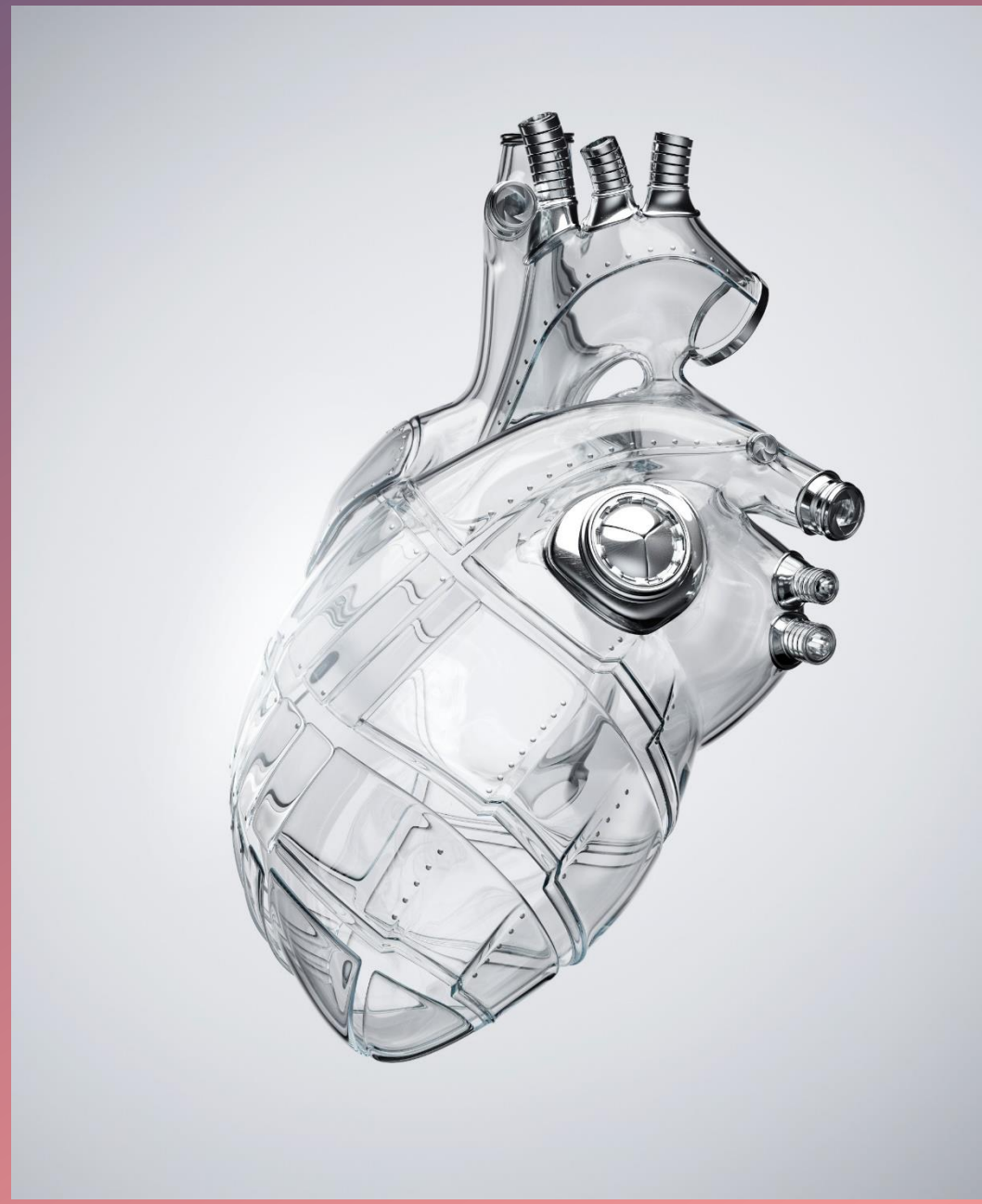
Preparing a Post Market Clinical Follow Up Plan and Evaluation Report

BSI Clinical Masterclass 2023
Session 4

22 February 2023



Where are we in the Clinical Masterclass series?

5 sessions focusing on the best practice for detailing your key clinical evaluation documents including:

- ~~The Clinical Evaluation Plan~~
- ~~The Clinical Evaluation Report~~
- **The Post Market Clinical Follow Up Plan**
- **The Post Market Clinical Follow Up Evaluation Report**
- The Summary of Safety and Clinical Performance

All sessions are recorded!

At the end of these sessions, we will be providing you with a specific best practice guide for documenting your clinical evaluation.

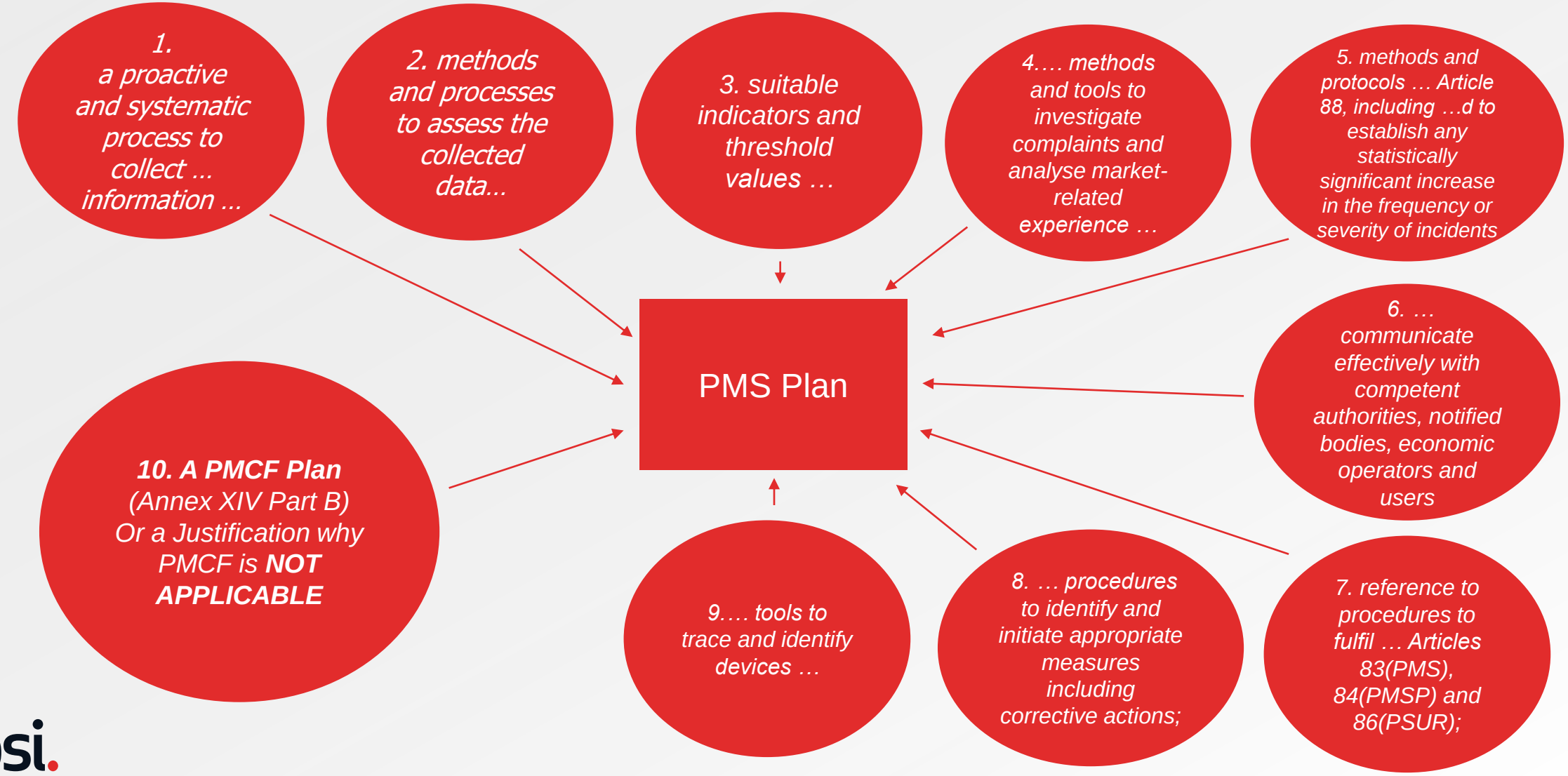
Topics covered in this Session on Post Market Clinical Follow-up:

- The PMS Plan
- What is PMCF?
- The PMCF Plan
- PMCF Study Design
- PMCF Evaluation report
- Questions!

