trials for medicinal products and medical device clinical investigations and can provide comprehensive statistical analysis, an advantage that some CROs may not be able to match.

8.2. Outsourcing aspects of the clinical evaluation process and CER preparation

ADAX can assist with many aspects of the clinical evaluation process and CER preparation (the activities referred to below are described in relevant sections of MEDDEV. 2.7.1 Rev.3 and will be performed to MEDDEV 2.7.1 Rev.3 specifications):

- scoping and identification of clinical data,
- literature searching (a brief outline of the searching/retrieval process would be included in the CER and cross-referenced to the literature search protocol and reports),
- collection of clinical experience,
- clinical investigation,
- appraisal of clinical data,
- analysis of the clinical data,
- concluding, reporting, and
- update of clinical evaluation, including PMCF (MEDDEV 2.12/2).

9. About ADAX

ADAX is a high quality provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical, regulatory and vigilance services. With an established Quality Management System, our medical device experts can identify gaps in your Medical Device Technical File, identify non-conformities in your existing Clinical Evaluation Report, perform a new Clinical Evaluation, set up, organize and manage a Clinical Investigation, if necessary, and support you in setting up and maintaining your vigilance system.

Add EXCELLENCE to your Medical Device with our KNOW-HOW!

Medical Device Technical File

Clinical Investigation

Clinical Evaluation

Post-Market Surveillance and Vigilance

Medical Device CE Marking

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