

JOURNAL of MEDICAL DEVICE REGULATION

FEBRUARY 2021

SPECIAL REPRINT

Journal of Medical Device Regulation, 2021, 18(1), 33-47

**A Notified Body's
perspective on the clinical
evaluation requirements
under Regulation (EU)
2017/745 on medical
devices**



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Published by Global Regulatory Press
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Tel: +44 (0)1305 264797
Email: editor@globalregulatorypress.com
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A Notified Body's perspective on the clinical evaluation requirements under Regulation (EU) 2017/745 on medical devices

Introduction

Regulation (EU) 2017/745 on medical devices (the MDR)¹ will apply from 26 May 2021. On that date, the MDR will repeal Directive 90/385/EEC on active implantable medical devices and Directive 93/42/EEC on medical devices. The scope of, and emphasis placed on, clinical evaluation is more comprehensive under the MDR than it was under the Directives. This article looks at the main requirements for clinical evaluation under the MDR and offers advice, from a Notified Body's perspective, on how to meet those requirements.

Clinical Evaluation Report (CER)

There are seven key points to consider when preparing a Clinical Evaluation Report (CER) under the MDR. These are indications, literature searches, clinical investigations, lifetime data, General Safety and Performance Requirements (GSPRs) versus the Essential Requirements (ERs), state-of-the-art, and benefit/risk conclusions.

Indications

According to [Medical Device Coordination Group] MDCG 2020-6, *Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC – A guide for manufacturers and notified bodies*², 'indication' or 'indication for use' refers to 'the clinical condition that is to be diagnosed, prevented, monitored, treated, alleviated, compensated for, replaced, modified or controlled by the medical device. It should be distinguished from 'intended purpose/intended use', which describes the effect of a device. All devices have an intended purpose/intended use, but not all devices have an indication (e.g. medical devices with an intended purpose of disinfection or sterilisation of devices)'. The terms are undefined in the MDR.

Although broad indications were generally accepted under the Directives, they are not accepted under the MDR. So, it is essential for a manufacturer to specify indications clearly in relation to the stage/severity of a specific clinical condition and/or intended patient population. The specified indications must be reflected by the available clinical data, so if any gaps in the clinical data exist then new data collection should be considered. Narrowing the indications appropriately will make the route to conformity easier and save time and effort in the long term.

Literature searches

A clinical literature review should address all device sizes, variants, models and accessories. It should also address the same clinical condition specified in the indications.

With respect to the selection criteria of the literature review, it is important to consider if the literature applies to the device under evaluation or to a device demonstrated to be equivalent. Also, does the literature relate to the state-of-the-art or an alternative available treatment option? According to MDCG 2020-13, *Clinical evaluation assessment report template*³, the ‘clinical evaluation should clearly describe the selection criteria with respect to the regulatory purpose to which it will apply. The CER should clearly differentiate between the two types of data referenced above. If the data does not relate to either of the above, provide a rationale with respect to its inclusion’.

Information on literature search methods is available in MEDDEV 2.7/1 revision 4⁴, section A5. Although the MEDDEV documents apply to the Directives not the Regulations, MDCG 2020-13 specifically refers the reader to MEDDEV 2.7/1 revision 4, section A5. Searches for the device in question, equivalent devices and other devices (e.g. to support a description of the state-of-the-art) should be described separately. A detailed analysis of search results is required, including a quantification of the benefit/risk where possible.

Clinical investigations

It is important to consider compliance of the Clinical Investigation Plan (CIP) to Annex A of ISO 14155⁵ and Annex XV of the MDR. It is also important to document clearly, with appropriate rationales and justifications, the following information:

- study design;
- devices identified, including accessories;
- patient population, which must be relevant to the European Union (EU) population;
- patient numbers, including a statistical analysis to support those numbers;
- clinical objectives and endpoints, which should align with similar devices and similar clinical investigations;
- length of follow-up and intervals to ensure appropriate lifetime data are collected;
- study locations, with justification as to why data obtained in these locations are relevant to the EU;
- overall conclusions.