The PMS Plan

The PMS Plan - Requirements

MDR Annex III 1(b) ***The post-market surveillance plan shall cover at least:***



What do Notified Bodies look for in a PMS Plan?

In General:

- Demonstration of meeting each of the MDR requirements.
- Clear description / summary of the methods to be implemented.
- Demonstration and justifications of adequacy of methods and thresholds implemented, considering device type and risk.
- References to the documentation (procedures and work instructions) where methods are implemented.

In Particular:

- Proper description and justification of methods to : collect and investigate complaints, analyse data and detect statistical trends, identify and report vigilance, and initiate corrective actions.
- Reference to the Vigilance Procedures, Identification, Evaluation and Reporting of Vigilance. *
- Clear reference to a **PMCF plan**, or a clear justification why a PMCF plan is NOT APPLICABLE

* MDCG 2023-3 - Questions and Answers on vigilance terms and concepts as outlined in the Regulation (EU) 2017/745 on medical devices.

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What is PMCF?

What is Post Market Clinical Follow-up (PMCF)

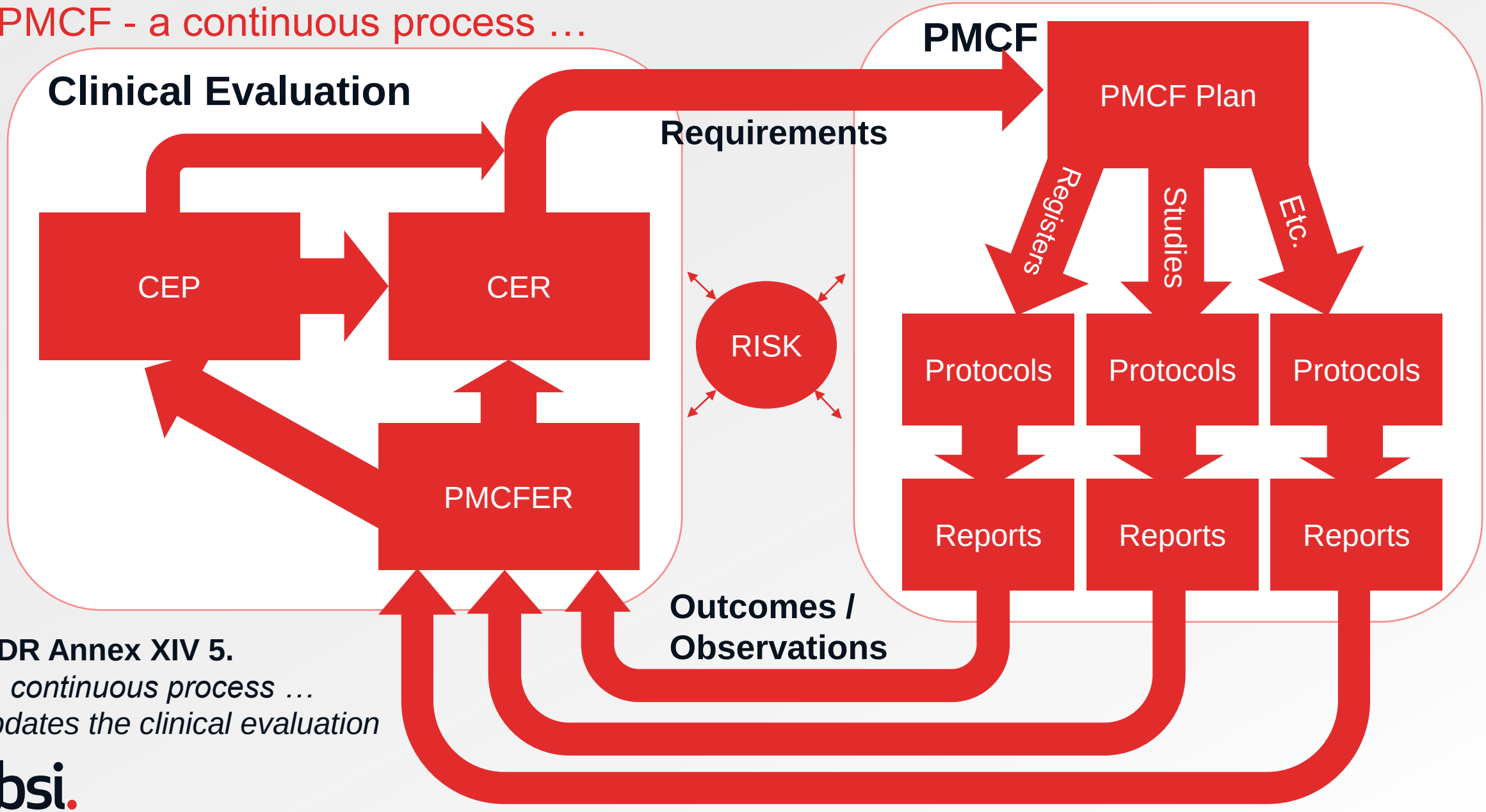
What it is:

MDR Annex XIV 5. : "***PMCF*** *…* ***continuous process*** *that updates the clinical evaluation … When conducting PMCF, …* ***proactively*** *collect and evaluate clinical data from the use in or on humans of a device …* ***put into service within its intended purpose*** *… with the aim of* ***confirming the safety and performance throughout the expected lifetime*** *of the device, of* ***ensuring the continued acceptability of identified risks*** *and of* ***detecting emerging risks*** *on the basis of factual evidence."*

What it is not:

- **A substitute for "sufficient clinical evidence"** prior to certification. Ref Article 61 1.: *"Confirmation of conformity … **shall be based on clinical data providing sufficient clinical evidence** …"*
- **A way to study off label use.** The MDR defines PMCF as on a device "***put into service within its intended purpose"*** (MDR Annex XIV 5.)

PMCF - a continuous process …



MDR Annex XIV 5.

