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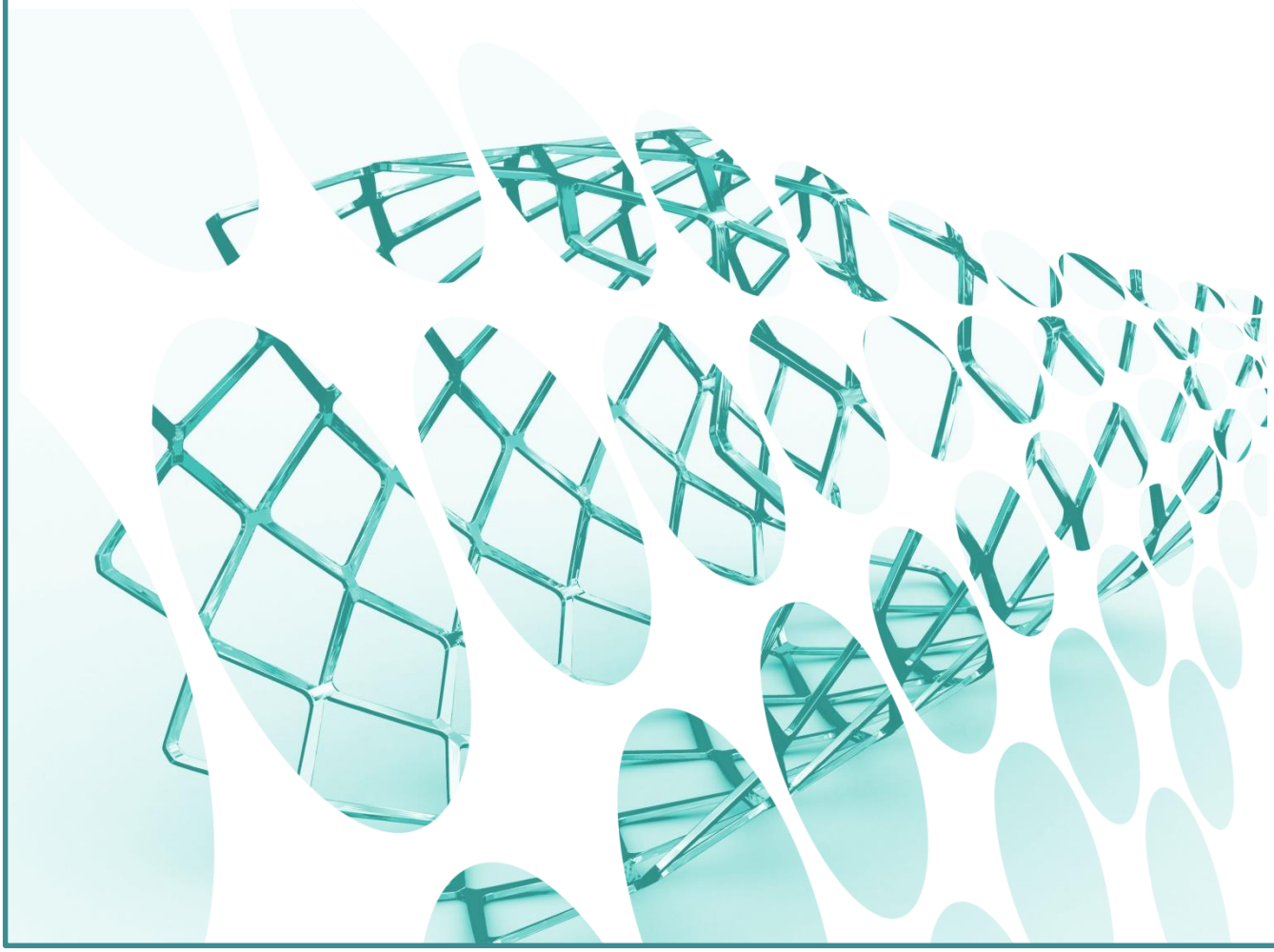
White Paper

Clinical Evaluation Reports

Meeting the demands of a more stringent regulatory environment

MEDICAL DEVICE



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1. Introduction: 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 a 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. FDA 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 summarised, 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.

