A METHODOLOGICAL APPROACH FOR THE DESIGN OF A UNIQUE POST MARKET CLINICAL FOLLOW-UP STUDY FOR STANDARD AND CUSTOM-MADE DEVICES ACCORDING TO EU MEDICAL DEVICE REGULATION 2017/745

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Introduction

The new European Medical Device Regulation 2017/745 (MDR) has set higher standards of evidence, demanding rigorous clinical evidence and continuous post-market surveillance, especially for high-risk devices. This implies the requirement for manufacturers to actively collect additional post-market clinical data throughout the life cycle of the device concerned, in order to submit regular assessments of device performance and safety through Post-Market Clinical Follow-up (PMCF) studies.[1]

PMCF studies become a valuable means to gather real-word data on the performance and safety of devices for which there might have been limitations in the clinical data available in pre-market phase.
For high-risk and custom-made devices (CMDs), it often occurs that limited evidence is available at marketing authorization, since they are highly personalized technologies. Therefore, collecting real-world long-term outcomes is essential to better describe their clinical outcomes and ensure the continued acceptability of the benefit-risk profile.

The aim of this poster is to report the methodological framework used for designing a unique PMCF study compliant with the EU Medical Device Regulation 2017/745 (MDR) to collect evidence on two different medical devices already marketed: a standard and a custom-made Thoracic Stent Graft systems.

Methods

To fulfill the notified body (NB) request, a PMCF study was evaluated as the best approach to collect long-term and short-term clinical information for the standard and custom-made device, respectively. The PMCF study was designed to describe clinical outcomes in terms of performance and safety of the two devices, measuring survival rate and treatment success, as well as occurrence of safety events and lesion changes.

Three methodological steps reported in *Figure 1* were followed to design a PMCF protocol consistent with the new European Regulation:

1. Regulatory framework was based on the analysis of EU MDR 2017/745 and guidance documents developed by the Medical Devices Coordination Group (MDCG), with a focus on requirements for class III and custom-made devices. The main findings of this in-depth analysis are reported in *Table 1*.
2. A pragmatic literature review was conducted to identify published experience regarding the management and designing of PMCF study protocols, with a focus on CMDs. The bibliographic research was conducted using the following combination of keywords *(((custom made device* [Title/Abstract])* OR *(designing [Title/Abstract])* OR *(post-market clinical follow up [Title/Abstract]))* AND *((medical device regulation [Title/Abstract])))*, and considering articles published between 2017 and 2021. Six articles were retrieved, and only one was selected based on the purpose of our analysis, as the others focused on stakeholders and therapeutic areas out of our scope. The main findings of the review are reported in *Table 2*.
3. The main findings of the research and the considerable team expertise in study design and epidemiology led to the draft of an MDR-compliant and risk-appropriate PMCF study protocol, additionally reviewed by clinician with scientific expertise in cardiovascular therapeutic area.

Results

To respond to the NB's request, a retro-prospective cohort PMCF observational study was designed to describe clinical performance and safety for two devices, a standard device and a custom-made device. Additional long-term evidence was needed for the standard device and additional short-term evidence was needed for the custom-made device.

The primary objective of the study is to describe overall and cause-specific survival rate after implantation procedure of devices in the two cohorts. The secondary objectives aim to describe the occurrence of safety events, including serious and device-specific events, and the success of the device implantation procedure, including changes in the original lesion and risk of other surgical procedures.

The PMCF study aimed to enroll two cohorts of patients (alive or dead) in 30 sites located in Italy. Eighty patients implanted with a standard device will be followed for 5 years after index date *(Cohort A)* and fifty patients with a custom-made device for 1 year after index date *(Cohort B)*. The date of device implantation is defined as "index date"; an enrollment visit must be performed after the implantation *(Figure 2)*. Before starting data collection, investigators must give the patients oral and written information about the study in an understandable way in order to obtain patient written consent.

The assessment time-points have been defined in agreement with the follow-up schedule, as set by current clinical practice. For Cohort A: at hospital discharge, 6, 12, 24, 48 and 60 months after index date, and for Cohort B: at hospital discharge, 6 and 12 months after index date *(Figure 2)*.

Source data are medical records usually collected during routine clinical practice. All data required for the study are entered into an electronic case report form (eCRF) by investigators and/or delegated members of the site staff.

Data analysis will be performed separately for the 2 cohorts. Interim analyses are foreseen on annual basis to provide pertinent results to inform the NB.

Figure 1. ***Scheme of the study framework***

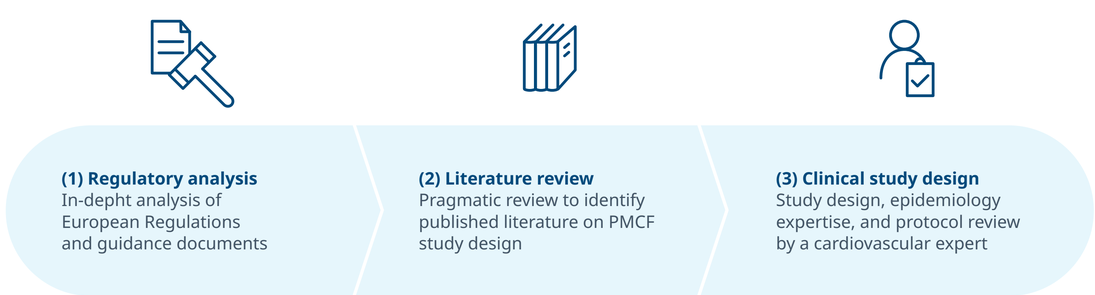


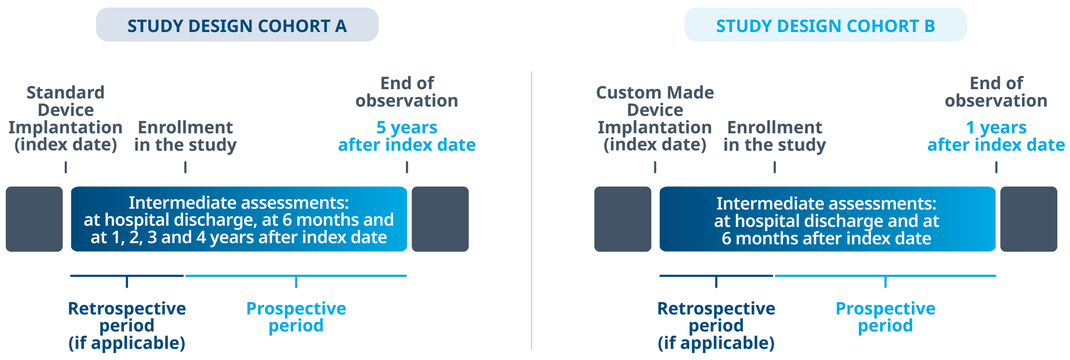
Table 1. ***Main findings of regulatory analysis***

REGULATORY FRAMEWORKS			
SOURCE	**PARAGRAPH**	**CONTENT**	**REQUIREMENTS**
MDR 2017/745[1]			
	Article 10	**General obligations of manufacturers**	• Manufacturers shall conduct a clinical evaluation in accordance with the requirements set out in the EU MDR 2017/745, including a PMCF that should be proportionate to risk class and type of the device in question
	Article 61	**Clinical evaluation**	• For implantable devices and class III devices, the notified body shall check that the PMCF plan is appropriate and includes post market studies to **confirm safety and performance of the device** • For class III devices and implantable devices, the PMCF evaluation report shall be **updated at least annually**
	Annex XIII	**Procedure for custom-made devices**	• Manufacturers shall review and document all experience gained in post-market phases in order to update their technical documentation and cooperate with national authorities • The gathering of post-market information shall include PMCF, comments from users and examination of literature or other **sources of clinical data**
	Annex XIV – Part B	**Post-Market Clinical Follow-up**	• PMCF must be intended as a **continuous process with the aim of updating clinical evaluation** of a CMD; when conducting a PMCF, manufacturers shall collect and evaluate clinical data resulting from the use of the device in real clinical settings • Manufacturers shall draw up a PMCF plan to document and specify methods and procedures followed to perform the PMCF process • Manufacturers shall analyze the findings of PMCF and document the results in a PMCF evaluation report
		Good clinical practice for clinical investigations of medical devices	• **Clinical investigations of medical devices** should be performed in line with international guidance such as the **international standard** UNI EN ISO 14155:2020 (3rd edition)[2], focusing on protection of study participants, appropriateness of scientific methods, and responsibilities of stakeholders involved (e.g., manufacturer, investigators)
MDCG			
	MDCG 2021-3[3]	**Questions and Answers on Custom-Made Devices**	• By implementing a PMCF study, manufacturers should **focus on demonstrating the clinical performance and safety of the CMD** related to its intended medical purpose in a real-world setting • To effectively perform a PMCF study, liaison with the person responsible for the written prescription is required, in addition to an **appropriate communication with healthcare professionals**, in order to collect feedback on clinical performance and safety of the device
	MDCG 2020-7[4]	**Post-market clinical follow-up (PMCF) Plan Template: A guide for manufacturers and notified bodies**	• The coordination group provides a template as a guide for writing down a PMCF plan, to ensure a harmonized and complete presentation of post market clinical data, and to facilitate the competent authorities in finding information

Table 2. ***Main findings of literature review***

PUBLISHED LITERATURE		
TITLE/ARTICLE	**CONTENT**	**KEY FINDINGS**
IDEAL as a guide to designing clinical device studies consistent with the new European Medical Device Regulation[5]	**New EU MDR Framework**	• EU MDR 2017/745 requires an explicit plan for post-market clinical studies and surveillance, this applies to all device risk classes, but more detailed surveillance is expected for high-risk devices • Manufacturers shall submit regular assessments of device performance through Post-Market Clinical Follow-up reports (PMCF) and Periodic Safety Update Reports (PSUR) • The preferred design of PMCF studies is not specified, but they shall include a **detailed description of patient selection, patient and disease characteristics and specify patient subgroups**

Figure 2. ***Scheme of the study for subjects in Cohort A and Cohort B***



Conclusions

In the current regulatory context, which requires rigorous and continuous evidence generation throughout the entire life cycle of devices, PMCF studies can be powerful tools to collect post-market real-world data on clinical performance and safety. Despite the improvement of the regulatory environment and boost of guidance documents, the Regulation does not provide any specification of which approach may be the most appropriate in providing the required evidence and manufacturers have to face a major challenge in planning effective post-market studies. Moreover, there is a lack of published experience in literature on the design of PMCF studies, especially in the context of CMDs. Therefore, for this kind of devices, designing a PMCF protocol becomes even more complex, being personalized and high-risk technologies, with limited number of eligible patients.
Under these circumstances, this analysis aims to provide a practical experience in adopting a well-developed framework for designing effective and MDR-compliant PMCF study protocols that could help in reducing uncertainties regarding safety and performance of medical devices. This may result in a valuable contribution to patients' experience and technology innovation.

REFERENCES

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5. Fleetcroft C., McCulloch P., Campbell B. *IDEAL as a guide to designing clinical device studies consistent with the new European Medical Device Regulation.* BMJ Surg Interv Health Technol. 2021

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