… continuous process …
updates the clinical evaluation

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The PMCF Plan

The PMCF Plan – MDR Requirements

Equivalence:

Equivalence (MDR Article 61 4.) *In the case of implantable devices and class III devices, clinical investigations shall be performed, except if :*

… (the notified body shall check that) the PMCF plan is appropriate and ***includes post market studies to demonstrate the safety and performance of the device.***

Stated Requirements:

PMCF Plan MDR Annex XIV 6.1:

(a) confirming the safety and performance of the device throughout its expected lifetime,

(b) identifying previously unknown side-effects and monitoring the identified side-effects and contraindications,

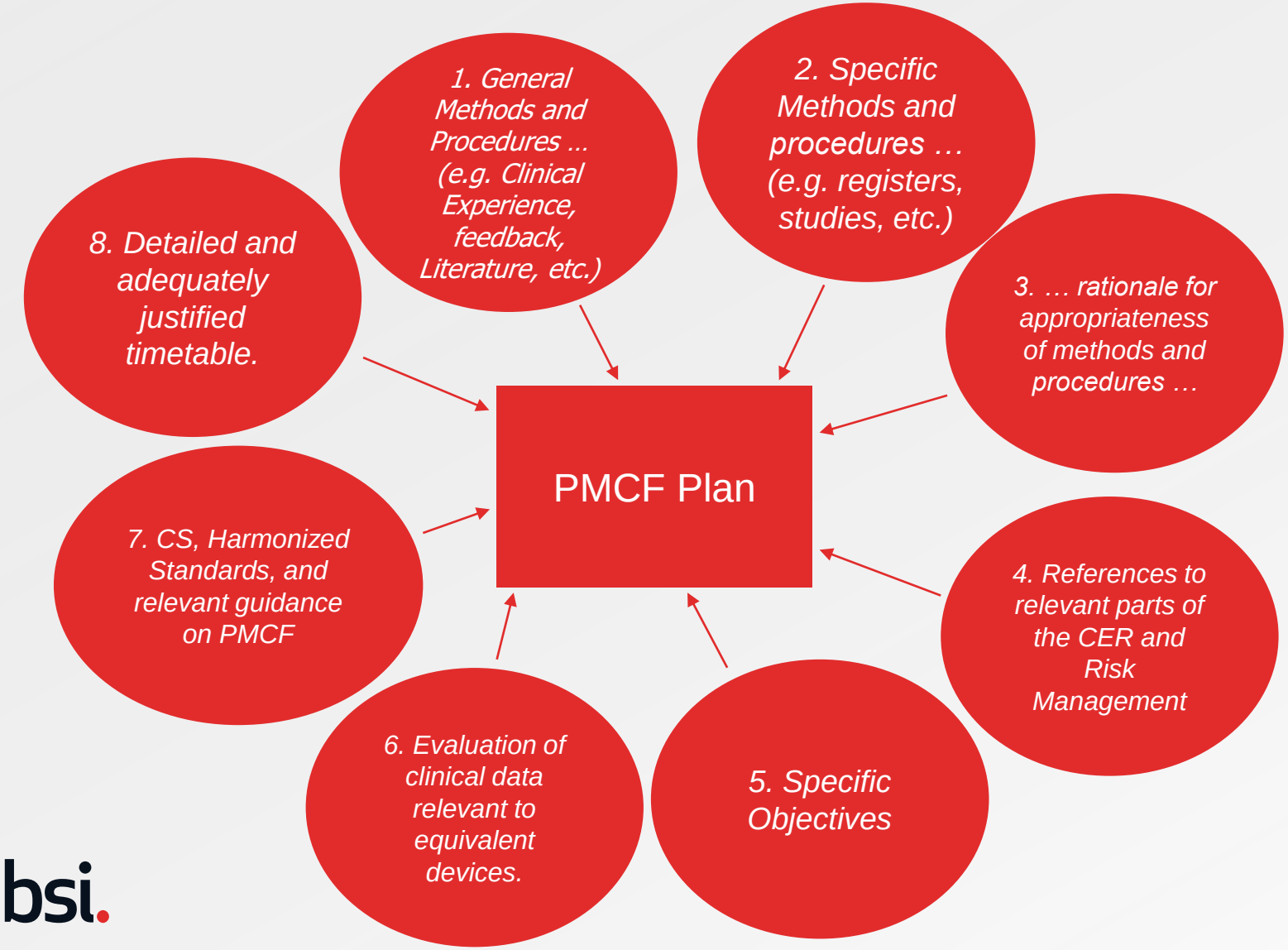
(c) identifying and analysing emergent risks on the basis of factual evidence,

(d) ensuring the continued acceptability of the benefit-risk ratio referred to in Sections 1 and 9 of Annex I, and

(e) identifying possible systematic misuse or off-label use of the device, with a view to verifying that the intended purpose is correct.

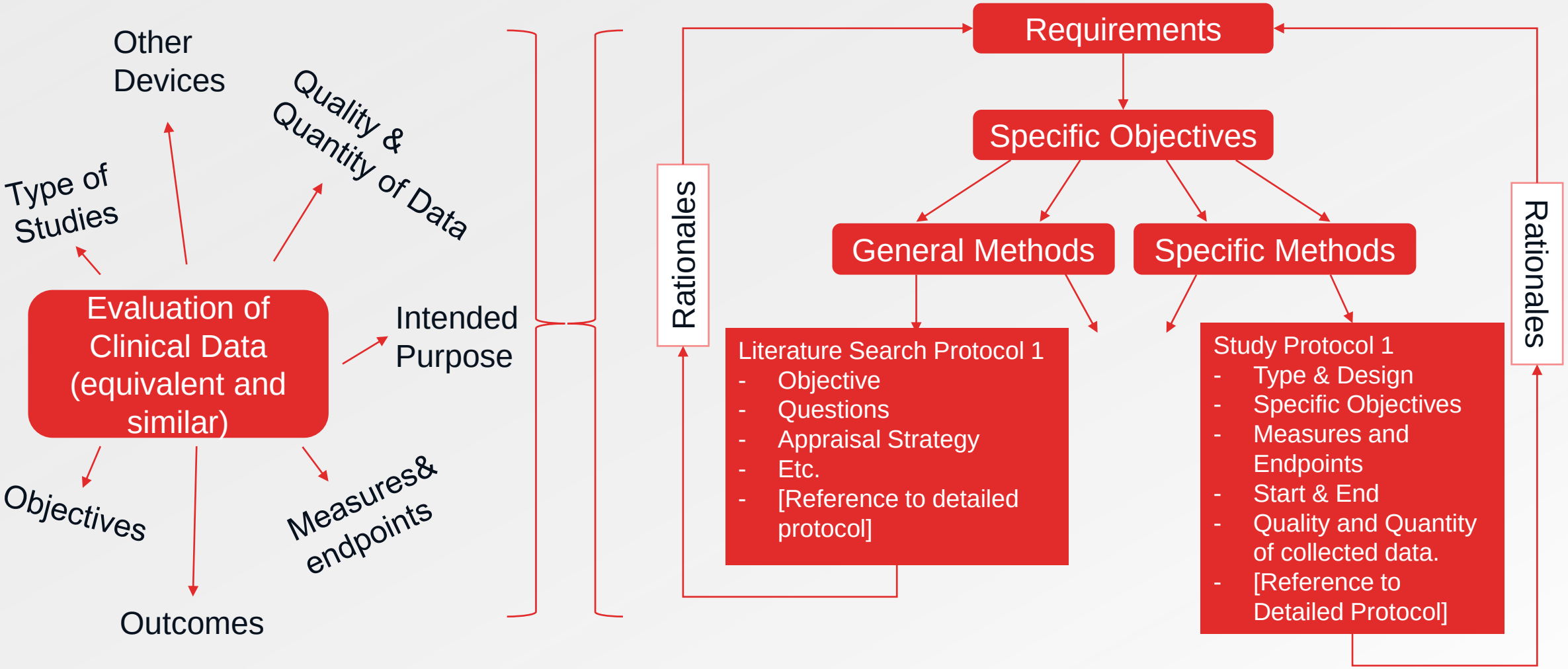
The PMCF Plan – Elements

MDR Annex XIV *6.2. The PMCF plan shall include at least :*



PMCF plan will be implemented via a series of detailed protocols designed to implement methods and satisfy requirements

PMCF – Creating a good plan



Follow the template in MDCG 2020-7!

