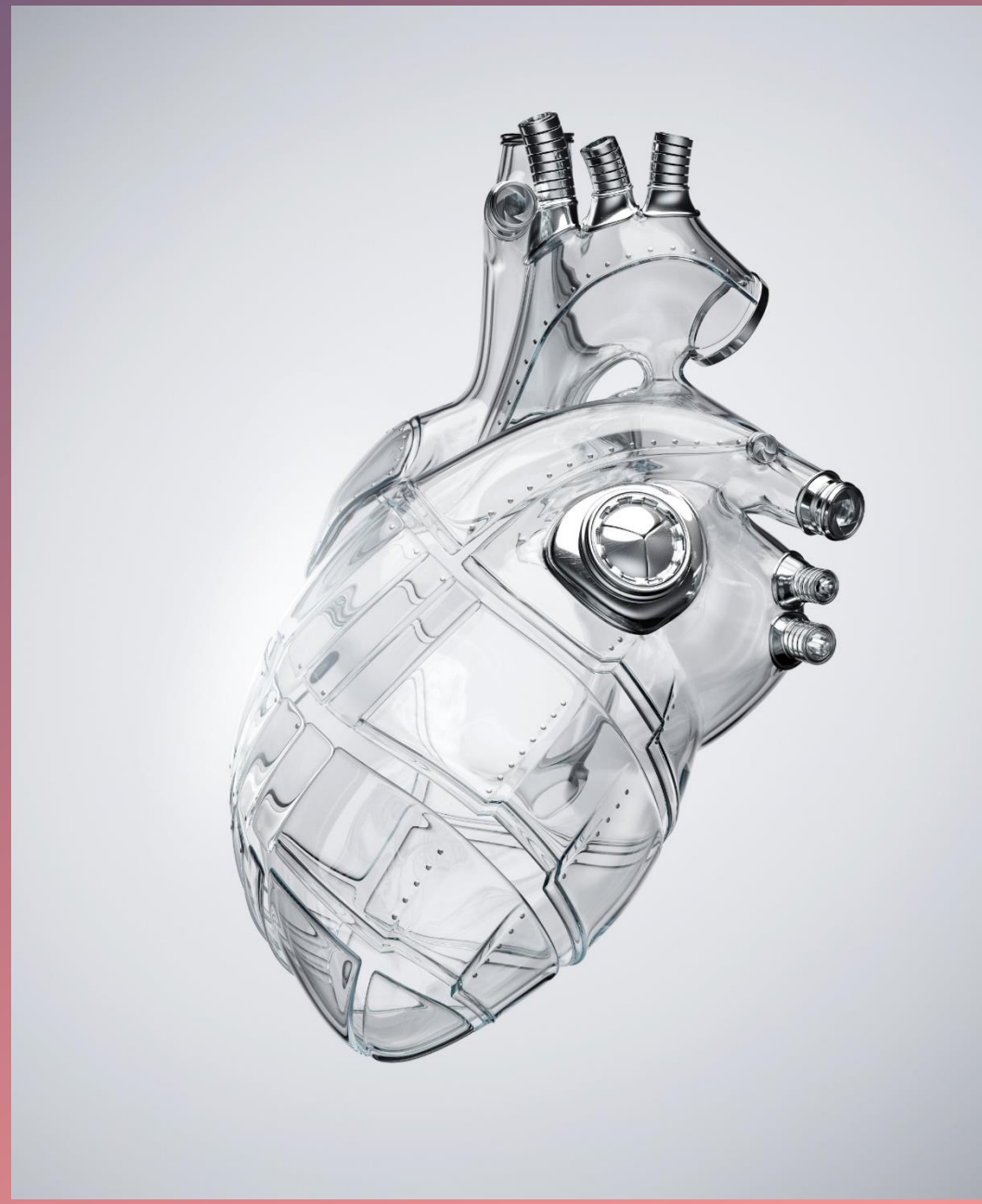
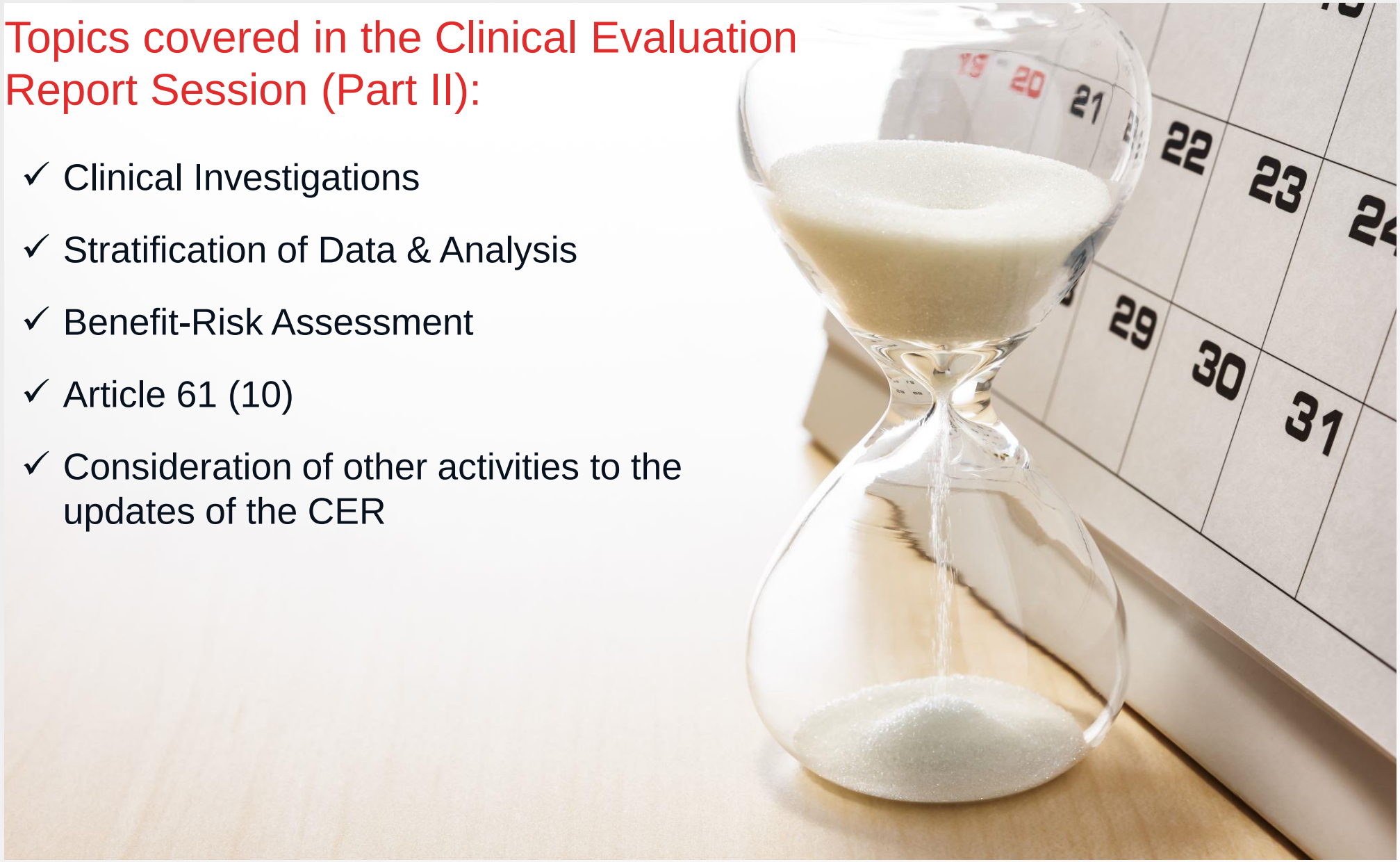
The Clinical Evaluation Report (Part II)

