CEPs: Parameters vs clinical outcome parameters, what's the difference?

Everyone involved in developing or reviewing clinical evaluation plans (CEPs) and clinical evaluation reports (CERs) for compliance with the Medical Device Regulation (MDR, EU 2017/745) will have an opinion on what is required and, often, opinions will differ. This is particularly true regarding the CEP requirement in MDR Annex XIV, Section 1(a), 6th indent and its reference to "parameters." This article will provide a view on how the requirement and its reference to "parameters" should be interpreted, based on the likely origin of the requirement.

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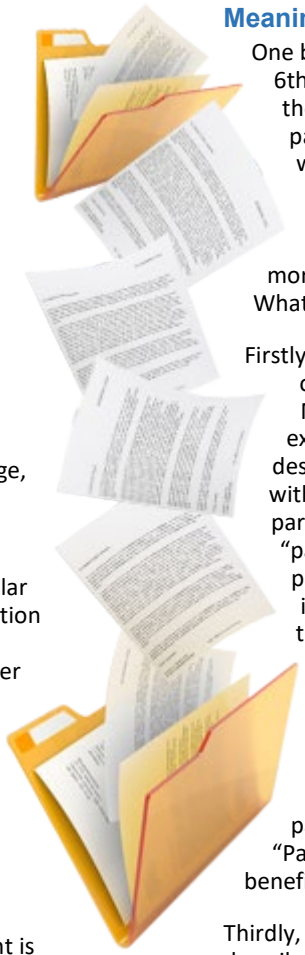
Clinical evaluation plan requirements

MDR Annex XIV, Section 1(a), requires that manufacturers establish and update a CEP and it lists the information that needs to be included in the CEP. In some cases, the required information is quite straightforward and there is little doubt how it should be interpreted. For example, the first indent in Section 1(a) requires the identification of the general safety and performance requirements (GSPRs) that require support from relevant clinical data. Another is the need to specify the intended purpose of the device. Other requirements are less clear and have led to differences in opinion regarding what they mean or how much information needs to be provided during the planning stage, namely in the CEP.

Indent concerning benefit-risk

This DLC Regulatory Recap concerns a particular various interpretation of MDR Annex XIV, Section 1(a), 6th indent, which concerns how the acceptability of benefit-risk of the device under evaluation will be assessed. This indent specifies that the CEP must include "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 accurate interpretation of this requirement is important because the acceptability of the benefit-risk ratio is a critical aspect of GSPR 1 (MDR Annex I, Sec 1), namely, "...any risks which may be associated with their [device] use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art."



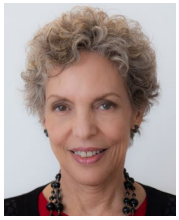
Meaning of "specification of parameters"?

One belief is that "specification of parameters" in the 6th indent of MDR Annex XIV, Section 1(a), refers to the need to specify only clinical outcome parameters (e.g. depth or rate of healing of a wound treatment device, degree of pain reduction in a device that claims this benefit, etc.). Instead, there are concrete reasons for interpreting "specification of parameters" in this section in a more general sense and more in line with "criteria." What are the reasons for these conclusions?

Firstly, where MDR requirements concern "clinical outcome parameters" this is specifically stated. MDR Annex XIV, Section 1(a), 4th indent states explicitly that the CEP must include "a detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters." If the MDR authors had intended "parameters" to mean "clinical outcome parameters" in MDR Annex XIV, Section 1(a), 6th indent, then they would surely have included these words here as well as in the 4th indent.

Secondly, MDR Annex XIV, Section 1(a), 6th indent concerns how the benefit-risk ratio for the device under evaluation is deemed to be acceptable. This evaluation should be much broader than considering only clinical outcome parameters. This concept is discussed below under "Parameters for evaluating the acceptability of the benefit-risk ratio."

Thirdly, a detailed process for evaluating benefit-risk is described in detail in MEDDEV 2.7/1 Rev 4, Clinical Evaluation: A Guide for Manufacturers and Notified Bodies Under Directives 93/42/EEC and 90/385/EEC. That is, MEDDEV 2.7/1 Rev 4, Appendix A7.2, Conformity assessment with the requirement on an acceptable benefit/risk profile (MDD ER1 / AIMDD ER1), lists a series of criteria, which can easily be considered as parameters for evaluating the acceptability of the benefit/risk profile, or as termed in the MDR, the "benefit-risk ratio."



