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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

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GRZAN

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This guidance document is not legally binding. It has been put together following contribution from national competent authorities, industry and relevant stakeholders and it should therefore be recognised as best practice. It also intends to support a harmonised approach with respect to clinical data providing sufficient clinical evidence necessary to demonstrate conformity with the relevant General Safety and Performance Requirements (GSPR) across European Union Member States.

1. Definitions

1.1. Terms defined in MDR Article 2

The following terms are used as defined in the Medical Device Regulation (EU) 2017/745 (MDR):

- 'performance';[1]
- 'risk';[2]
- 'intended purpose'[3]
- 'benefit-risk determination';[4]
- 'clinical evaluation';[5]
- 'clinical investigation';[6]
- 'clinical data';[7]
- 'clinical evidence';[8]
- 'clinical performance';[9]
  It should be noted that clinical performance may arise from either 'direct or indirect medical effects' 'leading to a clinical benefit for patients'; see comments for relevance to clinical benefit below
- 'clinical benefit'.[10]
  It should be noted that clinical benefits may be either direct or indirect; for example devices such as guidewires may assist other medical devices in achieving their intended purpose, without having a direct therapeutic or diagnostic function themselves.
- 'generic device group'.[11]

1.2. Additional terms not defined in MDR Article 2

Additional terms which are not explicitly defined in Article 2 of the MDR, but which are essential to evaluation of benefit-risk and clinical evaluation conclusions:

[1] MDR, Article 2(22).
[2] MDR, Article 2(23).
[3] MDR, Article 2(12).
[4] MDR, Article 2(24).
[5] MDR, Article 2(44).
[6] MDR, Article 2(45).
[7] MDR, Article 2(48).
[8] MDR, Article 2(51).
[9] MDR, Article 2(52).
[10] MDR, Article 2(53).
[11] MDR, Article 2(7).

- ‘legacy devices’: this is considered to include all devices previously CE marked under the European Medical Devices Directive 93/42/EEC (MDD) or Active Implantable Medical Devices Directive 90/385/EEC (AIMDD)
- ‘well-established technology’: this terminology is used in Article 52(5) and Article 61(8) of the MDR, but is not defined in these articles. The term is not restricted to the devices listed in Article 61(6b); Article 61(8) explicitly states that this includes devices *similar to* the exempted devices listed in Article 61(6b), which might be added to that list in future. The common features of the devices which are well-established technologies are that they all have:
    - relatively simple, common and stable designs with little evolution;
    - their generic device group has well-known safety and has not been associated with safety issues in the past;
    - well-known clinical performance characteristics and their generic device group are standard of care devices where there is little evolution in indications and the state of the art;
    - a long history on the market.

  Therefore, any devices that meet all these criteria may be considered “well-established technologies”.
- ‘scientific validity’, ‘scientifically valid’: this terminology is used in the MDR in reference to clinical data planning, evaluation and conclusions[12]. Clinical evaluations must follow a “defined and methodologically sound procedure”[13], for which expectations of scientific validity are implicit. Embedded in the term ‘scientific validity’ are concepts including adequacy of study design and controls for bias, appropriateness and relevance of research questions, adequacy of sample sizes and statistical analyses, completeness of data, adequacy of follow up period, and appropriateness of conclusions on the basis of objective evidence. Section 9.3.1 of MEDDEV 2.7/1 rev. 4 provides guidance for the evaluation of methodological quality and scientific validity under the MDD/AIMDD which are equally valid under the MDR which can be considered to apply when referencing ‘scientific validity’ in this guidance.
- ‘level of clinical evidence’: this terminology is used in the MDR with respect to requirements for demonstration of conformity with the relevant GSPR and overall benefit-risk[14]. It is understood to encompass the amount and quality of evidence (i.e. its characterisation by quality, quantity, completeness and statistical validity, etc.) required to demonstrate safety, performance and the benefit-risk conclusion of a medical device. It should not be confused with the term ‘levels of evidence’ (as used in evidence-based medicine) which is used to rank study designs, and is only a part of the concept ‘level of clinical evidence’. Regarding the assessment of the level of clinical evidence for the device in question, see sections 6.3 and 6.5d of this document.
- ‘state of the art’: IMDRF/GRRP WG/N47 provides the following definition:
  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.

[12] MDR Annex XV, Chapter I, Article 2(2.1) and (2.6).
[13] MDR Article 61(3).
[14] MDR Article 61(1), Annex IX section 5.1.

Note: The 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

- 'intended use': The MDR defines 'intended purpose', but not 'intended use'. 'intended use' should be considered to have the same meaning as 'intended purpose'.
- 'indication', '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).
- 'similar device': devices belonging to the same generic device group. The MDR defines this as a set of devices having the same or similar intended purposes or a commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics[15].

