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Clinical Evaluation Requirements - From MEDDEV to MDR

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Background and Introduction

The new European Union Medical Device Regulation (MDR 2017/745), was approved by the European Parliament on April 5, 2017 and published in the Official Journal of the European Union on 5th May 2017. It replaces the Medical Device Directive (MDD 93/42/EEC) in May 2021, after a 1 year delay due to the coronavirus crisis. After this date it will no longer be possible to put a new medical device on the market with a CE mark issued against the MDD. Devices placed on the market under the MDD before the MDR 'Date of Application' may continue to be made available on the market for 4 years after that date provided they have not expired (MDR Article 94.3a)[1].

The new Regulation consolidates two existing legal provisions and replaces both the MDD and the Active Implantable Medical Device Directive (AIMMD 90/385/EEC). It is a fundamental revision of the Directives and is intended to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices, which ensures a high level of safety whilst supporting innovation. It was triggered by the breast implants scandal (as well as other high risk events) where these implants had been approved but had very little safety and clinical evidence associated with them.

With this brings about a change in the requirements for clinical evaluation. The MEDDEV revision 4 was already significantly strengthened from the previous version that came into effect in December 2009[2] and is more detailed further clarifying requirements for robust evaluation and ensuring the validity of data. Revision 4 process involves requirement for a Clinical Evaluation Plan (CEP) and Clinical Evaluation Report (CER). Revision 4 released in July 2016 was already starting to align with the MDR.[3, 4] Some Notified Bodies were requesting Clinical Evaluation documents to be compliant to MEDDEV 2.7.1 rev 4 as early as January 2017, although the MEDDEV is a guidance document that is not legally binding.

Other Notified Bodies extended the deadline for implementation of the MEDDEV to match that of the MDR. Notified Bodies will still expect to see a plan on how the new regulations will be implemented.

Full compliance to both the MEDDEV and MDR is expected by May 26, 2024 where manufacturers still need to pay attention to ensuring that they have sufficient clinical evidence for their devices that they intend to transition to the MDR.

This document outlines a comparison of the differences between MEDDEV 2.7/1 revision 4 "A guide for Manufacturers and Notified Bodies Under Directives 93/42/EEC and 90/385/EEC" and MDR 2017/745 regarding clinical evaluation and what these mean in terms of potential deficiencies for approved products that must transition and any associated proposed actions to take as a legal manufacturer.

Evaluation of MDR v MEDDEV 2.7/1 (Rev 4)

Clinical evaluation requirement of the MDR is no longer just a report as it can be under MEDDEV. The clinical evaluation report is the final output of the "ongoing clinical evaluation process" which is a compilation of "clinical evidence" to claim conformity to the applicable General Safety and Performance Requirements (GSPR).[1, 6]

There are several items that have to be covered within the clinical evaluation process under MDR, inextricably linked to post-market surveillance (also expanded under MDR) and risk management[1, 6]:

- Clinical Development Plan (CDP)
- Clinical Evaluation Plan (CEP)
- Clinical Evaluation Report (CER)
- Clinical Investigations
- Summary of safety and clinical performance (SSCP)
- Common Specifications
- Post-market surveillance (PMS) / Product Safety Update Report activities (PSUR)
- Post-market Clinical Follow-Up (PMCF). These are summarised in more detail in Table 1.

Clinical Evaluation Plan and Clinical Evaluation Report are known elements of the clinical evaluation process. As are PMS and PMCF activities, but the requirements on these activities are no longer optional. PMS is now used for Class I products only and existing PMS under MEDDEV may be sufficient. The Product Safety Update Report is now required for Class IIa and higher-class products meaning that all devices of these classes must be reviewed, and new QMS procedures implemented in order to conduct PSUR reporting. Upon review it is possible that the risk-benefits analysis and the PMCF may be deficient and more work must be conducted there to evidence that the device is still safe to be placed on the market[4, 5, 6.]

