This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission.

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MDCG 2018-X

Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously certified under Directives 93/42/EC and 90/385/EC (legacy medical devices)

A guide for manufacturers and notified bodies

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It is to be noted that whilst 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 tries to support a harmonised approach on establishing and demonstrating of clinical data providing sufficient clinical evidence across European Union Member States.

1. Definitions

The following terms are used as defined in the MDR:

- 'clinical evidence';[1]
- 'clinical data';[2]
- 'clinical evaluation';[3]
- 'clinical investigation';[4]
- 'performance';[5]
- 'risk';[6]
- 'clinical performance';[7]
- 'clinical benefit';[8]
- 'benefit-risk determination';[9]

2. Introduction and scope

Article 61(1) of Regulation 2017/745 (MDR) notes:

> *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.*

This document seeks to provide guidance for clinical data providing sufficient clinical evidence for legacy devices, i.e. those certified with respect to Directives 93/32/EC and 90/385/EC.

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

"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". Therefore "sufficient clinical evidence" is understood as "the qualified assessment has reached a positive 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.

This guidance aims to provide facilitative guidance for manufacturers and notified bodies to prepare for the conformity assessment according to MDR of the medical devices currently certified under the directives. This guidance should be used during the period of the validity of existing certificates issued with respect to the Directives as referenced by article 120 (2) and (3) of the MDR.

It does not provide comprehensive guidance with respect to the process or methodology relating to clinical evaluation and it is general and not focussed towards any particular device technology or risk class. It also does not apply to considerations for products specified in Article 61(6)(b) of the MDR (sutures, staples, dental fillings etc…).

3. General comments

Compared to Directives 93/42/EC and 90/385/EC, Regulation (EU) 2017/745 (MDR) provides greater detail and changes with respect to the process of clinical evaluation and the demonstration of clinical data providing sufficient clinical evidence as part of a lifecycle approach to clinical evaluation for the purpose of market entry and the evaluation of clinical data from the post-market. In addition the MDR has changed the definition of clinical data, which makes it in case of legacy products necessary to analyse and re-assess existing data.

The MDR reinforced 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.[10]
- **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.[11]
- **The incorporation of post market surveillance (PMS) data** in particular the post-market clinical follow-up data into the process of clinical evaluation[12]. 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 should be incorporated into the clinical evaluation.
- **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.[13]
- **The definition of equivalence** is now included in the text of the MDR,[14] and the process to demonstrate equivalence is defined.

[10] MDR, Article 61(3)(c)
[11] MDR, Article 61(1)
[12] MDR, Article 61(1)
[13] MDR, Article 61(1) and Annex III
[14] MDR, Annex XIV, Part A, section 3.

- **A new definition of clinical data** is provided, which requires for all kinds of clinical data (except data from clinical investigations of the device in question) the demonstration of the equivalence to the concerned device.[15]

When it comes to the first MDR conformity assessment of a legacy product it is not sensible to perform this as a pure MDR re-assessment of conformity as the starting point (initial conformity assessment under MDD) is different. Nevertheless, as requirements and guidance developed over time, it is not necessarily the case that the clinical data used for conformity assessment for the Directives is clinical data providing sufficient clinical evidence for the purpose of MDR requirements. Legacy products which have been placed on the market have been subjected to conformity assessment and therefore are presumed to have been supported by clinical data. Post-market data together with the clinical data generated during the initial conformity assessment under the MDD will be the basis of the clinical evaluation process for legacy products under the MDR.
Legacy devices are not exempted from requirements concerning PMS, including PMCF, and clinical evaluation which apply to legacy devices. PMS data and clinical evaluation reports therefore need to be produced and updated. The MDR compliant clinical evaluation for a legacy product must contain the identification of available clinical data as well as their appraisal / analysis / evaluation and shall lead to a demonstration of clinical evidence based on clinical data providing sufficient clinical evidence as part of a lifecycle approach.

MEDDEV 2.12/2 regarding PMCF notes different instances where a PMCF study may have been justified:[16]

- **Route chosen for clinical evaluation**: In the instance that CE marking was based upon equivalence, PMCF studies may have been necessary. The PMCF MEDDEV 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,[17] in accordance with the relevant provisions of the Directives.[18]
- **Device related factors**: There are a number of device related factors where PMCF studies may have been necessary.[19]

When assessing the conformity of legacy devices under the MDR, it is therefore important [make use of the data gathered etc.] to verify whether PMCF studies considered necessary under the MDD, and where applicable, during the transition period, under the MDR, have been appropriately conducted, and to consider their results.