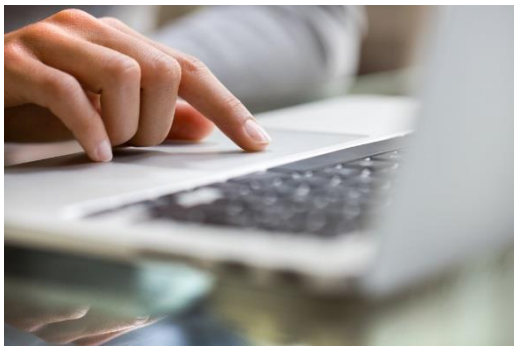
The clinical evaluation needs to cover: any design features that pose special performance or safety concerns; the intended purpose and application of the device; and the specific claims made about the clinical performance and safety of the device. It is important to describe the merit and limitations 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.

2. Background: The Regulatory Framework for Medical Devices in the EU

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 minimised 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.



Rules relating to the safety and performance of medical devices were harmonised in the EU in the 1990s. The core legal framework consists of three Medical Device Directives (MDDs): Directive 90/385/EEC regarding active implantable medical devices, Directive 93/42/EEC regarding "general" medical devices (CERs are mandatory for CE-marked medical devices in all four classes: class I, class IIa, class IIB, and class III) and Directive 98/79/EC [199 KB] regarding in vitro diagnostic medical devices. They aim at ensuring a high level of protection of human health and safety and the good functioning of the EU market. These three main Directives have been supplemented over time by several modifying and implementing Directives, including the last technical revision brought about by Directive 2007/47/EC.

Legally non-binding MEDDEV guidelines were created that promoted a uniform approach by manufacturers and notified bodies involved in the conformity assessment procedures of the Directives within the EU. The most recent revision of the European MEDDEV guidelines occurred in December 2009 (MEDDEV 2.7.1 Rev. 3), regarding creation of clinical evaluation reports. These guidelines incorporate changes introduced by Directive 2007/47/EC amending Council Directive 90/385/EEC and Council Directive 93/42/EEC and became applicable on 21st March 2010.

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:

- for devices subject to the Active Implantable Medical Device Directive (90/385/EEC), they are the Essential Requirements in sections 1, 2 and 5 of Annex I;
- for devices falling under the Medical Device Directive (93/42/EEC), these are, at a minimum, the Essential Requirements in sections 1, 3 and 6 of Annex I

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.

3. Challenge: Recent Developments Have Created a More Stringent Regulatory Environment

On 26 September 2012, the European Commission adopted two proposals to replace the existing three MDDs:

- Proposal for a Regulation of the European Parliament and of the Council on medical devices; and
- Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices.

These proposals have been submitted to the European Parliament and the Council. In order to become binding Union law, the European Parliament and the Council need to adopt the texts by the ordinary legislative procedure which is proving to be a time-consuming process.

However, the EU is moving towards a much tighter, and stricter controlled regulatory environment ahead of the adoption and implementation of new regulations. Following the scandal of defective breast implants produced by the French Poly Implant Prothèse (PIP) company, joint actions by the European Commission and competent authorities of the member states were initiated in February 2012 to restore confidence in the regulatory system. These actions are aimed predominantly at strengthening control over notified bodies. Medical device notified bodies are independent organisations appointed by member states to undertake conformity assessment of products. The Joint Plan aims to reach a uniformly high standard for both the designation by the member states of the notified bodies and the functioning of these bodies. This followed indications of significant divergences as regards the designation/monitoring of the notified bodies and the quality/depth of the conformity assessment performed by them. Concerns relating to conformity assessment centred on the assessment of the manufacturers' clinical evaluation and the use of notified bodies' existing powers such as unannounced factory audits or product checks. Notified bodies themselves acknowledged these differences.

In June 2014, the European Commission Staff Working Document communicated the achievements of the Joint Plan in a document entitled "Implementation of the Joint Plan for Immediate Actions under the existing Medical Devices legislation" As reported in this document[1], the European Commission and EU member states carried out joint audits on notified bodies between February 2013 and May 2014. To be able to keep their designation, the notified bodies were obliged to undertake corrective actions with regard to shortcomings identified. The most common shortcomings identified were:

- lack of evidence of staff qualifications;
- insufficient thoroughness of the review of manufacturers clinical evaluations; and
- inadequate sampling of technical files for class IIa and IIb devices.

The implementation of the Joint Plan means that the survival of individual notified bodies will depend on their commitment to enforcing high standards on manufacturers of medical devices. Notified bodies will be required to make unannounced audits upon manufacturers at least once every three years and to inspect product technical files including CERs and to issue non-conformities whenever shortcomings are identified.