The CEP should be a detailed document as to why the device was designed and what it is designed to do. The MEDDEV provides a description of how to define the scope of the clinical evaluation based on the Essential Requirements (now GSPR under MDR) that need to be addressed from a clinical perspective[4.] The CEP should assess the data already available to support the intended use, performance, safety, benefits and claims of the device. If this has been conducted appropriately for existing devices this is a great starting point, but now that the clinical evaluation lifecycle has additional requirements, these must be added to an updated plan. After assessing data available, research questions are created to specifically address gaps in data or to support existing data. Data can be taken from clinical literature, device registries, healthcare databases, or disease specific databases to answer the defined research questions. Clinical data from literature is a required first step[4,8.]

It is expected that many of the existing CERs will lack is an analysis of the data presented, and therefore not giving statistically relevant context and conclusions. The process of clinical evaluation starts with the origin of a research question based on the data at hand[4.] Once the evaluation(s) are performed it must be determined finally, if there are sufficient clinical evidence to support conformity to GSPR 1 and 8 (at a minimum depending on the device and its purpose)[1]. The data requirements for a new device are different to those for an already CE marked device; where after CE marking, Post Market Surveillance (PMS) data and Post Market Clinical Follow-up data must be included in the CER[4.]

The Clinical Development Plan is a new requirement for manufacturers in order to document plan for all pre-market and post-market clinical and non-clinical investigations. Again this will serve to challenge manufacturers if clinical investigations were non-existent or lacking. A gap analysis of available data and the robustness of that data is required v the new requirements[4]. Clinical investigations (pre-market) are also expected to be conducted, particularly for implantable and Class III devices. Article 61 does give some flexibility to waive this requirement if the device has been designed by modifications of a device already marketed by the same manufacturer, or, the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device, and the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.[1, 6, 8] So, if the original clinical evaluation was insufficient, this may not be able to be waivered.

Summary of safety and clinical performance (SSCP) is required for implantable devices and for class III devices, which is compiled entirely from Technical File/Design Dossier through design verification/validation reports, the risk management report/file, CER, PMS and PMCF plans and reports. The specifications for SSCP content is given in Article 32 of MDR[8].

Figure 1 – The continuous cycle of Clinical Evaluation under MDR[7]

The MEDDEVs are now expected to be replaced by guidance documents issued by Medical Device Coordination Group (MDCG), comprised of representatives of Member States and chaired by the EU Commission. These guidance documents are required to be followed ongoing basis to achieve precise compliance. The documents were issued prior to the postponement of the date of application of the MDR and as with all the MDCG guidance; it cannot be regarded as reflecting the official position of the European Commission, or as being legally binding[4, 9,11]. The four new documents add to the guidance on the summary of safety and clinical performance for manufacturers and notified bodies and highlight differences between the MDR and the MEDDEV 2.7/1(4):

- Clinical Evaluation – Equivalence - MDCG 2020-5
- Sufficient Clinical Evidence for Legacy Devices - MDCG 2020-6
- Post-market Clinical Follow-up (PMCF) Plan Template MDCG 2020-7
- PMCF Evaluation Report Template - MDCG 2020-8.

According to MDCG 2020-6, several sections of the MEDDEV 2.7/1(4) are still relevant to MDR as the information contained is useful guidance on how to perform activities associated with clinical evaluation:

- 6.4. Who should perform the clinical evaluation?
- 8. Identification of pertinent data (Stage 1)
- 9. Appraisal of pertinent data (Stage 2)
- 10. Analysis of the clinical data (Stage 3). This chapter includes references to the MDD, MDR requirements should be used instead
- A3. Device description - typical contents
- A4. Sources of literature
- A5. Literature search and literature review protocol, key elements
- A6. Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety
- A7.2. Conformity assessment with requirement on acceptable benefit/risk profile
- A7.3. Conformity assessment with requirement on performance
- A7.4. Conformity assessment with requirements on acceptability of undesirable side-effects
- A10. Proposed checklist for the release of the clinical evaluation report[1].