PMCF Plan – NB Expectations

The Notified Body will look for:

- Any gaps or differences noted during equivalence explicitly addressed with appropriate studies of sufficient quality and quantity (Class III and implantable).
- Clear plans to address each individual requirement in Annex XIV 6.1, in particular…
- Studies of sufficient quality and quantity to confirm safety and performance over device lifetime.
- Methods of sufficient quality and quantity to evaluate the “real world” use of device and associated side-effects, emergent risks, and systemic misuse, off label use, etc.
- Studies aimed at continued generation of clinical data to match the type, quality, and quantity available on the state of the art.
- Use of measures, endpoints, etc. to facilitate direct comparison of the subject device with the state of the art.
- Or clear justifications why any requirement is already sufficiently satisfied to not merit PMCF

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POLL: Can PMCF data be used to extend Intended Purpose?

Q: A manufacturer asks: During PMCF studies performed on our device, a substantial quantity of data was collected on the safety and performance of “off label” use. Can this data be used to extend the Intended Purpose of the device?

A: Of Course: All clinical data is good clinical data.

B: Likely: Because controls were implemented during collection, it is reasonably likely that a substantial quantity of data may be acceptable.

C: Unlikely: Because the studies were not designed to examine off label use, it is unlikely that the quality of clinical data will be sufficient.

D: No: Regrettably the MDR forbids data collected through PMCF to be used to examine Off Label use.

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POLL: Can PMCF data be used to extend Intended Purpose?

C: Unlikely

The MDR does not explicitly ban using clinical data collected via PMCF to support off label use, in fact all clinical data must be considered within the CER.

However it is unlikely to meet the quality expected in an application to extend the intended purpose of the device.

Ref TEAM-NB position paper on “Off-Label” use : “*Off-label data typically does not have ‘sufficiency’. Whilst it may hold sufficient quantity, … , it however will often fail to have sufficient quality in terms or meaningful conclusions*.”

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PMCF, and misuse or “Off Label” use

Where systematic misuse or off label use is identified the manufacturer is expected to **perform an appropriate analysis, and determine an appropriate course of action**.

When detected, actions should include:

- Identification as to the root causes of the misuse or off-label use
- Evaluations whether the risks related to misuse or off-label use have been minimized As Far As Possible (including the presence of appropriate contraindications, warnings and precautions against off label use) and if appropriate, field actions to reinforce the currently approved intended purpose and minimise misuse.
- Evaluations whether there is a genuine need and if appropriate, plans to examine and extend the intended use via a formal study. Note: “***Where a clinical investigation is to be conducted to assess, outside the scope of its intended purpose… Articles 62 to 81 shall apply***.” (MDR Article 74 2.)

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PMCF Plan – Tips on writing the plan

DO:

- Follow the Template provided in MDCG 2020-7.
- Provide sufficient information to understand HOW requirements are met by PMCF activities.
- Provide references to the protocols that implement these activities.
- Provide justifications WHY proposed PMCF will collect clinical data of sufficient quality and quantity
- Provide justified timelines for data collection and analysis.
- Keep it up to date and inform your notified body when substantial changes in the plan occur (since the plan was part of the condition of certification)

DON'T:

- Just repeat requirements or guidance without clearly addressing them.
- Make generic statements with no justification

PMCF Study Design

PMCF Study requirements: where are they defined?

Medical Devices Regulation:

- Chapter VI: Clinical Evaluation and Clinical Investigations
- Annex XIV (Part B): Post Market Clinical Follow Up
- Annex XV (Article 74)
- Annex IX: Conformity Assessment

Guidance documents:

- MedDev 2.12/2 rev. 2 – PMCF Studies: A Guide for Manufacturers and Notified Bodies
- MedDev 2.7.1 rev.4 - Clinical Evaluation: A Guide For Manufacturers And Notified Bodies
- MDCG 2021-6 – Q & A on Clinical Investigations

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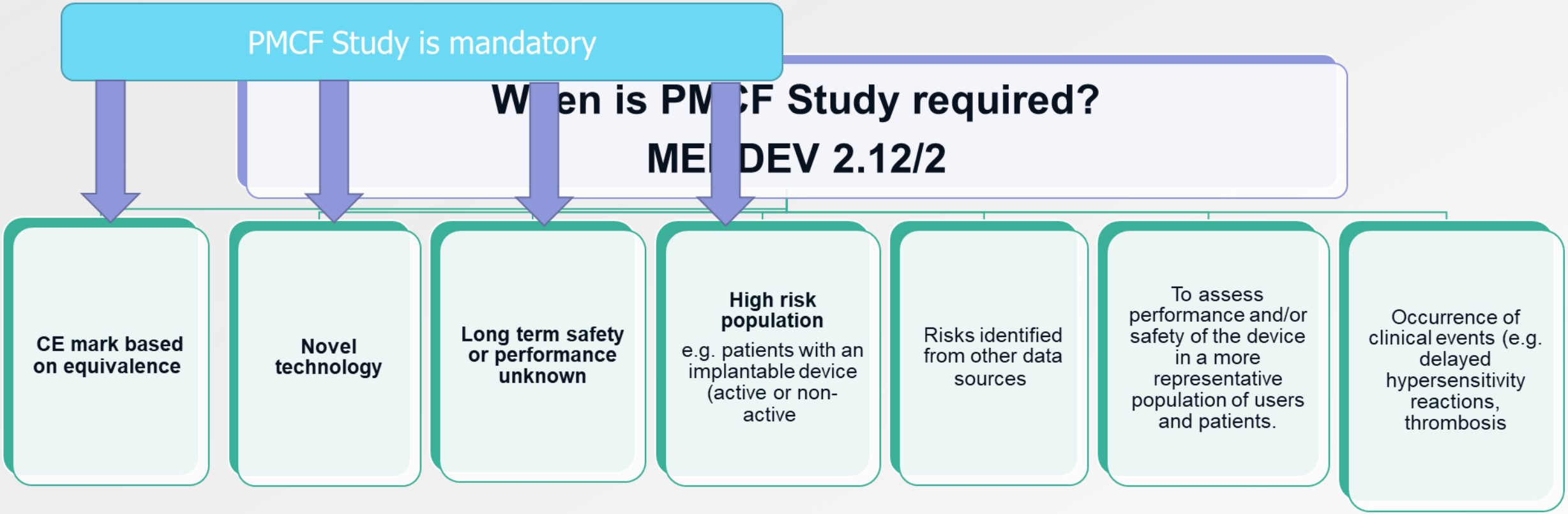
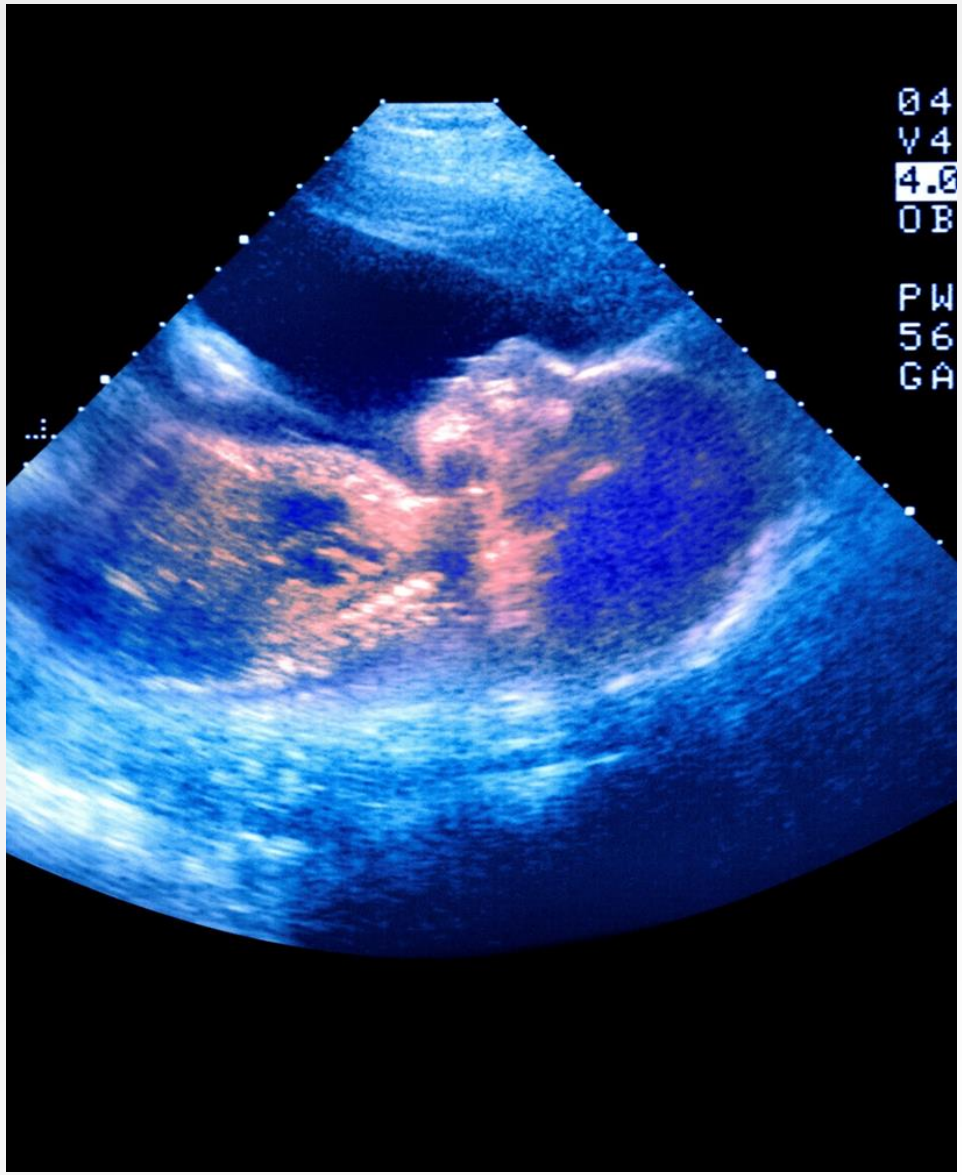