In October 2014 Clinica Medtech Intelligence published an interview with John Brennan, director of regulations and industrial policy at Eucomed, the EU medtech industry association ("Medtech companies must wake up to changed EU regulatory environment"). According to Mr Brennan, the European Commission's competent authority joint actions initiative is having a "very strong impact" in terms of how thoroughly notified bodies are checking the industry. In particular, notified bodies have been encouraged to pay a great deal of attention to technical files. Mr Brennan advised "companies that do not have a large portfolio of products and have not applied for a file renewal in the last two years need to make sure they are aware of and understand the thoroughness with which their files will be checked, not least because, with unannounced audits actually beginning to happen they may not be aware of when their next audit is".

4. Consequence: 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

[1] http://ec.europa.eu/health/medical-devices/files/swd_pip_14_en.pdf

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 trials will be required; if PMCF studies are not planned, a robust justification will need to be provided. In 2012, the European Commission revised its guidelines on PMCF studies. The MEDDEV 2.12/2 guidance emphasizes the increased need for PMCF studies to be considered in drafting the risk-based PMS plans; this follows the revised focus on clinical data introduced by 2007/47/EC revision of the MDD and AIMD Directives. Notified bodies will also be looking for evidence that all classes of devices are being treated appropriately.

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?

5. Solution: Work with an Experienced, Trusted Partner such as CROMSOURCE

CROMSOURCE is the leading independent provider of clinical life science services to the medical device and pharmaceutical industries. CROMSOURCE has twenty years of international experience in supporting medical device companies of all sizes to reach their clinical development goals and meet their regulatory obligations.

We can help you decide if a clinical trial 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 favourable and unfavourable data need to be included in the dataset that is assessed.

Jointly determine the most appropriate pathway to CER creation

The most efficient way to initiate CER preparation work is to have a meeting with all stakeholders (the clinical evaluation team). This might include regulatory and clinical colleagues as well as engineers and the author charged with the preparation of the CER. It is important that everyone understands the development and regulatory history of the device or family of devices, as well as how the device is to be used in clinical practice.

The team should obtain information on the following factors that must be considered when choosing the type of data to be used in the clinical evaluation:

- the design, intended use and risks of the device;
- the developmental context of the technology on which the device is based (new vs. established technology);
- for established technology, the proposed clinical application of that technology.

The manufacturer's risk management documents are expected to identify the risks associated with the device and how 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).