MDCG 2020-13³ encourages Notified Bodies to review all this information. MDCG 2019-9, *Summary of safety and clinical performance – A guide for manufacturers and notified bodies*⁶, also provides a list of detailed information in relation to reporting clinical investigations.

The MDCG is working on a CIP Template and Clinical Investigation Evaluation Template, which are due in spring 2021. A Summary Report of Clinical Investigation Template is due in summer 2021. These templates should provide manufacturers with a clear and concise way of reporting their investigations, which can then feed into their CERs.

Lifetime data

Annex XIV, Part B of the MDR states that a Post-Market Clinical Follow-up (PMCF) Plan ‘shall specify the methods and procedures for proactively collecting and evaluating clinical data with the aim of ... confirming the safety and performance of the device throughout its expected lifetime’. Therefore, it is important that a manufacturer defines the lifetime of the device in the CER. This claimed lifetime must be supported by clinical data so if there is a gap in the data it is important to identify how data will be collected (e.g. through surveys or registry data). A quantification of risks and benefits over the claimed lifetime is also required.

GSPRs versus the ERs

The CER must align with the GSPRs and the new requirements of the MDR. A gap analysis against the ERs or confirmatory statements are not sufficient. Although it is not necessary to have separate CERs for the MDR and Directive 93/42/EEC, the CER must adequately address both pieces of legislation without any shortcuts.

Benefit/risk conclusions

The MDR defines ‘clinical benefit’ as ‘the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health’.

When writing the benefit/risk conclusion for a CER, it is important to provide a description of the documented clinical benefits for patients with relevant and specified clinical outcome measures, and the success rate for achieving those outcome measures. If the device has several indications then the conclusion should include a benefit/risk assessment for each of the various indications, including the acceptability of the benefit/risk ratio and a summary of the evaluation of undesirable side-effects. The conclusion should also explain the device’s place on the market; for example, is it the state-of-the-art?

The conclusion must be scientific and presented in a clear and logical manner. It must not contain any marketing or unsubstantiated wording. As appropriate, the conclusion should also refer to current medical practice (i.e. what is generally accepted). For most devices, Notified Bodies would expect to see at least some review of the benefit/risk conclusions by appropriately qualified clinical personnel.

State-of-the-art

MDCG 2020-6² uses the definition of state-of-the-art provided by the International Medical Device Regulators Forum: ‘Developed stage of *current technical capability and/or accepted clinical practice* in regard to products, processes and patient management, based on the relevant consolidated findings of science, technology and experience’ [emphasis added]. MDCG 2020-6 goes on to explain that ‘state-of-the-art embodies what is currently and generally accepted as *good practice in technology and medicine*. The state-of-the-art does not necessarily imply the most technologically advanced solution. The state-of-the-art described here is sometimes referred to as the generally acknowledged state-of-the-art’ [emphasis added].

Demonstrating a device is state-of-the-art

As discussed previously, the MDR requires specific (narrow) rather than broad indications. One potential benefit of narrowing a device’s indications relates to demonstrating state-of-the-art. When demonstrating state-of-the-art, a manufacturer only needs to be reflecting the treatment for that stage of disease or what is indicated for that patient population. State-of-the-art should consider all alternative options, including pharmacological options, competitor devices (both similar devices and alternative technologies), and non-medical options. It should also consider what is acceptable in good clinical practice.

A common question that arises is, how can data be obtained to demonstrate state-of-the-art?

There are several avenues that can be used, such as:

- European medical societies/national medical organisations (e.g. European Society of Cardiology);
- literature searches (most current/recent publications relevant to indications);
- international guidance (relevant to the EU population) or national guidance documents (e.g. guidance from the UK National Institute for Clinical Excellence);
- Real World Evidence (e.g. registry data);
- non-inferior model (statistical) analysis of Post-Market Surveillance (PMS) data;
- physician surveys/usage data.