*Following a proper pre-market clinical evaluation, the **decision to conduct PMCF** studies must be based on the identification of **possible residual risks** and/or **unclarity on long term clinical performance** that may impact the benefit/risk ratio.*

Source: MEDDEV 2.12.2 rev2

Things to think about…

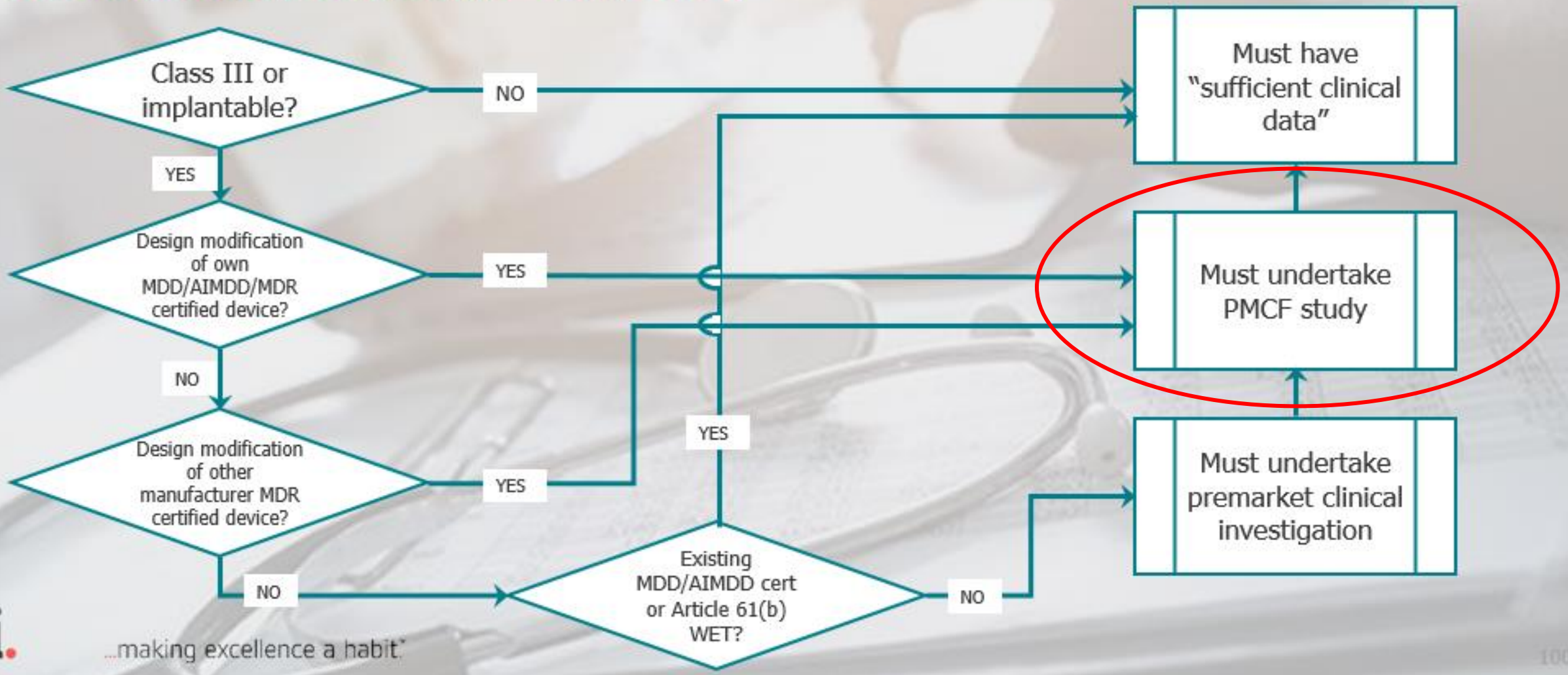
- What clinical data is PMCF seeking to generate?
- What is driving the need for the PMCF?
- What makes a good PMCF study?
- What is the state of the art and how will my PMCF study generate clinical data which can be used to compare safety and performance of my device to the state of the art?
- Does the PMCF Plan outline specific activities to answer specific questions – if so where is the more detailed documentation which supports the activity e.g. PMCF Study plan



MDCG 2020-6: "Sufficient clinical evidence" for legacy devices

Purpose of the guidance document

MDR clinical evidence requirements - Article 61(4-6)



MEDDEV 2.12/2 rev2

PMCF studies must be outlined as a well designed clinical investigation plan or study plan, and, as appropriate, include:

- *clearly stated research question(s), objective(s) and related endpoints;*
- *scientifically sound design with an appropriate rationale and statistical analysis plan;*
- *a plan for conduct according to the appropriate standard(s);*
- *a plan for an analysis of the data and for drawing appropriate conclusion(s).*


Ref. Ares(2015)2066706 - 18/05/2015

EUROPEAN COMMISSION
DIRECTORATE GENERAL for HEALTH and CONSUMERS
Consumer Affairs
Health technology and Cosmetics

MEDDEV 2.12/2 rev2

January 2012

GUIDELINES ON MEDICAL DEVICES

POST MARKET CLINICAL FOLLOW-UP STUDIES

A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

PMCF Study Plan, key elements:

Study population defined

Inclusion/exclusion criteria

Rationale and justification of the chosen study design

Quality control of data

Site selection and investigators

Ethical considerations

Objectives and related study endpoints

Procedures/criteria for early study termination

Number of subjects

Analysis plan

Data to be collected

Duration of follow-up

*source: MEDDEV 2.12/2 rev2

Poll question

Which of the following are considered invasive and/or burdensome?