Guidance on the general process of conducting clinical evaluation is also available in the Commission Guidance MEDDEV 2.7.1 Revision 4. Although this guidance was written with respect to the Medical Devices Directive 93/42/EEC, and for the purpose of the MDR, only the text of the Regulation is authentic in law, it contains practical guidance on several scientific and medical aspects that are relevant for conducting clinical evaluation. In particular, the a number of sections of MEDDEV 2.7/1 revision 4 are still relevant under the MDR. These are listed in Annex 1.

[15] MDR Article 2 para 48
[16] MEDDEV 2.12/2, section 5.
[17] MEDDEV 2.12/2, section 8.
[18] 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.
[19] MEDDEV 2.12/2, section 5.

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

4.1 Establish or Update a Clinical Evaluation Plan in accordance with Annex XIV of the MDR[20]

Annex 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 inputs for the clinical evaluation plan are in line with the device's *"label, instructions for use, promotional or sales materials or statements"*[21] and with the device's updated risk management documents. With respect to planning a clinical evaluation for a legacy device, a list of items to consider is listed in Annex II.

The level of clinical evidence required for the device under evaluation needs to be determined. The level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.[22]

The proposed level of 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. 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.[23]

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 clinical data providing sufficient clinical evidence at the end of the data analysis stage. It may be 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 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 is anticipated to have a clearly positive benefit–risk determination when alternatives are considered or a marginal one. Special consideration should be given to a device 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 of purposes of the device*" need to be based on the state of the art in medicine[24]. 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.

[20] MDR, Annex XIV, Part A, section 1.
[21] MRD, Article 2, section 12
[22] MDR, Article 61(1).
[23] MDR, Annex XIV, Part A, section 1 (a) 5th indent
[24] MDR, Annex XIV, Part A, section 1.

4.2 Identify available clinical data from the pre-market and post-market phase[25]

It is important to identify all available sources of data from both the pre 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 devices. Clinical data is defined in the MDR and the sources of data are specified.

For the purpose of legacy products, pre-market sources of 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;
- 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;[26]

Post-market sources of data may include:

- Post-market surveillance data, complaint and incident reports;
- Field safety notices or field safety corrective actions;
- PMCF studies, including post-market clinical investigations;
  device registries;
- Data retrieved from the literature.

In case of legacy products for all clinical data generated on other devices the equivalence must be demonstrated and it must be analysed if these data are clinical data according to the MDR.

It may be possible to demonstrate clinical data providing sufficient clinical evidence with reference to data other than that collected as part of a PMCF study, for example from independent clinical studies conducted using the device or from registries.

4.3 Appraisal

The data sets should be subject to an appraisal with respect to their relative contribution to the overall data set. Guidance can be found in section 9 and Annex A6 of MEDDEV 2.7/1 Revision 4. It is important to perform analysis of the methodological quality of data obtained from different sources to account for the level of evidence, bias, other inherent weakness or other possible shortcomings.

Clinical investigations[27] or post-market sources of data can be of variable methodological quality and therefore an appraisal of the design of these studies is important. The use of vigilance data, in general is appropriate for identification of any new risks, outcomes 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

[25] 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.

[26] It is important to note that data arising from sources other than pre-market clinical data, are in majority of cases uncontrolled and vulnerable to bias.

[27] [Take wording from ISO 14155 that clinical investigation / study / etc. Is synonomous]

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. The use of estimates such as [number of incidents] / [number of device sales] as proof of safety, should therefore be limited to cases where data from pre- or post-market clinical investigations or PMCF studies are not required.

However, 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 letter (c) of MEDDEV 2.7/1 rev. 4.

For devices which were not based exclusively on clinical data from the legacy product, it is necessary to demonstrate the equivalence with respect to the MDR requirements.[28]

PMCF studies which were conducted in compliance with MEDDEV 2.12/2 for these legacy devices would have examined the residual risk with respect to the equivalent device. In the event that a demonstration of equivalence is no longer possible under the definition of equivalence in the MDR, a new PMCF study may be necessary; in such a case this shall be planned, designed and performed as soon as possible, taking into account all clinical safety and/or performance issues which were identified as those requiring clinical follow-up at post-market stage.