Manufacturers of Class III and implantable devices must also be aware of a clause in MDCG 2019-9, *Summary of safety and clinical performance – A guide for manufacturers and notified bodies*⁶, concerning state-of-the-art: ‘If reference is made to the “state of the art”, that statement should be supported for example by referring to relevant *recognised guidance documents* generated by specialty medical societies or educational bodies’ [emphasis added]. In other words, if a manufacturer claims state-of-the-art within the Summary of Safety and Clinical Performance (SSCP), the manufacturer needs to provide evidence of acceptance by relevant guidance documents from medical societies/educational bodies.

An example

The safety and performance profile of a manufacturer’s cardiac pacemaker aligns with its competitors and there are no safety or performance concerns. However, the pacemaker is not magnetic resonance imaging (MRI) conditional whereas all other pacemakers manufactured currently are MRI conditional. [The term ‘MRI conditional’ is applied to devices that pose no known hazards in a specific MRI environment under specific device and MRI scanner conditions.] In fact, it is doubtful whether any medical practitioner would implant a non-conditional MRI device. So, in this example, even though the safety and performance profile of the manufacturer’s cardiac pacemaker aligns with its competitors, the manufacturer would not be able to claim state-of-the-art because the device does not reflect what is being used in true clinical practice.

However, if the manufacturer had presented a better safety and performance profile, then it is possible that state-of-the-art could be demonstrated if there is a subset of the population that could benefit from better safety even without the MRI properties. This would have to be assessed on a case-by-case basis.

Additional clinical documentation under the MDR

Table 1 summarises a manufacturer’s clinical documentation required under the MDR. New documents are in italics.

Table 1. Clinical documentation that must be prepared by the manufacturer according to the MDR

Documentation	Classification	Article /Annex	Supporting guidance
<i>Clinical Development Plan</i>	All classifications	Annex XIV, Part A (1) Annex XIV, Part B	–
<i>Clinical Development Strategy Response</i> (for those devices that	Class III and Class IIb devices designed to	Article 61 (2)	–

Documentation	Classification	Article /Annex	Supporting guidance
have undergone the process described in Article 61 (2))	administer or remove a medical substance		
Clinical Evaluation Plan	All classifications	Article 61 (1)	MDCG 2020-6
Clinical Evaluation Report (CER)	All classifications	Article 61 (1) Annex IX, Chapter II Annex XIV, Part A	MEDDEV 2.7/1 Rev 4 MDCG 2020-5 (equivalence) MDCG 2020-6 (legacy devices)
Post-Market Clinical Follow-up (PMCF) Plan	All classifications	Annex XIV, Part B	MDCG 2020-7
Post-Market Surveillance (PMS) Plan	All classifications	Article 84 Annex III (1.1)	–
PMCF Evaluation Report	All classifications	Article 61 (11) (12) Annex XIV, Part B	MDCG 2020-8
<i>Summary of Safety & Clinical Performance (SSCP)</i>	Class III and implantable devices	Article 32	MDCG 2019-9
<i>Periodic Safety Update Report (PSUR)</i>	Class IIa, IIb and III devices	Article 86 Annex III (1.2)	Expected in spring 2021

Class I devices are still required to produce a PMS Report.

Additionally, a Clinical Evaluation Assessment Report (CEAR) is generated by the Notified Body based on the technical documentation provided by the manufacturer, and a copy is always sent to the manufacturer.

Figure 1 (*opposite*) illustrates where these new clinical documents prepared by a manufacturer fit within the MDR clinical process.



Figure 1. Clinical process under the MDR

Clinical Development Plan

The Clinical Development Plan defines how a manufacturer will collect sufficient clinical data for later clinical evaluation. It is the first step of the overall Clinical Evaluation Plan. This document should map out the exploratory investigations, first-in-man studies, feasibility studies and pilot studies, etc. Where appropriate, it could also present an outlook for possible PMCF activities.

It is also important that at each of these stages of investigation and study, the Clinical Development Plan indicates potential acceptance criteria. Manufacturers should also consider what happens when acceptance criteria are not met. For example, what decisions or actions are required to fulfil those unanswered questions?

The Clinical Development Plan may also include information where the manufacturer intends to perform clinical investigations ‘off label’ to expand the indications of the medical device in the future. ‘Off label’ studies are not PMCF studies and are subject to the same scrutiny by, and processes of, the Competent Authority as non-CE marked investigations.