2. Reference documents

This document provides facilitative guidance to the requirements of MDR Chapter VI and Annex XIV, and references the following MDD/AIMDD guidance documents:

- MEDDEV 2.7/1 rev. 4: Clinical Evaluation: A Guide for Manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC
- MEDDEV 2.12/2 rev 2: Post Market Clinical Follow-Up Studies: A Guide for Manufacturers and Notified Bodies

3. Scope

This document seeks to provide guidance for clinical data providing sufficient clinical evidence necessary to demonstrate conformity with the relevant GSPR, as per Article 61(1) MDR, for legacy devices CE marked with respect to Directives 93/42/EEC (MDD) or 90/385/EEC (AIMDD).

This document aims to provide guidance for manufacturers and notified bodies to prepare for the conformity assessment procedure according to the MDR.

This document does not provide comprehensive guidance with respect to the process or methodology relating to clinical evaluation. It is general and not restricted to any particular device technology or risk class. Following on from the principles described in Section 3 however, special attention is given to those described in Article 61(6).

[15] MDR, Article 2(7).

4. Introduction and context

This section is intended to provide an introduction and context, and not to modify the interpretation of the MDR.

MDR Article 61(1) states:

> *Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III.*
>
> *The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.*
>
> *To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.*

MDR Article 61(4) states that clinical investigations shall be performed for Class III and implantable devices, but distinct exemptions from this requirement are identified both in this article and in Articles 61(5) and 61(6). The common theme of these exempted devices is that they have been previously marketed (Article 61(6)) or have been demonstrated to be equivalent to devices previously marketed (Article 61(5)).

Article 61(6a and b) further distinguishes between legacy devices (Article 61(6a)) which have been previously marketed under 93/42/EEC or 90/385/EEC and a specific subset of well-established technologies (WET) (Article 61(6b)).

The following should be noted:

- all such exemptions from clinical investigations require that the clinical evaluation is based on “sufficient clinical data”;
- the basic clinical evaluation requirements for the legacy devices described in Article 61(6a) and the devices of Article 61(6b) are the same: “sufficient clinical data” and compliance to common specifications where these exist. The distinction between the two is that the devices listed in Article 61(6b) are not explicitly required to have had prior certification under the Directives to be exempted from the requirement for clinical investigations that otherwise apply to Class III and implantable devices;
- both the Directives and the MDR require the quantity and quality of clinical data to be sufficient to demonstrate safety, performance and the acceptability of the benefit-risk ratio: both the Directives and the MDR require clinical evidence to be sound and the conclusions derived from this evidence to be scientifically valid.

Article 61(10)[16] allows for the use of non-clinical data for demonstration of conformity with GSPRs:

> *Without prejudice to paragraph 4,where the demonstration of conformity with general safety and performance requirements based on clinical data is not deemed*

[16] See MDCG guidance on the CEAR template for notes related to use of Article 61(10).

appropriate, adequate justification for any such exception shall be given based on the results of the manufacturer's risk management and on consideration of the specifics of the interaction between the device and the human body, the clinical performance intended and the claims of the manufacturer.

Article 61(10) cannot be applied to Class III or implantable devices. In exceptional cases Article 61(10) may be applied for all other device classifications.

5. General aspects

"Sufficient clinical evidence" is not defined in the MDR. The definition of "clinical evidence" itself contains the word "sufficient" but it is related to the amount and quality of the clinical data and the clinical evaluation results which "allow a qualified assessment of whether the device is safe and achieves the intended clinical benefits when used as intended by the manufacturer".[17] Sufficient clinical evidence is also mentioned in the MDR Article 61 where it is provided that the confirmation of conformity with the relevant GSPR shall be based on sufficient clinical evidence. Therefore, "sufficient clinical evidence" is understood as "the present result of the qualified assessment which has reached the conclusion that the device is safe and achieves the intended benefits". It is important to note that clinical evaluation is a process where this qualified assessment has to be done on a continuous basis.

Compared to Directives 93/42/EEC and 90/385/EEC, MDR provides greater detail and additional requirements with respect to the process of clinical evaluation, for the purpose of confirmation of conformity with relevant GSPR. The generation of clinical data and their evaluation providing sufficient clinical evidence is part of a lifecycle approach to medical devices.

The MDR reinforces a number of important factors which are relevant to clinical evaluation. This includes:

- **Consideration of available alternative treatment options** is required for the confirmation of the acceptability of the benefit-risk ratio.[18]
- **The acceptability of the benefit-risk ratio** must be based upon clinical data providing sufficient clinical evidence including where applicable relevant data from post-market surveillance.[19]
- **The term "clinical evidence" is introduced and the level of clinical evidence** must be specified and justified by the manufacturer, taking the characteristics of the device and the intended purpose into account.[20]
- **The incorporation of post market surveillance (PMS) data** in particular the post-market clinical follow-up (PMCF) data into the process of clinical evaluation.[21] Manufacturers are required to establish a post-market surveillance plan in accordance with Annex III of the MDR and the clinical data arising from this PMS shall be incorporated into the clinical evaluation.
- **The definition of equivalence** is now included in the text of the MDR,[22] and the process to demonstrate equivalence is defined[23].

[17] MDR, Article 2(51).
[18] MDR, Article 61(3)(c).
[19] MDR, Article 61(1) and Annex III.
[20] MDR, Article 61(1).
[21] MDR, Article 61(1) and (11).
[22] MDR, Annex XIV, Part A, section 3.
[23] MDCG 2020-5 Clinical Evaluation – Equivalence, A guide for manufacturers and notified bodies.

- **A definition of "clinical data"** is provided.[24]

When it comes to the first MDR conformity assessment of a legacy device the pre-market and post-market clinical data generated for the purpose of MDD/AIMDD can be taken into account. As requirements and guidance developed over time, it is not necessarily the case that the clinical data used for conformity assessment under the Directives is clinical data providing sufficient clinical evidence for the purpose of MDR requirements. Legacy devices which have been placed on the market have been subjected to conformity assessment and therefore are presumed to have been supported by clinical data[25]. Post-market clinical data together with the clinical data generated for the conformity assessment under the MDD/AIMDD will be the basis of the clinical evaluation process for legacy devices under the MDR.

During the period of validity of the MDD/AIMDD certificates, the MDR requirements for the PMS apply from the MDR date of application. Legacy devices are therefore not exempted from the additional requirements in MDR concerning PMS, including PMCF. PMS data and clinical evaluation plans and reports need to be produced and updated. The MDR compliant clinical evaluation for a legacy device must contain the identification of available clinical data as well as their appraisal / analysis / evaluation and shall lead to a demonstration of conformity to the MDR GSPR based on clinical data providing sufficient clinical evidence as part of a lifecycle approach.

The European Commission guidance MEDDEV 2.12/2 regarding PMCF studies notes different instances where a PMCF study may have been justified:[26]

- **Route chosen for clinical evaluation**: where CE marking for legacy devices was based upon equivalence, PMCF studies may have been necessary. The European Commission guidance MEDDEV 2.12/2 regarding PMCF also notes that in the case that clinical evaluation was based exclusively on clinical data from equivalent devices for initial conformity assessment, the certifying notified body shall verify that PMCF studies have been conducted,[27] in accordance with the relevant provisions of the Directives.[28]
- **Device related factors**: There are a number of device-related factors where PMCF studies may have been necessary.[29]

When assessing the conformity of legacy devices under the MDR, it is important to verify whether PMCF studies considered necessary under the MDD/AIMDD (and where applicable, during the transition period, under the MDR), have been appropriately conducted, and results are taken fully into account for in the clinical evaluation for the conformity assessment under MDR.

Guidance on the general process of conducting clinical evaluation is also available in the MEDDEV 2.7/1 rev. 4. This guidance was written with respect to the MDD and AIMDD to provide practical guidance on several scientific and clinical aspects that are relevant for conducting clinical evaluation. However only the text of the MDR is authentic in law, sections relevant to the MDR are listed in Appendix I to this document.

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[24] MDR, Article 2(48).
[25] Except where non-clinical testing were demonstrated to be adequate (MDD, Annex X, 1.1(d); AIMD, Annex 7, 1.5).
[26] MEDDEV 2.12/2, section 5 https://ec.europa.eu/growth/sectors/medical-devices/current-directives/guidance_en
[27] MEDDEV 2.12/2, section 8.
[28] Annex II.4, Annex II.7, Annex III, Annex V.6 and Annex VI.6 of Directive 93/42/EEC and Annex II.4, Annex II.7, Annex III and Annex V.6 of Directive 90/385/EEC.
[29] MEDDEV 2.12/2, section 5.

6. Guidance on specific aspects of clinical evaluation for legacy devices

Sections 6.1 – 6.5 below provide guidance on each stage of the clinical evaluation process of MDR Annex XIV Part A Section 1.

6.1. Annex XIV Part A Section 1a: Establish or update a clinical evaluation plan[30]

Manufacturers are required to document a clinical evaluation plan to meet the requirements of MDR Annex XIV Section 1a.

Premarket elements of the plan as described in the final indent of MDR Annex XIV Section 1a (first-in-man studies, feasibility and pilot studies) are not generally relevant to legacy devices which are unchanged in design or indications. However, the context for the plan as described in indents 1-7 and the basis for the PMCF as described in indent 8 of MDR Annex XIV Section 1a are considered relevant and necessary for demonstration of compliance to the MDR. Appendix II of this guidance document suggests a minimum content for clinical evaluation plans for legacy devices. Further advice regarding specific sub-indents of MDR Annex XIV Section 1a are provided below.

a. Identification of the relevant GSPRs (indent 1 of MDR Annex XIV Section 1a): clinical evaluation planning under the Directives required an identification of the relevant Essential Requirements (ER) for which demonstration of conformity required clinical data. The manufacturer should conduct an analysis with respect to the GSPRs of the MDR, to determine if additional data to support the clinical evidence are required to meet additional MDR requirements. This could be achieved either through a gap analysis with respect to new MDR requirements, or by creation of an entirely new analysis for the MDR. As noted in Section 3, Article 61(10) cannot be applied to Class III or implantable devices, but may be applied to some or all requirements for confirmation of conformity with relevant GSPRs for all other device classifications if adequately justified.
b. Specification of the intended purpose, target groups, indications, contraindications (indents 2-3 of MDR Annex XIV Section 1a): Appendix A3 of MEDDEV 2.7/1 rev. 4 lists additional information to Annex II of the MDR about device description that can be relevant for planning clinical evaluations. The manufacturer needs to 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"*[31] and with the device's updated risk management documents.
c. Detailed description of intended clinical benefits with relevant and specified clinical outcome parameters (indent 4 of MDR Annex XIV Section 1a): MEDDEV 2.7/1 rev. 4 Appendix A7.2 Section b provides relevant additional information with respect to the definition of clinical benefits. MEDDEV 2.7/1 rev. 4 Appendix A7.2 Section c provides relevant information with respect to the quantification of benefits and determination of relevant outcome parameters, which may be useful for clinical evaluation planning.
d. Specification of qualitative and quantitative aspects of clinical safety and performance (indents 5-7 of MDR Annex XIV Section 1a): The level of clinical evidence required for the device under evaluation needs to be determined by the manufacturer and verified by the notified body. The level of clinical evidence shall

[30] MDR, Annex XIV, Part A, section 1.
[31] MDR, Article 2 (12).

be appropriate in view of the characteristics of the device and its intended purpose.[32]

The proposed level of clinical evidence should take into account the specification of methods to be used for examination of qualitative and quantitative aspects of clinical performance and clinical safety with clear reference to the determination of residual risks and side-effects. MEDDEV 2.7/1 rev. 4 appendix A6 describes examples of studies that lack scientific validity for the demonstration of adequate clinical performance and/or clinical safety. MEDDEV 2.7/1 rev. 4 section 9.3.2 also provides relevant guidance. It also has to take into account the intended clinical benefits to patients with relevant and specified clinical outcome parameters as well as 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.[33]

For medical devices which have been subject to conformity assessment according to Directives, it should be possible to provide a clear justification for the level of clinical evidence required to reach a demonstration of conformity based on clinical data providing sufficient clinical evidence at the end of the data analysis stage. Manufacturers should identify benefits and risks of the device under evaluation, take into account available alternative treatment options and a clinical assessment of residual risks associated with the device before justifying the level of clinical evidence. As an outcome of this step, it should be possible to conclude if the device is one which has a clearly positive benefit–risk determination, when alternatives are considered, or a marginal one. Special attention is required, with respect to devices with a marginal benefit-risk, at both the stage of initial conformity assessment and when designing the post-market surveillance or clinical follow-up of the device.

According to the MDR, parameters to be used to "*determine…. the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device"* need to be based on the state of the art in medicine.[34] Section 8.2. of MEDDEV 2.7/1 rev. 4 indicates how data on the current state of the art in medicine can be identified.

6.2. Annex XIV Part A Section 1b: Identify available clinical data[35]

It is important to identify all available sources of clinical data from both the pre-market and post-market phases. This will include all of the clinical data which is generated and held by the manufacturer as well as clinical data for equivalent or similar devices[36]. Clinical data is defined in the MDR and the sources of data are specified in Article 2(48). Sections 6.2.1 and 6.2.3 below provide additional guidance with respect to the use of these data sources for legacy devices.

It should be noted that, apart from devices for which Article 61(10) may be applied, the MDR requires confirmation of conformity with the relevant GSPRs to be based on clinical data as defined in Article 2(48). However, other types of data may provide supportive or clarifying information: this may include data derived through evaluation of state of the art,

[32] MDR, Article 61(1).
[33] MDR, Annex XIV, Part A, section 1 (a) 5th indent.
[34] MDR, Annex XIV, Part A, section 1.
[35] Guidance with respect to identification of clinical data is provided in section 8 and Appendix A4 and A5 of MEDDEV 2.7/1 rev. 4.
[36] Section 5, MDCG 2020-05 Clinical Evaluation – Equivalence, A guide for manufacturers and notified bodies.

evaluation of clinical data for similar devices (as described in Section 1.2 of this document), usability or simulated use testing, etc. A summary of considerations related to use of clinical and non-clinical data sources is provided in Appendix III of this document.

6.2.1. Pre-market sources of clinical data

For the purpose of legacy devices, pre-market sources of clinical data may include:

- Clinical investigation reports of the device concerned;
- Clinical investigation reports or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated in accordance with the MDR;
- Reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated;
- Other pre-market data, e.g. case reports on experience with the use of the device in question, such as compassionate or humanitarian exceptional use reports. Note that this kind of pre-market data may be more prone to bias, compared to those listed above.