BSI Clinical Masterclass 2023
Session 3



Topics covered in the Clinical Evaluation Report Session (Part II):

- ✓ Clinical Investigations
- ✓ Stratification of Data & Analysis
- ✓ Benefit-Risk Assessment
- ✓ Article 61 (10)
- ✓ Consideration of other activities to the updates of the CER



Documenting Clinical Investigations

Documenting Clinical Investigations

Clinical investigations are mandatory for all new class III and implantable devices under the MDR. There are some exemptions including;

- devices considered WET per article 61 (6b),
- where there is a successful claim of equivalence
- When modifications are made for a device already marketed by the same manufacturer.

This does not exempt class IIa and IIb non-implantable from performing clinical investigations and consideration should be given to the device under evaluation.

The notified body is required to evaluate all clinical investigations as part of the conformity assessment.

Documenting sufficient detail on the clinical investigations and ensuring the correct documentation is accompanied with the CER is essential to ensure the reviewer can sufficiently document their evaluation.

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Documenting Clinical Investigations

Clinical investigations initiated on or after 26th May 2021 must be conducted to the requirements of articles 62-82 and Annex XV of the Medical Devices Regulations 2017/745 or ISO14155

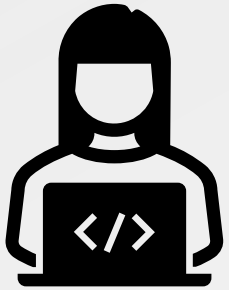
Clinical investigations initiated before 26th May 2021 must have been conducted to the Medical Device Directive 93/42/EEC.

ISO14155 was updated in 2020 to reflect the changes being made under the MDR to clinical investigations. Compliance to ISO14155:2020 is considered compliance to the MDR. (Although we are yet to see any official announcement of its adoption to the MDR other than reference within MDCG 2020-13).

Compliance to ISO14155:2020 is typically required when clinical investigations are conducted outside of the EU.

Understanding the differences of assessment of clinical investigations between the notified body and competent authority.

- The competent authority is responsible for the approval/assessment of the clinical investigation plan
- The competent authority is responsible for enring the manufacturer fulfils their obligations during the clinical investigation.



- The notified body is required to ensure that the data presented for conformity assessment has been obtained legally and in a responsible manner.
- The notified body needs to ensure that the clinical data sufficiently supports the intended purpose for conformity assessment.

This is important because it will give you insight into why we need to see supporting documentation and why we ask questions about the supporting paperwork.

What does the notified body focus on…

Considerations

(Pre-Market Study)

- **Ethics**
- Study design.
- Patient population.
- Patient numbers.
- Objectives and endpoints.
- Length of follow up and intervals.
- Study locations.

Annex XV Chapter I Section 1 of the MDR requires regarding clinical investigations to have been carried out with recognised ethical principles.

- The initial study design, through to publication should consider ethical principles.
- Ethics and the practice of obtaining consent should be considered including vulnerable populations. (Note articles 63-69 of the MDR).
- Recognised ethical principles should be considered the most recent version of the declaration of Helsinki.
- Evidence of ethics committee approval/no objection and a sample of the consent form is always required for review.

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What does the notified body focus on…

Considerations

(Pre-Market Study)

- Ethics
- Study design.
- Patient population.
- Patient numbers.
- Objectives and endpoints.
- Length of follow up and intervals.
- Study locations.

Section 2, Annex XV of the MDR discusses the need for the procedures and study design to be appropriate to the device under investigations.

- The study design should be appropriate to the device under investigation e.g. RCT, Single Blinded, Double Blinded, Retrospective Vs Prospective, Interventional Vs Observational ….
- It can often be difficult for the notified body to understand the chosen method of investigation. *Hindsight of clinical investigations is something we all wish we had!*
- Always provide a justification/rationale in the CER as to why that study design was chosen considering why it was more likely to confirm or refute the claims related to safety or performance than other designs.
- A rationale may also point to other similar device clinical investigations to demonstrate that this study design/method is common for these device types.

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What does the notified body focus on…

Considerations

(Pre-Market Study)

- Ethics
- Study design.
- Patient population.
- Patient numbers.
- Objectives and endpoints.
- Length of follow up and intervals.
- Study locations.

Annex XV section 2.4 requires the clinical investigation to be performed in a clinical environment that is representative of the intended normal conditions of use of the device in the *target patient population.*

- The patient population should be clearly described for the investigation include stage and severity of disease, age, co-morbidities and how that compares to your claimed intended purpose. This should align to your clinical evaluation plan.

- Consideration/justification should also be given to why certain inclusion and exclusion criteria have been selected, particularly when the claimed intended purpose includes patients who were excluded from the study.

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What does the notified body focus on…

Considerations

(Pre-Market Study)

- Ethics
- Study design.
- Patient population.
- Patient numbers.
- Objectives and endpoints.
- Length of follow up and intervals.
- Study locations.

Section 2.1, Annex XV of the MDR requires that the clinical investigation shall include a minimum number of observations to guarantee scientific validity.

- Note the term ‘observations’ and not ‘subjects’.
- A statistical analysis plan (SAP) is always required alongside the clinical investigation plan.
- A strong/rationale for the SAP design and chosen methodology is always required. Ensure your biostatistician has had input into the justification.
- Unusual statistical plans using rare methods will invite scrutiny from the notified body and will likely involve a review by an expert biostatistician.

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What does the notified body focus on…

Considerations

(Pre-Market Study)

- Ethics
- Study design.
- Patient population.
- Patient numbers.
- Objectives and endpoints.
- Length of follow up and intervals.
- Study locations.

Section 2.6 of Annex XV of the MDR requires that clinical investigation will address the intended purpose, clinical benefits, performance and safety and that all endpoints are scientifically validated. The primary endpoint must be appropriate and clinically relevant.

- A feasibility study is not a confirmatory investigation of intended purpose, clinical benefits, performance and safety.
- The primary endpoint should reflect the clinical benefit – i.e.. *quantifiable and meaningful benefit.*
- Primary endpoints that are safety orientated are typically associated with feasibility studies.
- The CER should discuss why those endpoints were chosen and how they have been scientifically validated.

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What does the notified body focus on…

Considerations

(Pre-Market Study)

- Ethics
- Study design.
- Patient population.
- