The clinical development plan

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Abstract

The Medical Device Regulation (MDR) mentions the term "Clinical Development Plan" (CDP) only twice, both of which are in Annex XIV. This article aims to delve deeper than the MDR into what the CDP entails and to propose the best strategies for a manufacturer to plan their medical device's clinical evaluation.

Although there is no official definition of the CDP, one may simply refer to it as an overview of all the clinical investigations that have either been performed, are ongoing, or are planned in the near future, presented in the Clinical Evaluation Plan (CEP) of the medical device under evaluation.

This article is intended to assist medical device manufacturers and medical writers to leverage the CDP as a tool to showcase their clinical evaluation strategy and plan.

The Clinical Development Plan (CDP) as per the Medical Device Regulation (MDR)

The MDR provides a complete list of criteria to continuously conduct and document a clinical evaluation in Annex XIV,[1] where we get introduced to the term CDP for the first time as follows:

"To plan, continuously conduct and document a clinical evaluation, manufacturers shall establish and update a clinical evaluation plan, which should include (amongst other criteria):

- *a **clinical development plan** indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF [Post-Market Clinical Follow-up] as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria.*
- *generate, through properly designed clinical investigations in accordance with the **clinical development plan**, any new or additional clinical data necessary to address outstanding issues."*

The relationship between CDP and CEP

The CEP outlines the clinical strategy that the manufacturer shall follow to justify the safety and performance of their device in accordance with the General Safety and Performance Requirements (GSPR) of the MDR. The CDP is a subset of the CEP focusing specifically on the clinical investigations for the given device that:

a. Have already been conducted, preferably with a full clinical investigation report available
b. Are being conducted with a full clinical investigation protocol available, or
c. Are planned in the future – these could include pilot, pivotal, or PMCF studies. Preferably, the synopsis of this study should be included in the CDP in this case.

How to present the CDP in the CEP

Annex I of ISO 14155:2020 explains, in detail, the differences between pilot, pivotal, and PMCF clinical investigations and acts as an excellent reference for the CDP. (See the September 2021 issue of MEW for a flowchart of ISO 14155:2020, p. 96) .

As for the presentation itself, the CDP may be written in paragraphs or presented as a table. Questions to ask during the formulation of a CDP may include:

1. Based on the literature review results and the CE mark status of the device (i.e. pre-CE mark or already CE marked), what kind of clinical investigation (CI) are we looking at for the evaluated device? Is it a pilot/pivotal or post market clinical follow-up (PMCF) CI?
2. Has the possibility to do a statistically sound, non-randomized CI, instead of a randomised one, been explored? (Randomized studies are not always essential for regulatory approval of medical devices depending on the specific case, type and class of device. It should however be ISO 14155:2020 compliant irrespective of study design).
3. Have we outlined the inclusion/exclusion criteria in the CDP of our CIs?
4. What were the endpoints/acceptance criteria of our previous clinical investigations? Has it been clearly presented in the CDP? Based on the results of that study, do we want to test something new or gather more robust information on safety? In which case, the study design for the upcoming CI may include these new parameters as the primary and/or secondary endpoints.
5. Is this study design in line with our regulatory strategy and business plan for market access?
6. Might we gain a high-quality publication out of this CI?
7. Do we plan to perform "off-label use" clinical investigations to expand the indications of the evaluated medical device? If so, then this may be included as part of the CDP as well.

MDCG document references for the CDP writing

A. The Medical Devices Coordination Group (MDCG) Document – *MDCG 2020-13 – Clinical evaluation assessment report template* – helps outline what the notified bodies are looking for whilst reviewing the Clinical Evaluation documentation. Regarding the CDP/Strategy, the document states that the notified body should ensure that the CDP is outlined as per Part B of MDR Annex XIV. Interestingly, the document outlines that "*A detailed description of the clinical development plan is not required for the purpose of this template unless there are specific concerns*", which may be interpreted that the notified bodies are not obliged to scrutinise the nitty-gritty details of the CDP at this stage of review unless something is inherently questionable in the clinical development strategy. Hence, one may assume that a well-presented CDP in the CEP is sufficient for the notified body review.

The document also states, notably with regards to the clinical development strategy:

"Section K: The voluntary clinical consultation on the clinical development strategy (Article 61(2))

1. *Expert Panel consultation reference*
2. *Expert Panel recommendations:*

- *Have the views of the Expert Panel been given due consideration by the manufacturer?*
- *Has this been included in the clinical evaluation report?*
- *Is there any divergence between the manufacturers' clinical development strategy and the views of the expert panel? If yes – what is the justification for this?*
- *Is this acceptable? Explain why.*

B. Another MDCG guidance document titled *The MDCG Guidance on Clinical Evaluation (MDR)/Performance Evaluation (IVDR) of Medical Device Software (MDSW)*, published in March 2020, also mentions the CDP twice. The first reference is to quote Annex XIV of the MDR, and the second mention is regarding the continuous update of the clinical evaluation, which mentions the following:

"The safety, effectiveness, and performance of the MDSW should be actively and continuously monitored by the manufacturer.

Such data may include, but is not limited to, post-market information such as complaints, PMCF/PMPF data, real-world performance data, direct end-user feedback or newly published research / guidelines and should be subject to the clinical evaluation (MDR) / performance evaluation (IVDR) principles. The unique level of connectivity of MDSW facilitates access to Real-World Performance data, which can be used for multiple purposes, including, but not limited to:

- *timely detection and correction of malfunctions;*
- *detection of systematic misuse;*
- *understanding user interactions;*
- *conducting ongoing monitoring of clinical performance;*
- *improving effectiveness;*
- *developing the claims in the clinical development plan (MDR) or future releases".*

Although the above MDCG guidance document is meant for medical device software, it focuses our attention on how the real-world data may be leveraged to develop the claims in the CDP. This is an important consideration as performance and safety claims are seldom well thought out at the clinical evaluation stage by some manufacturers. By using the data gathered from the clinical investigations as well as during post-marketing surveillance (PMS), the manufacturer may revisit the safety and performance claims and take these considerations for their CDP and designing of upcoming clinical investigations.

Conclusion

The CDP is an effective tool that could facilitate manufacturers to demonstrate the extent of the clinical evaluation planning for their medical devices. It summarises the clinical investigations that are either planned, ongoing or already performed, based on the risk class and CE mark status of the device. The addition of this section to the CEP helps reinforce and demonstrate the regulatory and clinical strategy where standards such as ISO 14155:2020 and MDCG guidance documents further act as supportive references to ensure appropriate methodology and wording.

The role of a medical writer to create such a section is of particular importance as they not only foresee the entirety of the clinical evaluation at the very early stages of the clinical evaluation planning but also offer early support to the Regulatory, Marketing, R&D and Clinical departments to harmonise their language and facilitate the overall goal of achieving regulatory approval for the medical device. This unique, in-depth, and bird's-eye view of a complex clinical evaluation process is a stronghold of the medical writer and should be leveraged by manufacturers to ensure high-quality deliverables.

Overall, through a well-presented CDP, the manufacturer may demonstrate, early on in their clinical evaluation process, the safety and performance claims for their medical device with a strategy on how the clinical evidence shall be gathered to justify these claims. Therefore, despite the sparse mention of the term "Clinical Development Plan" in the MDR, one may appreciate the hidden importance of such a tool to enhance the quality of their technical and regulatory documentation.

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Disclosures and conflicts of interest

The author declares no conflicts of interest.

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1. Medical Device Regulation (MDR) 2017/745 [cited 2022 Apr 07]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745

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