It should be noted that MDR Article 2(48) provides a narrower definition of what constitutes clinical data sources as compared to the Directives which allow unpublished reports on other clinical experience to contribute to the clinical evaluation. Such data sources may provide informative context for the clinical evaluation of legacy devices.

6.2.2. Post-market sources of clinical data

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[37];
- 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.[38,39]

6.3. Annex XIV Part A Section 1c: Appraisal of the clinical data

The clinical data sets should be subject to an appraisal with respect to their relative contribution to the overall clinical evaluation. It is important to perform analysis of the methodological quality of data obtained from different sources to identify and assess the level of evidence, bias, other inherent weakness or other possible shortcomings.

Clinical investigations, other sources of clinical data and post-market sources of clinical data can be of variable methodological quality and therefore an appraisal of the design of

[37] Including for example devices used during clinical trials of pharmaceutical substances, or accessories to other medical devices, where the device is clearly identified.
[38] MDR, Annex XIV and Article 2(48).
[39] MDCG 2020-5 Clinical Evaluation – Equivalence, A guide for manufacturers and notified bodies.

these studies is important. Examples of studies that lack scientific validity for demonstration of adequate clinical performance and / or clinical safety can be found in Appendix A6 General principles of clinical evaluation of MEDDEV 2.7/1 rev. 4. The use of vigilance data, in general is appropriate for identification of any new risks, events in subpopulations, examining trends in PMS reports etc. With respect to the utilisation of post-market surveillance data for the purpose of conformity assessment, it is important to recognise that uncontrolled sources of clinical data – for example complaint or incident report data – cannot always provide reliable data with respect to the incidence of risks and cannot provide an estimate of uncertainty i.e. a confidence interval. Due to limitations of complaints reporting, the use of estimates such as [number of incidents or complaints] / [number of device sales] cannot generally be considered sufficient to provide proof of safety; their use should be limited to cases where data from pre-market or post-market clinical investigations or PMCF studies are not deemed appropriate.

Additional information on the use of information derived from vigilance data, device registry data, case series, patient dossiers and other use data can be found in section 9.3.1 (c) of MEDDEV 2.7/1 rev. 4.

Clinical data appraisal should be conducted using verified/validated assessment tools. Examples include methodological quality assessment tools developed by medical researchers and scientists to assess published clinical data such as Appendix F of IMDRF MDCE WG/N56 on Clinical Evaluation, Cochrane Collaboration's tool for Randomized Controlled Trials (RTC), MINORS (Methodological index for non-randomized studies), Reisch tool (for non-randomized interventional studies), Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Their detailed description, the inclusive list of major components of each tool is included in the paper by Zeng X, Zhang Y, Kwong JS et al. "The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review"[40]. This list is not exhaustive. Additional validated tools may become available in the future.

6.4. Annex XIV Part A Section 1d: Generation of new clinical data

Legacy devices following the MEDDEV 2.12/2 guidance for PMCF should normally have collected data on the devices themselves in the post-market phase. In the event that the postmarket data on the device itself (including PMCF) is not adequately comprehensive to provide sufficient clinical evidence, and the demonstration of equivalence is no longer possible under the definition of equivalence in the MDR, new data may need to be generated prior to CE-marking under the MDR.

In general, there shall be sufficient clinical evidence to confirm safety, performance and the acceptability of the benefit-risk determination in relation to the state of the art for the legacy devices prior to CE-marking under the MDR, and such demonstration should not rely on new PMCF studies started under the MDR to bridge gaps (e.g. indications not supported by clinical evidence). Where other evidence, for example results of pre-clinical testing etc. as described in MDR Article 61(10), is used for confirmation of safety and performance, PMCF studies may be undertaken to confirm these conclusions.

[40] J Evid Based Med. 2015 Feb;8(1):2-10. doi: 10.1111/jebm.12141. Review. https://www.ncbi.nlm.nih.gov/pubmed/25594108

6.5. Annex XIV Part A Section 1e: Analysis of the clinical data

The aim of this stage is the determination if all clinical data collected and appraised, as described in previous stages, demonstrate together conformity with relevant GSPR. In order to determine the benefit-risk ratio, it is necessary to identify the benefits and risks associated with the device and the alternatives (if any). Practical guidance is available in section 10 of MEDDEV 2.7/1 rev. 4.[41]

Demonstration of compliance with the GSPR, relevant for the device in question have to be based on:

- The usage of reliable, justified and sound analytical methods (where applicable qualitative, quantitative, or both);
- Results of performed comprehensive analysis;
- Identification of any missing data and/or gaps;
- Determination of PMCF needs.

a. Clinical benefits

Clinical benefit means *"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".*[42] The type of clinical benefit associated with a device depends upon the device under evaluation and its intended purpose. Examples of clinical benefits and their quantification can be found in Appendix A7.2 letters (b) and (c) of MEDDEV 2.7/1 rev. 4.