Table 1 – Description of Clinical Evaluation Steps under MDR[1, 7, 10, 11]

	Stage	Description
1	CDP – Clinical Development plan	At the start of the development process, the clinical development plan defines how sufficient clinical data for later clinical evaluation is collected. This may include exploratory investigations, feasibility and pilot studies to confirmatory investigations; a proposal for possible PMCF activities can also be initiated at this stage.
2	CEP – Clinical Evaluation Plan	Prior to conducting the clinical evaluation, the CEP defines the scope of the clinical evidence. Available pre- and clinical data, remaining residual risks, newly identified risks (from PMS/PMCF/complaints) as well as all other claims (also from marketing) are considered. Clinically relevant questions as well as open questions from risk management are generated. The search strategy is defined (sources, search terms, selection and evaluation criteria) that is to be applied for the clinical evaluation.
3	CER – Clinical Evaluation Report	The CER represents the results of the clinical evaluation. Clinical data is collected, selected, evaluated, and analysed. It is checked whether the device meets the requirements for safety, performance, undesired side effects and the benefit-risk ratio defined by the MDR. Furthermore, currently available alternative treatment options also have to be taken into consideration. Finally, the need for further clinical data is discussed (PMCF activities) and passed on to PMS.
4	PMS Plan / PCMF Plan	In the PMS plan the manufacturer defines how the device will be monitored after the market launch and what data is to be collected. Product-specific planning of activities needs to take into account the findings from the clinical evaluation and the device's risk potential. The methodologies for analysing the data and the criteria for the analysis are defined and should be state of the art. The manufacturer is responsible for collecting the data on the market proactively. PMCF is part of PMS and intended to close the gaps that could not be answered in the scope of the clinical evaluation (e.g. long-term behaviour, monitoring of side effects and contra indications).
5	SSCP – Summary of Safety and Clinical Performance	A SSCP report must be prepared only by manufacturers of class III and implantable devices. The report is referenced in the user manual or the label and is made publicly available via EUDAMED. The report must be understood by laypersons. The purpose of the report is to introduce the device in the context of its application and explain alternative therapeutic or diagnostic options as well as residual risks and undesirable effects. Prior to publication, the report is validated by the notified body.
6	Vigilance Report, PCMF, Trending	The proactive PMS phase is where PMCF activities are conducted including evaluation of evaluate market data. The strategies originally defined in the PMS plan must identify reportable events such as vigilance cases and can be reported in a timely manner. Vigilance describes the reporting of serious incidents and field safety corrective actions to the authority. For this purpose, every manufacturer needs an appropriate system in which it ensures that the evaluation and analysis of such events are enabled and that the deadlines for reporting them may be adhered to. The results of PMCF activities are documented and analysed in one or several PMCF reports. The conclusions of the PMCF report must make considerations for the clinical evaluation and risk management. Statistically significant increases in the frequency or severity of non-serious incidents or expected undesirable side effects must be reported to the responsible authority if they affect the benefit-risk ratio.
7	PMS Report / PSUR	The purpose of the PMS report is to gain insights into the behaviour of the device on the market across the entire product life cycle. A PMS Report is created for class I devices and includes a summary of the results from market data collected over the observation period, the outcomes are passed on to clinical evaluation. CAPA are defined and explained. These may then be used for further product development as well as for ensuring the device's safety and compliance with the requirements of the regulation at all time during the lifecycle. A PSUR is prepared for class IIa, IIb, and III products and it includes a summary of the results and CAPA as the PMS report does. In addition, the PSUR also includes the conclusions from the benefit-risk assessment and any critical results from PMCF.

Regulatory Strategy for Compliance (for a Manufacturer)

Table 2 below provides a summary of the key areas of focus to ensure regulatory compliance for example, for a legal manufacturer.

Topic or Area	Comparison, change or new requirement	Actions
Clinical evidence and evaluation	MDR is more specific about the need for clinical evidence and clinical evaluation, proportionate with the risk associated with a given device (Annex XIV, Part A). Reliance on the scientific literature to demonstrate equivalence will be more tightly regulated, clinical evaluations will be more closely aligned with clinical trials associated with medicinal products. Manufacturers are required to document a clinical evaluation plan to meet the requirements of MDR Annex XIV Section 1a. The manufacturer must ensure that inputs for the clinical evaluation plan are in line with the device's label, instructions for use, promotional or sales materials or statements and with the devices' updated risk management documents. The manufacturer shall identify all available sources of clinical data from both the pre-market and post-market phases. This is all of the clinical data which is generated and held by the manufacturer as well as clinical data for equivalent or similar devices.	The manufacturer should conduct an analysis with respect to the GSPR of the MDR, to determine if additional data to support the clinical evidence are required to meet additional MDR requirements, through a gap analysis with respect to new MDR requirements or by creation of an entirely new analysis for the MDR. The level of clinical evidence required for the device under evaluation needs to be determined by the manufacturer and verified by the notified body.
Post-Market Surveillance	Under the new Regulation manufacturers will be required to collect post-market clinical data as part of their on-going assessment of potential safety risks. Post Market Clinical Follow up (PMCF) is a continuous process with the objective of constantly updating the clinical evaluation (MDR Annex XIV, Part B). Post-market sources of clinical data refer to data collected following the initial CE marking under the Directives (or prior to introduction of a new indication or design variant). This may include: • PMS clinical data, complaint and incident reports; • PMCF studies, including post-market clinical investigations; • Independent clinical studies conducted using the device; • Device registries; • Data retrieved from the literature. For well-established technologies the clinical evaluation can be based on data coming from similar devices, under the conditions detailed in paragraph 6.5 (e). With respect to legacy devices, when clinical data from equivalent devices is used, equivalence must be demonstrated according to the requirements of the MDR.	Manufacturers must therefore at minimum develop a strategy and methodology to systematically collect, summarise and assess post market surveillance data to demonstrate continuing safety and performance, and to what extent complaints with regards to safety and performance have been observed with the legacy devices.
Common Specifications (CS)	The Medical Devices Regulation has described use of CS in Article 9. These are defined in Article 2 as a set of technical and/or clinical requirements other than standards that provide a means of complying with the legal obligations applicable to a device, process or system. Article 9 states that CS will be adopted where no harmonised standards exist–OR–where relevant harmonised standards are not sufficient–OR–where there is a need to address public health concerns. Devices in conformity with CS shall be presumed to be in conformity with the relevant requirements of the MDR. The MDR states that manufacturers shall comply with applicable CS unless they can duly justify that their solutions ensure at least an equivalent level of safety and performance. Finally, manufacturers of the devices without a medical purpose as listed in Annex XVI are required to comply with any relevant CS for those products.	Unfortunately, despite the delay in implementation of MDR, CS are not yet available. Manufacturers should monitor the Commission website for developments. CS will likely be published in the Official Journal of the European Union, as is currently done for the in vitro diagnostic 'Common Technical Specifications.'