Summary of Safety & Clinical Performance (SSCP)

As mentioned previously, the SSCP is only required for Class III and implantable medical devices. The SSCP is intended for healthcare professionals, although a patient version may be required. If the device is Class III and is intended to be used by the patient, or the device is to be implanted and requires an implant card as part of the MDR, then an SSCP must be supplied. In all other cases, a justification would be expected as to why an SSCP is considered unnecessary.

An English language version of the SSCP is always needed but copies should also be produced in the languages of the Member States where the device is envisaged to be used.

The SSCP is intended to be an executive summary of the CER, and it should be scientific in its approach and avoid marketing/commercial material. It should also be updated with the most current information. So, for example, if a Periodic Safety Update Report (PSUR) identifies new information such as a new risk then it is important that the SSCP is updated to reflect this. The SSCP will be validated by the Notified Body as part of the technical documentation assessment.

The instructions for use of the device should contain a statement or link to the location of the SSCP in EUDAMED with unique identifiable metadata such as the Basic UDI-DI [Unique Device Identification-Device Identifier].

MDCG 2019-9, *Summary of safety and clinical performance – A guide for manufacturers and notified bodies*⁶, provides helpful advice and a template for preparing an SSCP.

Periodic Safety Update Report (PSUR)

The PSUR is intended for all Class IIa, Class IIb, and Class III devices, including legacy devices. It must be updated annually for Class IIb and Class III devices and biennially for Class IIa devices. The PSUR must contain all the information from the output of activities listed in Annex III of the MDR. Also, Article 86 mentions the need for an estimation of the size and volume of sales, as well as the characteristics of, and usage by, the population.

The activities that feed into the PSUR include serious incidents, field safety actions, trend reporting, feedback/complaints from users, importers and distributors, and data/information from PMCF activities.

When the PSUR is produced, if new data are available, then the PSUR may trigger an update to the CER and ultimately the SSCP. The PSUR is essentially confirming the benefit/risk of the device from real world data.

MDCG guidance on the PSUR is in development and is expected to be published in spring 2021. Manufacturers with an MDD certificate will be required to produce a PSUR after the date of application of the MDR (26 May 2021). The MDCG guidance will specify when those PSURs will be due, and it is expected that the dates will be based on the initial validation date of the MDD certificate issued by a Notified Body. Manufacturers who are required to submit PSURs before the guidance is issued should take into consideration the requirements stated in Article 86. Manufacturers should also report the output of PMS activities as described in Annex III to the MDR in the PSUR for the Notified Body evaluation and, where appropriate, Competent Authority scrutiny.

Report timings

The PMCF Evaluation Report and the PSUR must be updated at least annually. If the PSUR contains information rendering any information in the SSCP incorrect or incomplete, the SSCP must be updated to align with the information in the most recent PSUR.

As vigilance/trending reports and the PMCF Evaluation Report feed into the PSUR, it is important to think about the timing of those reports to avoid having to update the PSUR (and consequently the Clinical Evaluation Plan/CER and SSCP) several times a year.

MDCG guidance

As of January 2021, there are seven MDCG guidance documents listed as relevant to clinical investigation and evaluation on the Commission website⁷:

- MDCG 2020-13, *Clinical evaluation assessment report template* (July 2020)
- MDCG 2020-10/1, *Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745* and MDCG 2020-10/2, *Clinical Investigation Summary Safety Report Form v1.0* (May 2020)
- MDCG 2020-8, *Post-market clinical follow-up (PMCF) Evaluation Report Template – A guide for manufacturers and notified bodies* (April 2020)
- MDCG 2020-7, *Post-market clinical follow-up (PMCF) Plan Template – A guide for manufacturers and notified bodies* (April 2020)

- MDCG 2020-6, *Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC – A guide for manufacturers and notified bodies* (April 2020)
- MDCG 2020-5, *Clinical Evaluation – Equivalence – A guide for manufacturers and notified bodies* (April 2020)
- MDCG 2019-9, *Summary of safety and clinical performance – A guide for manufacturers and notified bodies* (August 2019)

There are also a few other clinically related guidance documents, such as MDCG 2020-1, *Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software* (March 2020).

Key points of MDCG 2019-9

MDCG 2019-9² covers the SSCP for Class III and implantable devices. An SSCP should be transparent, both to the healthcare professional and, where appropriate, to the patient. It is also important that where a patient version is provided, it is validated adequately. It is not acceptable, for example, to rely on the terminology for risks used in a clinical investigation patient consent form approved by an Ethics Committee, as the professional support available to the patient may differ in general use and also additional risks may have been identified during the clinical investigation which were not discussed at the consent phase of the patient. Validation should use appropriate methods such as patient groups or specialist software. Additionally, it is important that the document quantifies the benefit/risk of the device over the claimed lifetime of the device.

Key points of MDCG 2020-5

MDCG 2020-5⁸ covers equivalence in clinical evaluation. It directs the reader to MEDDEV 2.7/1 revision 4 and does not replace Appendix A1 or the interpretation of equivalence in the MEDDEV. Within this MDCG guidance, consideration is given to access to data and use of similar device data for well-established technologies. From a Notified Body perspective, it is important to make sure that there is proper scientific justification for any differences between devices when claiming equivalence. The guidance provides a very specific template for manufacturers to use when considering aspects of equivalence.

Key points of MDCG 2020-6

MDCG 2020-6² provides guidance on what is considered ‘sufficient’ clinical data for legacy devices. Appendix III of the MDCG guidance lists a suggested hierarchy of clinical evidence for confirmation of

conformity with relevant GSPRs under the MDR, ranked roughly in order from strongest to weakest. For example, results of high-quality clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc may not be feasible or necessary for certain well-established devices with broad indications (e.g. Class IIb legacy sutures, which could be used in every conceivable patient population). It is therefore important to look at what clinical data exists for a device, what is set out in the Clinical Evaluation Plan, and how the indications can be narrowed and defined to reflect it.

Key points of MDCG 2020-7

MDCG 2020-7⁹ provides a template for the PMCF Plan. Under the MDR, PMCF is a continuous process and this guidance provides manufacturers with plans for conducting PMCF activities (e.g. the information required). The activities must be proactive and statistically powered (e.g. What will be the return rate for surveys? Will it provide the quality of evidence to justify statistically what is needed?).

Key points of MDCG 2020-8

MDCG 2020-8¹⁰ concerns the PMCF Evaluation Report template. Information presented in the PMCF Evaluation Report will impact the PSUR, CER and SSCP, if relevant. The guidance talks about Real World Evidence and data collection, and the minimum amount of information that must be presented in the report.

Key points of MDCG 2020-13

MDCG 2020-13³ sets out a template for the Clinical Evaluation Assessment Report. This is a document that Notified Bodies will produce upon completion of a conformity assessment. It is the Notified Body's interpretation of what clinical data the manufacturer holds and whether the device is state-of-the-art. Although this guidance is aimed at Notified Bodies, manufacturers should utilise it to familiarise themselves with the evaluation methods of the Notified Bodies, what Notified Bodies will consider, what is the minimum amount of information they need to report, etc.

PMCF activities

Surveys

There are two different types of surveys: low quality ones would focus on things like usability whereas high quality surveys would focus on patient reported outcome measures, although usability questions could be included as well. It is important to consider the clinical endpoints of surveys: What is being measured? Is it a quantitative assessment of safety and performance? Where appropriate, is a

qualitative assessment required? Other points to consider are whether the surveys are statistically powered, the distribution circle of the surveys to ensure it reflects clinical practice across all Member States where the device is used, and methods for ensuring a high survey return rate.

Registries

Registries are a good way to capture Real World Evidence data about how the device is being used, including off-label use. Access to registry data is the first factor to consider. Some larger registries may allow manufacturers to participate or obtain a report from that registry data, and national registries may provide access to comparable device data. Registries can also help with the collection of lifetime data, for example for implantable devices where the expected lifetime is over five years. For any registry, it is important to consider the quality of the data input (e.g. is it mandatory), and the population covered by the data capture (does it reflect the EU population). The ethics, consent, data confidentiality and legalities of registry data must also be considered.

Manufacturers are increasingly looking at developing registry-based studies within patient registries (so-called ‘nests’). A registry-based study is an investigation of a research question or hypothesis using data from an existing patient registry or from a registry newly set-up for the study. A patient registry is a data collection system on a group of people defined by a particular disease or condition, established for a specific purpose and used to conduct a registry-based study.

Design considerations

Table 2 summarises the primary design considerations for registries and what questions manufacturers should be asking.

Table 2. Key registry design considerations

Consideration	Relevant questions
Research question	What are the clinical and/or public health questions of interest?
Resources and limitations	What resources, in terms of funding, sites, clinicians, and patients, are available for the study?
Exposures and outcomes	How do the clinical questions of interest translate into measurable exposures and outcomes?
Data sources	Where can the necessary data elements be found?
Study design	What types of design can be used to answer the questions or fulfil the purpose?
Study population and inclusion criteria	What types of patients are needed for the study? Is a comparison group needed? How should patients be selected for the study?

Consideration	Relevant questions
Study size and duration	How long should data collection last, and how many patients should be included?
Internal and external validity	What are the potential biases? What are the concerns about generalisability of the results (external validity)?

Resources and limitations of registries

A number of questions arise with respect to use of registries and these should all be considered by manufacturers:

- Who will input the data (e.g. nurse, physician, patient)? Is it the right person?
- Where will data be captured (hospital or community)? Is this appropriate?
- Will it be data from a single site, or national, or multi-national, or international?
- Do these data already exist?
- Who will check the quality of the data?
- Who will perform the analysis (ideally this should be someone with a medical background)?
- Are follow-up data required?
- Is now the time to collaborate with other manufacturers? Will this increase the quality of the data?

Registries can be labour intensive and operationally difficult to manage, and require defined protocols and responsibilities.

Literature searches

Based on the text of the MDR, manufacturers are not obligated to specify the methods used for screening of literature within their PMCF Plan. However, whilst the routine act of screening literature is reactive, it is an important PMS activity to demonstrate continually the safety and performance of a device along with confirming state-of-the-art. Therefore, when these activities are conducted, there is an expectation that manufacturers identify the methods used in screening literature within their PMCF Plan to strengthen and demonstrate further their commitment to PMCF and surveillance activities.

PMCF studies

PMCF studies require significant operational commitments from manufacturers and are a big investment. It is therefore essential that PMCF studies are designed appropriately to ensure the

clinical evidence obtained is adequate. Notified Bodies often find the following common mistakes with PMCF studies:

- they do not cover all indications;
- they do not have primary endpoints that are clinically meaningful;
- they do not cover the lifetime of the device;
- there is poor statistical design behind the study plans;
- there is an over-estimation of study numbers;
- accessories/device interaction are not considered as part of PMCF.

Conclusion

Notified Bodies appreciate that that the MDR introduces many new challenges and requirements for manufacturers in relation to the documentation of clinical evaluation and PMS activities. The truth is that the underpinning requirements to collect and hold these data have always been there as part of the Directives and MEDDEV guidance, but the MDR is now driving all actors to be consistent and transparent across the industry in their approach to clinical evaluations. This consistency and transparency will ultimately lead to improved patient safety, effective devices on the market, drive innovation and ensure that the right device is selected for the right patient.

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BSI plans to follow the Directives as a UK Conformity Body to ensure continued certification in the UK market from January 2021. Manufacturers who wish to sell in the EU and UK must take this into account.

Get ready for the MDR

Medical device manufacturers must ensure they meet the relevant requirements outlined in the Medical Device Regulation (MDR) (EU) 2017/745 before placing products onto the EU market. With the MDR coming into force on 26 May 2021 it is critical to work with a notified body that understands the industry and has the experience to review and confirm products' readiness for market – efficiently, promptly and robustly.

Our technical specialists have extensive experience and can support you through the process of certifying your medical device. We are currently accepting MDR CE marking applications from active device and active implantable device manufacturers as well as other technology areas.

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