It should be noted that while direct clinical benefits should be supported by clinical data, indirect clinical benefits may be demonstrable by other evidence such as:

- pre-clinical and bench test data (eg compliance to product standards or common specifications);
- real world data such as registries, information deriving from insurance database records, etc;
- data from another device that is used with the subject device which does have direct clinical data (eg, data from a stent used to justify safety and performance of a guidewire).

A determination of the level of clinical evidence required to demonstrate an indirect clinical benefit should be made on the basis of a thorough risk assessment and evaluation of short, medium and long term clinical risks (for example, a guidewire, although used transiently, may have long term clinical risks if it leads to vessel dissection).

b. Risks

Risk means the combination of the probability of occurrence of harm and the severity of that harm.[43] The MDR requires manufacturers to establish, document, implement and maintain a system for risk management.[44] The standard ISO 14971[45] provides such a process for managing risks associated with medical devices, as part of an ongoing,

[41] This chapter includes references to the MDD, MDR requirements should be used instead, ie. reference to 'Essential requirements' should be replaced by GSPR and reference to PMCF should be replaced by the relevant MDR requirements, i.e. in Annex XIV, part B.
[42] MDR, Article 2(53).
[43] MDR, Article 2(23).
[44] MDR, Article 10(2).
[45] Medical devices — Application of risk management to medical devices.

lifecycle approach. The Annex I of the MDR require that manufacturers reduce risks as far as possible, and to do this, manufacturers must estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse.[46]

The determination as to which risks require the generation of clinical data to support either the probability and severity of a particular harm, or the effectiveness of a risk control measure, is one which must be reached upon a case by case basis,[47] and the decision as to when it is necessary to generate further clinical data is not addressed by ISO 14971 and should be an output of the process of clinical evaluation.

Considerations on aspects of risk evaluation, and considerations on the number of patients needed to obtain sufficient data can be found in Appendix A7 of MEDDEV 2.7/1 rev. 4.

c. Benefit-risk determination, state of the art, alternative treatment options

The MDR requires that any risks which may be associated with the use of the device are *"compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art"*[48] and that the determination of the acceptability of the benefit-risk ratio is "*based on the state of the art in medicine*".[49]

It is important to remember that a medical device may be used for an indication for which there are many alternative medical options. This may include the use of medicinal products, other medical devices, other medical or allied health professional interventions, a combination of any of these or no intervention. As such, in order to determine a benefit-risk ratio, up-to-date alternatives must be considered for legacy devices. The appropriateness and relevance of an alternative treatment option depends upon a wide range of factors, including the nature of the healthcare system and patient preferences. To help to describe alternatives, it is necessary to describe the 'state of the art' for the treatment of the indicated clinical condition taking alternative treatments into account. The state of the art in this context can be taken to mean the generally accepted most effective treatment option, for the intended purpose relevant to the device under consideration. Occasionally, this may be subject to differences of opinion between clinical evaluators as to what is the state of the art, and where such differences exist, these should be described and taken into account insofar as is possible. In such cases, a thorough evaluation of the results from published clinical studies of high methodological quality shall be taken into account. Moreover, where applicable, particular attention shall be paid to therapy guidelines grounded on principles of evidence based medicine. Novel and innovative device technology may be subject to a rapidly evolving state of the art for a particular indication, and where this exists, it should also be noted.

Aspects that influence the acceptability of benefits and risks can be found in Appendix A7.2 letter (e) and in Appendix A7.4 of MEDDEV 2.7/1 rev. 4.

[46] MDR, Annex I, Chapter 1, section 3(c).
[47] ISO14971:2007, page v, notes that an individual's perception of risk can depend upon a range of factors including their cultural background, the socio-economic and educational background of the society concerned, the actual and perceived state of health of the patient, and many other factors.
[48] MDR, Annex I, Chapter 1, Section 1.
[49] MDR, Annex XIV, Part A, Section 1(a).

d. The level of clinical evidence available to demonstrate conformity based on clinical data providing sufficient clinical evidence

The MDR requires that the level of clinical evidence is justified and specified by the manufacturer. The required level of clinical evidence has to be identified, specified and justified by the manufacturer during the clinical evaluation process. This level has to be appropriate to demonstrate conformity with the relevant GSPR.

To reach a determination of sufficiency, when considering the available level of clinical evidence, the manufacturer may use widely available and validated tools when examining clinical data. These tools are methodological quality assessment tools developed by medical researchers and scientists to assess published clinical data.[50] Examples of these tools include the Cochrane Collaboration´s tool for RCT or NOS checklist for analytical studies (see Footnote 40). See MEDDEV 2.7.1 rev 4, Section 9.3.2 'How to determine the relevance of a data set for the clinical evaluation', for further information.

e. Lack of clinical data providing sufficient clinical evidence

Manufacturers should conduct a gap analysis with respect to the MDR requirements. If data gaps have been identified, there are different possibilities to bridge those gaps.