A) Quality of life telephone survey follow-up in addition to routine appointments.

B) Subjects are required to undergo CT Scans as part of PMCF study data collection.

C) Running additional blood testing on a blood sample taken as part of routine follow-up.

D) All of the above

Poll answer

What is considered invasive and/or burdensome?

A) Quality of life telephone survey follow-up in addition to routine appointments.

B) Subjects are required to undergo CT Scans as part of PMCF study data collection.

C) Running additional blood testing on a blood sample taken as part of routine follow-up.

D) All of the above

It depends!

Invasive and burdensome…

- Where possible invasive and burdensome procedures should be avoided.
- If in doubt whether additional procedures performed within the context of a PMCF study are invasive or burdensome – member state opinion should be sought.
- Per MDR article 82, investigations not considered invasive and burdensome may still be required to follow national provisions according to the member state in which the clinical investigation is taking place and national authority notification/public registration may be required.
- Examples of burdensome procedures: those which may cause pain, discomfort, fear, potential risks or complications/side-effects, disturbances of lives and personal activities or otherwise unpleasant experiences.
- Examples of invasive procedures include (but are not limited to): penetration inside the body through the surface of the body, including through mucous membranes of body orifices, or penetration of a body cavity via a body orifice.

*Information source: MDCG 2021-6

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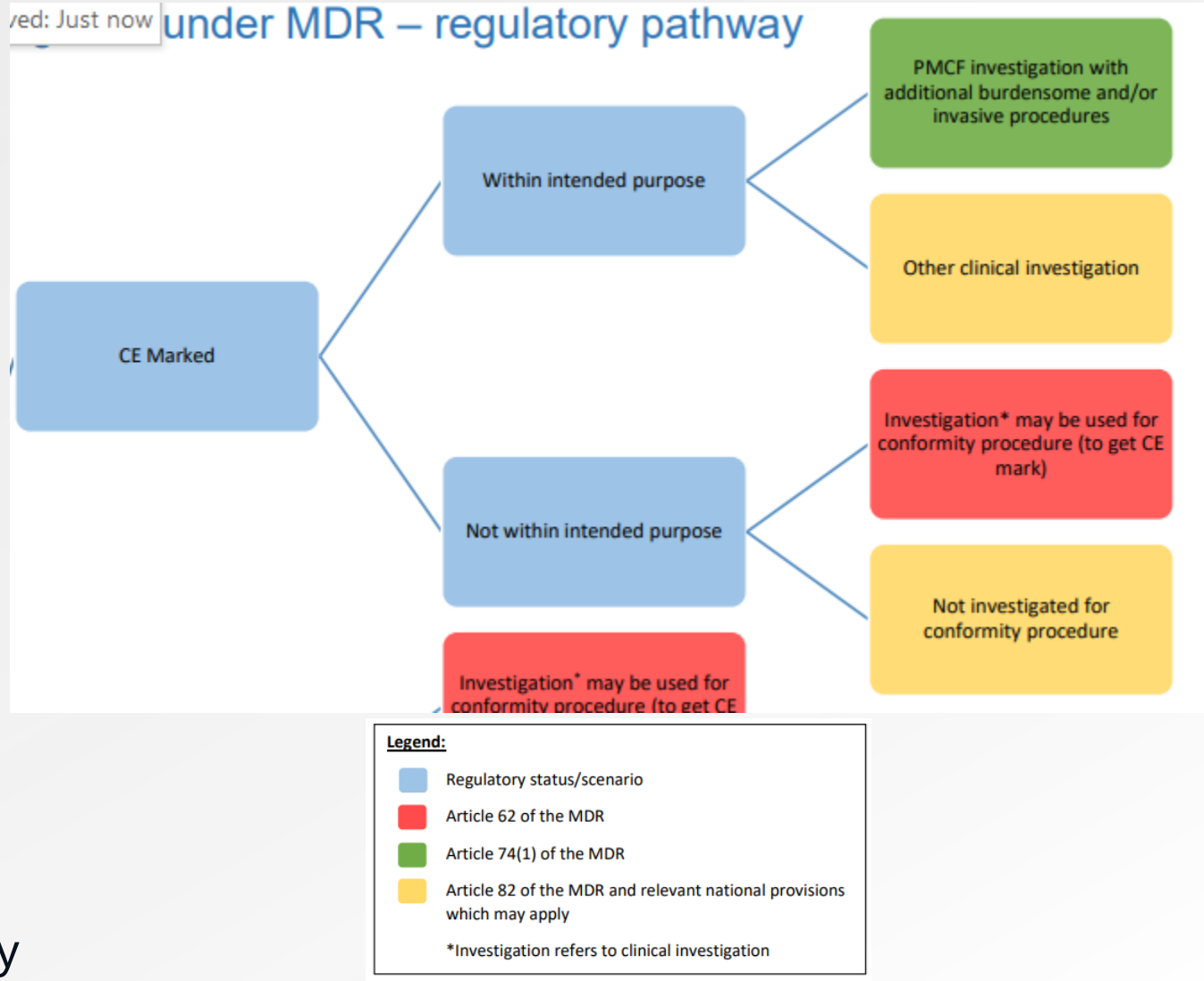
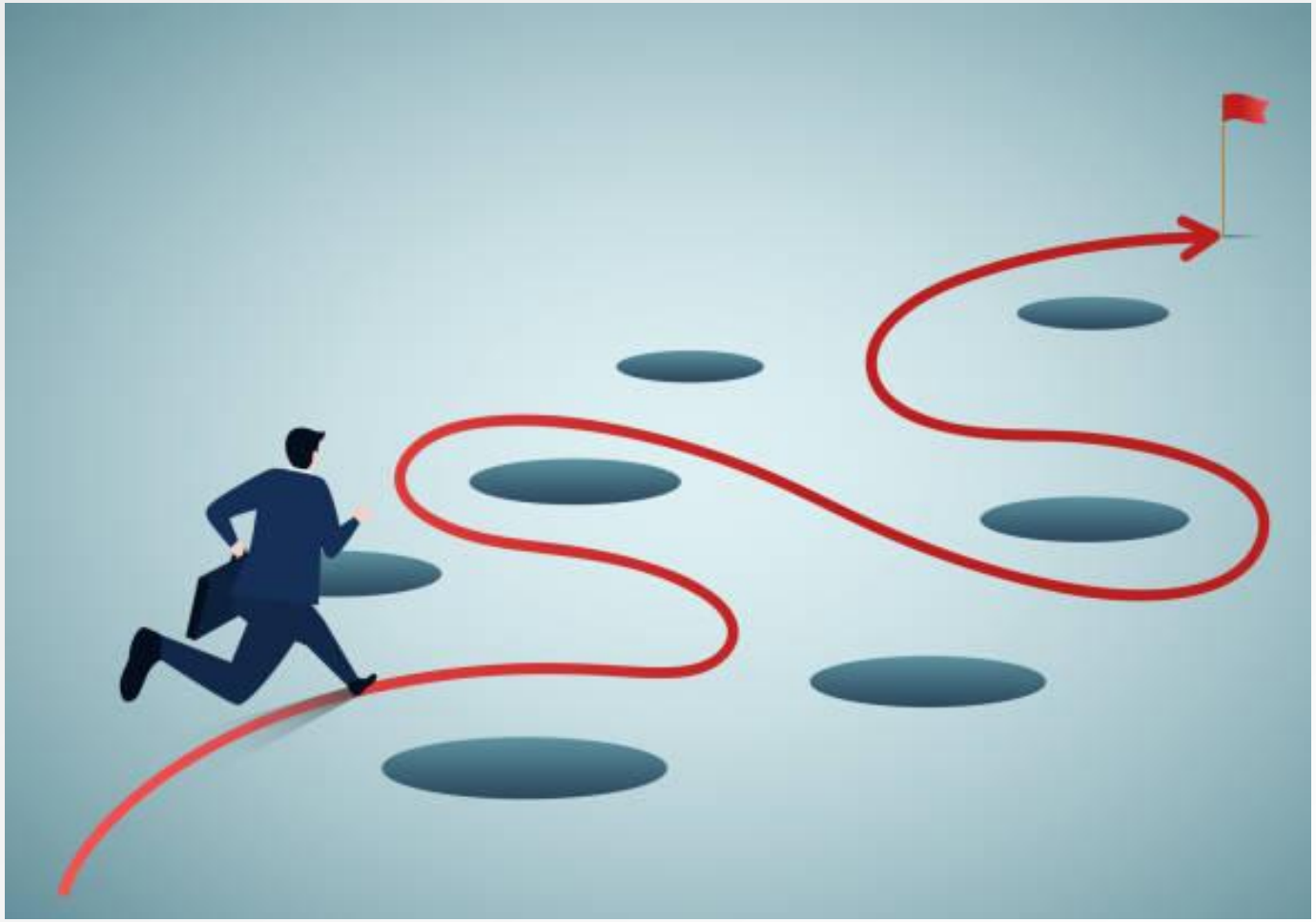
In summary