4.4 Analysis

The aim of this stage is the determination if all clinical data collected and appraised, as described in previous stages, demonstrate together conformity with each general safety and performance requirements, relevant for the device in question. 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 revision 4.[29]

Demonstration of compliance with each general safety and performance requirements, relevant for the device in question have to be based on:

- the usage of reliable, justified and sound analysing methods (where applicable qualitative quantitative, or both)
- results of performed comprehensive analysis
- identification of any missing data and/or gaps
- determination of PMCF needs

<u>a. Clinical benefits</u>

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"*.[30] 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 Annex A7.2 letters b and c of MEDDEV 2.7/1 rev. 4.

[28] MDR, Annex XIV, Part A, section 3.

[29] This chapter includes references to the MDD, MDR requirements should be used instead.

[30] MDR, Article 2(53)

b. Risks

Risk means the combination of the probability of occurrence of harm and the severity of that harm.[31] In general, manufacturers are required to establish, document, implement and maintain a system for risk management.[32] The standard, ISO14971 provides such a process for managing risks associated with medical devices, as part of an ongoing, lifecycle approach. The Annex I requirements 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.[33]

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,[34] and the decision as to when it is necessary to generate further clinical data is not addressed by ISO14971 and should be an output of the process of clinical evaluation.

under the definition of equivalence in the MDR Aspects of risk evaluation and factors influencing the extent of risk(s) can be found in Annex A7.2 letter d of MEDDEV 2.7/1 rev. 4. Considerations on number of patients needed to obtain sufficient data on the device's safety can be found towards the point 4 of the Annex A7.

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

The MDR requests an evaluation of risks and benefits that is *"compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art"*[35] and benefit-risk determinations "*based on the state of the art in medicine*"[36]

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 - riskratio, it is necessary for legacy devices to consider up-to-date alternatives. 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' of the alternative. 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 due and diligent evaluation of the results from published clinical studies of high methodological quality shall be take into account. Moreover, where applicable, particular attention shall be paid to therapy guidelines grounded on principles of

[31] MDR, Article 2(23).
[32] MDR, Article 10(2).
[33] MDR, Annex I, Chapter 1, section 3(c).
[34] 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.
[35] MDR, Annex I, Chapter 1, Section 1
[36] MDR, Annex XIV, Part A, Section 1, Letter a

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 Appendix A7.2 letter e and Annex A7.4 of MEDDEV 2.7/1 rev. 4.

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

The MDR requires that the level of evidence is justified and specified by the manufacturer. The required level of evidence will have been identified by the manufacturer as part of clinical evaluation planning, and at the analysis stage, it is necessary to confirm that the level of evidence available to support the device is appropriate.

To reach a determination of sufficiency, when considering the available level of 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. Examples of these tools include the Cochrane Collaboration´s tool for RCT (randomized controlled trials) or NOS (Newcastle-Ottawa Scale) checklist for analytical studies.

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 evaluating results from PMCF studies such as scientifically sound questionnaires or registries etc.

If there is not sufficient supportive clinical data with regard to the declared intended purpose, manufacturers might narrow the intended purpose of the device until sufficient clinical data has also been generated to cover the entire formerly declared intended purpose of the device in question.

Annex I - Sections of MEDDEV 2.7/1 revision 4 which are still relevant under the MDR

- 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
- A10. Proposed checklist for the release of the clinical evaluation report

Annex II – Clinical Evaluation Plan for Legacy Devices

A modified Clinical Evaluation Plan for legacy products shall include at least:[37]

- an identification of the general safety and performance requirements that require support from relevant clinical data.
- a specification of the intended purpose of the device.[38]
- 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.
- 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 and the need to demonstrate equivalence.
- 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.[39] [40] [41]
- A strategy and methodology to systematically collect, summarise and assess post market surveillance data to demonstrate to what extent complaints with regards to safety and performance have been observed with the legacy product.

[37] Annex 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.

[38] 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 Annex A3 of MEDDEV 2.7/1 rev. 4.

[39] MDR, Article 61(1).

[40] The proposed level of 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.

[41] 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