While controlled clinical investigations might be the preferred method for collecting clinical data as part of the PMCF studies for some products, there are other possibilities to gather relevant clinical data in the field in order to close the clinical data gap. Other alternatives include, but are not limited to systematic reviews of clinical data published in the literature, evaluation of results from PMCF studies such as clinically relevant scientifically sound questionnaires[51] or registries. Scientifically sound studies will normally include (note, this is not a complete list):

- Clearly stated research question(s), objective(s) and related endpoints;
- An evaluation of potential sources of bias or study distortion, and the impact of these factors on the potential validity of results;
- Design with an appropriate rationale and statistical analysis plan;
- A plan for an analysis of the data and for drawing appropriate conclusion(s).

If there is not sufficient supportive clinical evidence with regard to the declared intended purpose[52] including the indications and claims as appropriate, manufacturers shall narrow the intended purpose of the device under evaluation until it is supported by the available clinical evidence.

As noted in Section 4, some legacy devices may have limited clinical data, particularly if they were marketed prior to the publication of the Directives. In some cases, it may be necessary for the manufacturer to undertake PMCF to generate new data for these legacy devices prior to CE marking under the MDR, whereas in other cases, particularly for low risk standard of care devices where there is little evolution in the state of the art, it may be possible to demonstrate conformity with the relevant GSPRs with a more limited clinical data set.

Devices previously certified under the Directives might not be considered to have sufficient clinical data for certification under the MDR. Reasons may include:

[50] The suggested tools may also be relevant for unpublished data.
[51] Clinically relevant and where possible validated.
[52] MDR, Article 2(12).

- changes in the state of the art
- data arising from PMS may identify new risks or provide additional clarity with respect to indications and contraindications
- devices previously certified under Quality System annexes of the Directive may not have been sampled prior to an application for MDR certification, and the clinical evidence therefore not subject to Notified Body scrutiny
- the MDR introduces new requirements on the use of equivalence, which may reduce the overall volume of data available for demonstration of conformity with the relevant GSPRs
- the MDR has a more explicit definition of what constitutes clinical data, which may remove some data sources previously used

Although the Directives indicate that data shall be collected in the post-market phase for all devices[53], in practise the data collected may not meet MDR criteria, if the devices were considered standard of care and were not associated with safety concerns. Stable, well-established technologies that perform as intended and are not associated with safety concerns, and where there has been no innovation, are less likely to be the subject of research, and therefore literature data may be limited or non-existent. In some cases, it may be necessary for the manufacturer to undertake PMCF to generate new clinical data for these devices prior to certification under the MDR, even if they are well-established and have been on the market for several decades, to enable an evaluation of their safety and clinical performance in relation to an evolving state of the art.

In exceptional cases, particularly for low risk standard of care devices where there is little evolution in the state of the art, and the device is identified as belonging to the group of 'well-established technologies' (see section 1.2 and Appendix III in this document) a lower level of clinical evidence may be justified to be sufficient for the confirmation of conformity with relevant GSPRs. This may be supported by clinical data from the PMS provided that there has been a quality management system in place to systematically collect and analyse any complaints and incident reports, and that the collected data support the safety and performance of the device.

[53] MDD, Annex II(3.1) indent 7, Annex IV(3), Annex V(3.1) indent 8, Annex VI(3.1) indent 8, Annex VII(4).

Appendix I - Sections of MEDDEV 2.7/1 rev. 4 which are still relevant under the MDR for the application of this guidance

The identified sections of MEDDEV 2.7/1 rev. 4 are considered relevant to MDR as they contain helpful information regarding 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.

Appendix II – Clinical Evaluation Plan for Legacy Devices[54]

A modified Clinical Evaluation Plan for legacy devices should include at least:[55]

- An identification of the GSPR that require support from relevant clinical data.
- A specification of the intended purpose of the device.[56]
- A clear specification of intended target groups with clear indications and contra-indications.
- 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[57].
- 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.[61]

[54] MDR, Annex VII, 4.11.
[55] Appendix A3 of MEDDEV 2.7/1 rev. 4 lists information that can be relevant for planning clinical evaluations. The manufacturer needs to make sure that input 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 device's updated risk management documents.
[56] In order to fully identify the intended purpose(s) of a legacy device, the manufacturer needs to consider the data that is foreseen on the label, in the instructions for use or in promotional or sales materials or statements that are foreseen for the device. Typical elements of the intended purpose can be found in Appendix A3 of MEDDEV 2.7/1 rev. 4.
[57] MDR, Article 61(3)(c).
[58] MDR, Article 61(1).
[59] The proposed level of clinical evidence should take into account the 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.
[60] To determine the level of clinical evidence it is necessary to identify benefits and risks of the device under evaluation and to take into account available alternative treatment options, and a clinical assessment of failure modes associated with the device.
[61] MDR Article 83 and MDR Annex III.