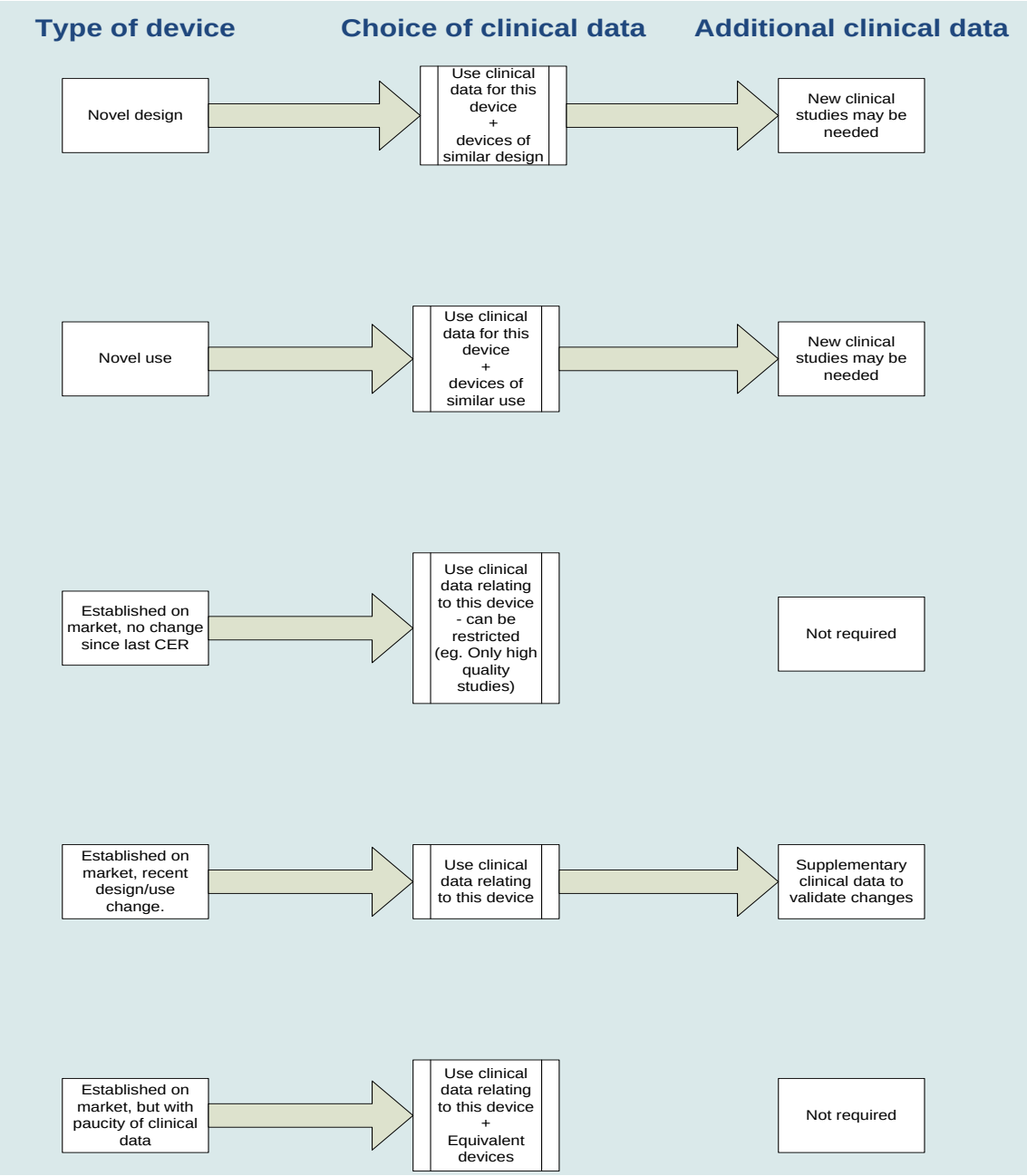
Clinical evaluation of medical devices that are based on existing, well established technologies and intended for an established use of the technology is most likely to rely on compliance with recognised standards and/or literature review and/or clinical experience of equivalent devices.

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 flow-chart below summarises the main pathways to CER creation:



Outsource aspects of the clinical evaluation process and CER preparation

Legislative changes in the EU will impact medical device companies as well as companies with previously unregulated products; all will need to prepare CERs to high standards. Time-consuming new requirements also mean that more companies will need to consider outsourcing all or part of CER preparation. Due to the increasing requirement for clinical studies of medical devices, more companies will need to consider outsourcing them as well.

CROMSOURCE 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 (section 5);
- literature searching (section 6.1; 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 (section 6.2);
- clinical investigation (section 6.3 and EN ISO 14155);
- appraisal of clinical data (section 7);
- analysis of the clinical data (section 8);
- concluding, reporting (section 9); and
- update of clinical evaluation, including PMCF (MEDDEV 2.12/2).

6. About the Author

Beata Wilkinson, Regulatory and Scientific Writing Manager, CROMSOURCE

After gaining her PhD in biomedical science from the University of Glasgow (UK), Beata has worked as a university lecturer, biomedical business consultant and medical writer. She has extensive experience of producing clinical and market reports for customers in the pharmaceutical and medical device industries. Beata researched and wrote over 50 off-the-shelf biomedical technology and market reports for sale by global publishers of healthcare business information, including Informa plc. Prior to joining CROMSOURCE, Beata was at the Regulatory Affairs Department at ConvaTec where her responsibilities included preparation of the company's clinical evaluation reports. At CROMSOURCE, Beata is supporting the expansion of CER and other professional writing services.

7. About CROMSOURCE

CROMSOURCE is a high quality ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

Operating through offices across all regions of Europe and North America CROMSOURCE delivers a comprehensive breadth of services. We seamlessly move biopharmaceutical products from first in human conducted in our exceptional early phase unit, through all subsequent phases of pre- and post-approval research internationally. Our Medical Device experts oversee projects through regulatory strategy and submission, to pilot and pivotal clinical investigations in Europe and North America. Our Staffing Solutions Team ensures that high quality professionals are available to support your work whenever you need more resources.

It's a simple concept, really. Quality data. On time. On Budget. Guaranteed.

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