- Invasive and/or burdensome PMCF studies are required to be conducted as Clinical Investigations in accordance with article Annex XV.
- As the sponsor, it is the manufacturer's responsibility to determine the correct regulatory pathway for a clinical study.
- Clinical investigations involving use of the device outside of the intended purpose are not considered PMCF.
- If in doubt – **DO** get an opinion from a member state.
- **DO** document rationale for regulatory pathway chosen.



PMCF Study pitfalls

- Poor study design; too many variables; no control; sample size to small
- Undefined or unjustifiable research questions; objectives; study endpoints
- Wrong study population: indications, location
- Inadequate statistical justification for sample size
- Poorly defined or no statistical analysis plan
- Missing reports/planned analyses.
- Device not used according to CIP



PMCF Evaluation Report

PMCF Evaluation Report requirements: where are they defined?

Medical Devices Regulation:

- Annex II (6): Product Verification and Validation
- Annex III: Technical Documentation on Post-Market Surveillance
- Annex XIV (Part B): Post Market Clinical Follow Up
- Annex IX: Conformity Assessment

Guidance documents:

- MedDev 2.7.1 (rev. 4) – Clinical Evaluation: A Guide for Manufacturers and Notified Bodies
- MDCG 2020-8: PMCF Evaluation Report. A guide for manufacturers and notified bodies

PMCF Evaluation Report, update frequency and contents (MDCG 2020-8)

When Should it be Updated?

- At the conclusion of any PMCF study.
- When significant (in terms of risk/benefit) new data has been collected, or observations made.
- “At Least Annually” (Class III and implantable)
- Does the SSCP also need to be updated?

MDR Article 61 11: *The clinical evaluation and its documentation shall be updated throughout the life cycle of the device concerned with clinical data obtained from the implementation of the manufacturer's PMCF plan in accordance with Part B of Annex XIV and the post-market surveillance plan referred to in Article 84.* ***For class III devices and implantable devices,*** *the PMCF evaluation report and, if indicated, the summary of safety and clinical performance referred to in Article 32* ***shall be updated at least annually with such data.***

What Should it Contain?

MDCG 2020-8 Contents:

Section A/B: Manufacturer and Device Details

Section C: Activities Undertaken related to PMCF: Results

Section D: Evaluation of Clinical Data relating to Equivalent or Similar Devices

Section E: Impact of results on the technical documentation.

E.1 : CER

E.2 : Risk Analysis

Section F: Reference to common specifications, harmonized standards, or guidance documents applied.

Section G: Conclusions

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PMCF Evaluation Report: What are the expectations?

In order to conduct a complete clinical evaluation, the manufacturer should consider **all** available data.

The PMCF evaluation report **shall form a part of** the clinical evaluation.

All general and specific activities outlined in the compliant PMCF plan, should be **reported on**.

An **objective assessment** should be made regarding the findings whether positive or negative towards the device under evaluation.

PMCF findings should be used as an **ongoing input** for clinical evaluation and risk management.

PMCF evaluation should incorporate **analysis of clinical data available for equivalent** or **similar devices.**

Take Home Points

Take Home Points

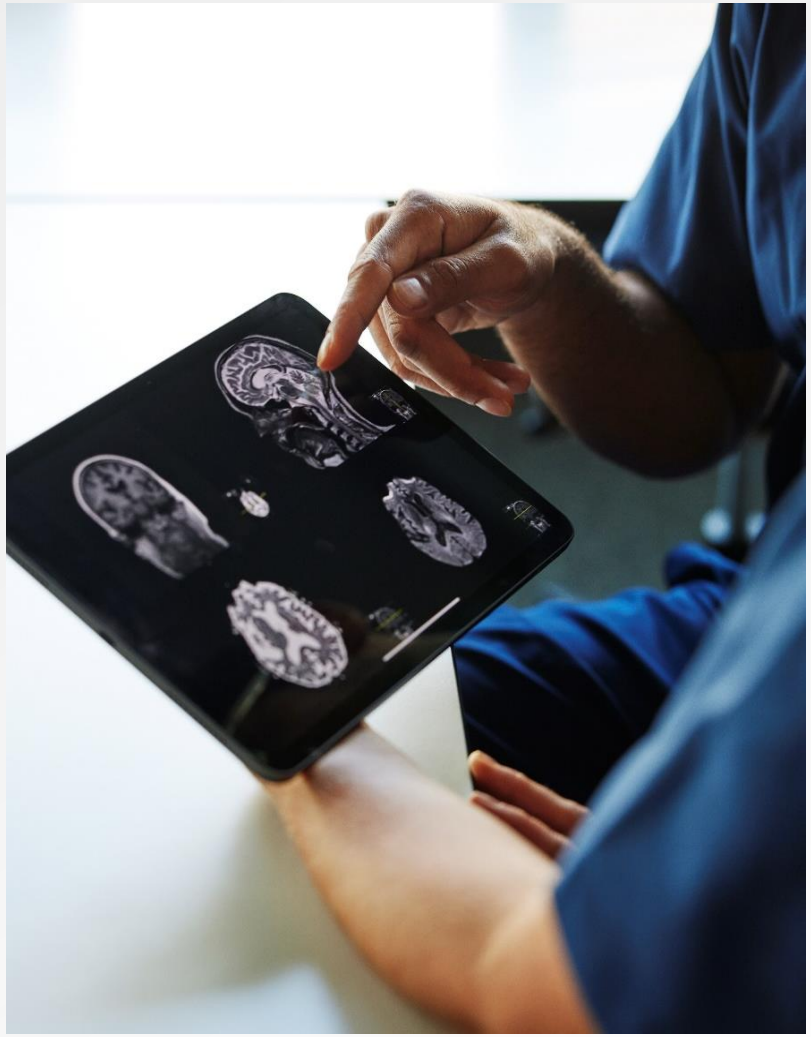
PMCF is a **continuous process** to maintain and update the clinical evidence on a medical device, when used within its **Intended Purpose**.

PMCF plan should **address any gaps** in clinical knowledge on the subject device, such as via the use of equivalence, or those not fully covered by premarket clinical studies, such as **device lifetime, real world use and misuse, emergent risks and other observations made within the state of the art**.

PMCF **studies should be designed and conducted appropriately**, when considering the **risk of the device**, the **quality and quantity** of data required, the **study type** and the **burden** on the patients enrolled.