Topic or Area	Comparison, change or new requirement	Actions
GSPR	Essential Requirements (ER) are the equivalent in the MDD and AIMDD of the GSPR in Annex I of the MDR. There are 13 ER in the MDD and 16 in the AIMDD, there are 23 GSPR in the MDR. The text and requirements are expanded, but the scope and topics are consistent overall with the previous directives with a few exceptions – notably clinical evaluation and medicinal consultation have moved from the requirements list into the articles, while other topics are new to the requirements list, including devices without a medical purpose and requirements for devices used by lay persons. A number of areas now have increased emphasis and more explicit requirements, which in many cases align with harmonised standards and industry guidance. The areas in Annex I considered to have highest impact to manufacturers are: medicinal substances (and substances absorbed or locally dispersed); devices incorporating materials of biological origin; substances of concern; labelling requirements; emphasis on cybersecurity. MDR Annex II Section 4 (Technical Documentation) requires manufacturers to demonstrate conformity with the applicable general safety and performance requirements of Annex I, including an explanation for those which are not applicable, methods used to demonstrate conformity with all applicable requirements, and the precise identity of the documents offering evidence of conformity. This is more prescriptive and detailed than the Directives which more generally require a description of the solutions adopted to fulfil the ERs. Annex II also requires the Technical Documentation to be readily searchable and unambiguous.	Manufacturers must demonstrate compliance with the applicable GSPR and clearly denote which are not applicable; a document such as a checklist or table referencing other documents and data may be a practical way to achieve this. A full gap analysis of the safety and performance requirements in the new MDR against the ER in the MDD and AIMDD should identify any new requirements and areas of increased emphasis. Some of the new requirements will require novel work required of the manufacturer, others will align with current practice according to harmonized standards and best practices. Many 'state of the art' requirements from harmonized standards have been incorporated directly into the Regulations' GSPR. These will have a smaller impact on manufacturer's activities, as many of these requirements are likely to be addressed already. A suggested approach is to determine which of the new 'safety and performance requirements' will be considered as applicable, and to ensure an appropriate rationale for requirements deemed not applicable. The relevant requirements will then have to be considered with respect to existing documentation, to identify gaps which may need to be addressed. For some of the most novel requirements, manufacturers will have to consider how clearly demonstrate compliance through testing, risk management, and other means. Ensure that all required information is included for expanded IFU.
A Clinical Evaluation Plan for legacy devices should include the following actions[13]: • Identification of the GSPR that require support from relevant clinical data. • A specification of the intended purpose of the device. • A clear specification of intended target groups with clear indications and contraindications. • A detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters. • A strategy to identify, analyse and assess alternative treatments. • A specification of methods to be used for examination of qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects • An indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device. • An indication how benefit-risk issues relating to specific components such as use of pharmaceutical, non- viable animal or human tissues, are to be addressed. • A strategy and methodology to identify, analyse and appraise all relevant available clinical data in light of the changed definition for clinical data. • Evidence for equivalence, if clinical data from an equivalent device is included in the clinical evaluation. • A definition of the required level of clinical evidence, which shall be appropriate in view of the characteristics of the device and its intended purpose.58 59 60 • A strategy and methodology to systematically collect, summarise and assess post market surveillance data to demonstrate continuing safety and performance, and to what extent complaints with regards to safety and performance have been observed with the legacy devices.		

Table 2 – Action Plan between MDR and MEDDEV 2.7/1(4)[1,6,8,12,13]

Summary and Conclusions

It's clear that the area of clinical evaluation, never intended to be lacking but with expanded more prescriptive requirements, now highlights what could be a mountain of work to for many manufacturers as they transition to MDR. Specific focus and attention to detail is needed to ascertain the requirements most relevant to a manufacturer's own devices as the clinical evaluation and evidence requirements are linked to other facets of the MDR in varying levels of depth – i.e. risk management, GSPR, conformity assessment etc. The transition to meet clinical requirements cannot be planned in isolation and a holistic review of requirements must be conducted with multi-functional groups across a company in Regulatory, Quality, Engineering, R&D, Commercial, Sales & Marketing, Finance, HR and Project Management, as well as Production representatives.

Manufacturers should read and understand the MDR to prepare for the changes ahead, and check with their notified bodies for consistency or agreement in interpretation. A commercial review of a product's value and forecast is essential as the cost of implementing the new requirements could be more than the product value and be commercially unviable, unless it is a route to other markets or platform for selling other products. A manufacturer must also consider any devices not previously classified as in many cases, these are unlikely to have any technical documentation and this must be prepared retrospectively in its entirety.

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