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Parameters for evaluating the acceptability of the benefit-risk ratio

MEDDEV 2.7/1 Rev 4, Appendix A7.2 lists the types of evaluations and quantification recommended for determining conformity with benefit-risk ratio requirements, which are:

- Evaluation of the description of the intended purpose of the device
- Evaluation of the device's benefits to the patient
- Quantification of benefit(s) to the patients
- Evaluation of the clinical risks of devices
- Evaluation of acceptability of the benefit/risk profile

Each type of evaluation and quantification includes explanatory text, in some cases very detailed. For example, in evaluating the intended purpose of the device, evaluators (those persons performing the clinical evaluation) should evaluate if the description provided by the manufacturer correctly identifies those medical conditions and target groups in question. In evaluating the device's benefits, the nature, extent, probability, and duration of benefits should be considered, and one or more of these may constitute a positive impact on clinical outcome, quality of life, diagnostic accuracy, or other type of impact.

Regarding the quantification of benefits(s) to the patient, the guidance points out the importance of endpoints, the potential need to consider the probability of the patient experiencing one or more benefits, and the possible relevance of the duration of effects. As might be anticipated, the section on the evaluation of clinical risks is quite detailed and addresses the importance of identifying risks associated with the device, how such risks have been addressed, and the significance of residual risks. It also addresses post-market incident data on the nature, severity, number and rates of incidents and harmful incidents, identification of any clinical data identifying hazards not previously considered in risk management documentation, and other relevant risk-related information.

While MEDDEV 2.7/1 Rev 4 lists a series of evaluations and a discussion of quantification of benefits, information required to be provided in the CEP by MDR Annex XIV, Section 1(a), 6th indent, could be presented as parameters instead of evaluations. The following list provides possible examples of such parameters, but these would, of course depend on the device under evaluation:

- Intended purpose
- Nature of clinical benefits
- Clinical outcome parameters
- Results of clinical data generated
- Nature of residual risks identified in risk management documentation
- Information in the IFU (or User Manual) aimed at reducing the risk of use error and information on residual risks

What does "indicative" mean?

The requirement in MDR Annex XIV, Section 1(a), 6th indent refers to "an indicative list and specification of parameters..." So, how should "indicative" be interpreted? One can spend a significant amount of time on the definitions of "indicative" used as an adjective, namely, "indicative list."

A logical meaning of the word used in this context appears to be "suggestive of" (Oxford English Dictionary, https://www.oed.com/) given its use for a requirement concerning CER planning and not the actual CER itself. If this is an accurate interpretation, an "indicative list" would be one which exists at the planning point in time, but which may need to be modified in the CER. This means that the list as it appears in the CEP may differ, hopefully not significantly, from the one that appears in the CER.

What is acceptable, of course, will likely vary amongst those involved in judging the acceptability of this potential variation. In some cases, some evaluators may return to the CEP and modify it to correspond exactly with what is in the CER, which this author believes should be unnecessary, but will likely be done in some cases to avoid potential criticisms and deficiencies from notified bodies.

State of the art in medicine

MDR Annex XIV, Section 1(a), 6th indent, requires that the CEP includes 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. To what does "state of the art" apply?

One interpretation is that it applies to the acceptability of the benefit-risk ratio. This interpretation is supported by the text in GSPR 1, which requires that any risks associated with the use of devices must constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.

That is, a reference to the state of the art in MDR Annex XIV, Section 1(a), 6th indent, is consistent with GSPR 1 and can be understood to mean that the determination of acceptability of the benefit-risk ratio is made taking into consideration the information included in the state-of-the-art section developed during the clinical evaluation process.

Conclusions

It is likely that many readers will agree that certain requirements in the MDR are not easy to understand and are leading to differences in opinion regarding their meaning and subsequently variations in how best to demonstrate compliance. This article is an attempt to provide a logical interpretation to an important requirement.

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