PMCF **observations and outcomes should be appropriately evaluated** and fed back into the overall clinical evaluation and the risk analysis. This may result in additional actions.

PMCF conducted successfully will **keep supporting clinical evidence current, relevant, appropriate, and complete**, when comparing with that available on state of the art.



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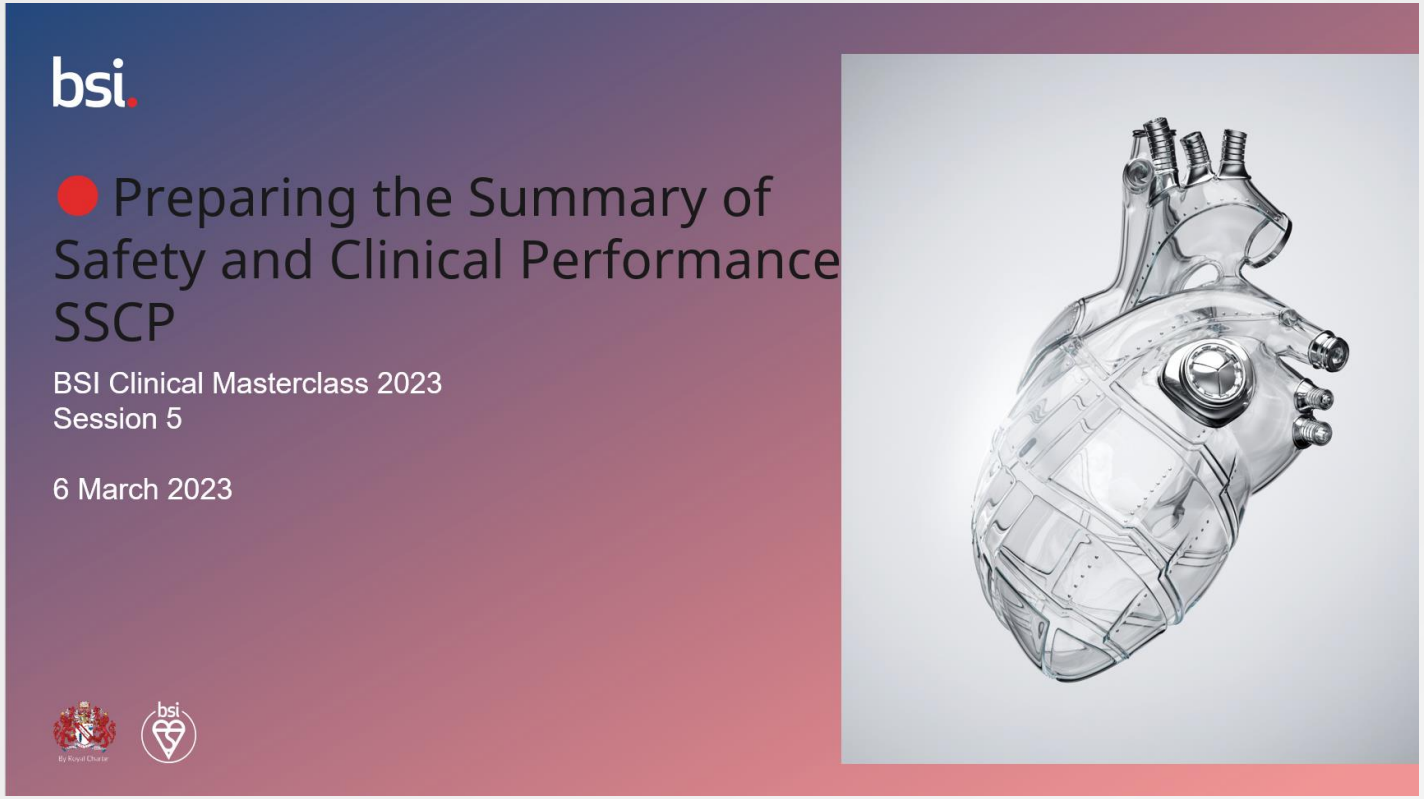
Next Session Slide:



How to document:

The SSCP

Next Session: **Wednesday 8nd March 2023**
Summary of Safety and Clinical Performance SSCP

Series 1 Masterclass -

Well-established technologies - defining the criteria from MDCG 2020-6

Date: 19 January 2022

This webinar will discuss the concept of well-established technologies under the medical device regulations and how to interpret the four criteria defined in MDCG 2020-6. This session will also cover the levels of clinical evidence required for these devices to support your clinical evaluation.

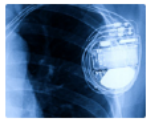
Watch on demand webinar

Understanding Article 61 (10) – when clinical data is not deemed appropriate

Date: 02 February 2022

This webinar will elaborate on BSI's understanding of the unusual occasions when it is appropriate to claim that no clinical data is required for clinical evaluation. We will focus on examples of device(s) where clinical data is not required or could be impracticable. This session will also cover what can be considered a 'claim' under MDR considering Article 7.

Watch on demand webinar



Claiming equivalence under the MDR – regulatory considerations

Date: 16 February 2022

The medical device regulations introduce many new requirements on the regulatory aspects of claiming equivalence. This webinar will help manufacturers understand the required regulatory process in order to claim equivalence with a focus on the new requirements in relation to Class III and implantable devices. This session will also discuss the interpretation of MDCG 2020-5.

Watch on demand webinar

Clinical evaluation for medical software & AI devices

Date: 02 March 2022

With an increasing number of applications being received for medical device software, this session will look at BSI's interpretation of MDCG 2020-1. The webinar will also help clarify when a clinical evaluation is required and the steps of a clinical evaluation process for these devices considering appropriate levels of clinical evidence for this group of devices.

Watch on demand webinar

Post market clinical follow up under MDR

Date: 16 March 2022

The medical device regulations specifically state that post-market clinical follow-up is a continuous process under the regulations. This webinar will look closely at the requirements relating to general and specific PMCF activities, how to document PMCF plans and reports using the MDCG 2020-7 and MDCG 2020-8 templates, and clarify when justifications for no PMCF are appropriate.

Watch on demand webinar

https://www.bsigroup.com/en-GB/medical-devices/resources/webinars/2022/mdr/clinical-masterclass/

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Brochures, Guides and Documents

MDR guidance

MDD Best Practice Guidelines >
MDR Best Practice Guidelines >
MDR Mapping Guide >
MedDev 2.7.1 Rev 4 changes >
MDR Conformity Routes >
MDR Readiness Review >

Webinars

MDR Conformity Assessment Routes webinar

MDR - What we know

Download the presentation >

White Papers and Articles

Person responsible for regulatory compliance (PRRC) - MDR/IVDR Article 15

With the MDR and IVDR, European regulators aim to ensure companies have a regulatory expert – a Person Responsible for Regulatory Compliance (PRRC) – at their disposal, to ensure that the company is meeting certain specific EU requirements.

Software as a medical device - A comparison of the EU's approach with the US's approach

The International Medical Device Regulators Forum (IMDRF) aims to accelerate international medical device regulatory convergence. Through the IMDRF, regulators reached consensus on what software is considered a medical device. Regulators call it 'software as a medical device' (SaMD). This paper provides a comparison of how SaMD is regulated in the US and in the EU.

Machine learning AI in medical devices

How is AI different from traditional medical devices and medical software and what are the implications of those differences? What controls are necessary to ensure AI in healthcare is safe and effective?

Medical device clinical investigations – What's new under the MDR?

The conduct of a clinical investigation is one of the most time consuming and resource intensive activities that a medical device manufacturer can face. This paper discusses important new requirements for pre-market and post-market clinical investigations under the European MDR.

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