Appendix III – Suggested hierarchy of clinical evidence for confirmation of conformity with relevant GSPRs under the MDR

Sources of pre- and post- market clinical data are described in Sections 6.2.1 and 6.2.2 of this document. Reference is also made to clinical evidence which may provide contextual, supportive or clarifying information for demonstration of conformity with the relevant GSPRs. A suggested hierarchy of evidence and considerations to apply is provided in the table below, ranked roughly in order from strongest to weakest (some variations may apply dependent on the device, GSPR for which evidence is required, and quality of individual data sources):

Rank	Types of clinical data and evidence	Considerations / comments
1	Results of high quality[62] clinical investigations covering all device variants, indications, patient populations, duration of treatment effect, etc	This may not feasible or necessary for certain well-established devices with broad indications (eg Class IIb legacy sutures, which could be used in every conceivable patient population)
2	Results of high quality clinical investigations with some gaps	Gaps must be justified / addressed with other evidence in line with an appropriate risk assessment, and clinical safety, performance, benefit and device claims. Assuming the gaps can be justified, there should be an appropriate PMCF plan to address residual risks. Otherwise, manufacturers shall narrow the intended purpose of the device until sufficient clinical data has also been generated.
3	Outcomes from high quality clinical data collection systems such as registries[63]	Is there sufficient evidence of the quality of the data collected by the registry[64, 65]? Are the devices adequately represented? Are the data appropriately stratified? Are the endpoints appropriate to the safety, performances and endpoints identified in the clinical evaluation plan?
4	Outcomes from studies with potential methodological flaws but where data can still be quantified and acceptability justified[66]	Many literature sources fall into this category, due to limitations such as missing information, publication bias, time lag bias, etc. This applies equally to publications in the peer-reviewed scientific literature. However, for legacy devices

[62] Refer to data appraisal considerations described in Section 6.3 of this guidance.
[63] Please note that the Considerations / Comments listed in point 2 also apply to these studies.
[64] http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-methodological-principles.pdf
[65] http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-160930-principles-system-registries.pdf
[66] Please note that the Considerations / Comments listed in point 2 also apply to these studies.

		where no safety or performance concerns have been identified, these sources can be sufficient for confirmation of conformity to the relevant GSPRs if appropriately appraised and the gaps are identified and handled. High quality surveys may also fall into this category.
Class III legacy devices and implantable legacy devices which are not well-established technologies should have sufficient clinical data as a minimum at level 4. Those devices which are well-established technologies may be able to confirm conformity with the relevant GSPRs via an evaluation of cumulative evidence from additional sources as listed below. Reliance solely on complaints and vigilance is not sufficient.		
5	Equivalence data (reliable / quantifiable)	Equivalence must meet MDR criteria. It is normally expected that manufacturers should gather data on their own devices in the post-market phase, therefore reliance on equivalence should be duly justified, and linked to appropriate PMCF or proactive PMS.
6	Evaluation of state of the art, including evaluation of clinical data from similar devices as defined in Section 1.2 of this document	This is not considered clinical data under the MDR, but for well-established technologies only can be considered supportive of confirmation of conformity to the relevant GSPRs. Data from similar devices may be also important to establish whether the device under evaluation and similar devices belong to the group of devices considered as "well established technologies" (WET). See section 1.2 in this document for the criteria for WET. Data from similar devices may be used, for example, to demonstrate ubiquity of design, lack of novelty, known safety and performance profile of a generic group of devices, etc.
7	Complaints and vigilance data; curated data	This falls within the definition of clinical data under MDR Article 2(48), but is not generally considered a high quality source of data due to limitations in reporting. It may be useful for identifying safety trends or performance issues. High volume data collected within a robust quality system may provide supportive evidence of device safety.
8	Proactive PMS data, such as that derived from surveys	This falls within the definition of clinical data under MDR Article 2(48), but is not generally considered a high quality source of data due limitations associated with sources of bias and quality of data collection. It may be useful for

		identifying safety concerns or performance issues.
9	Individual case reports on the subject device	This falls within the definition of clinical data under MDR Article 2(48), but is not considered a high quality source of data due to limitations in generalising findings to a wider patient population, reporting bias, etc. It may provide supportive or illustrative information with respect to specific claims.
10	Compliance to non-clinical elements of common specifications considered relevant to device safety and performance	Common specifications which address clinical investigation or data requirements directly would rank higher in this hierarchy. Common specifications may address clinically relevant endpoints through non-clinical evidence such as mechanical testing for strength and endurance, biological safety, usability, etc.
11	Simulated use / animal / cadaveric testing involving healthcare professionals or other end users[67]	This is not clinical data, but may be considered evidence of confirmation of conformity to relevant GSPRs, particularly in terms of usability, such as for accessories or instruments.
12	Pre-clinical and bench testing / compliance to standards[62]	Pre-clinical and bench testing may address clinically relevant endpoints through non-clinical evidence such as mechanical testing for strength and endurance, biological safety, usability, etc.

[67] This may be of interest in the case of application of Article 61(10).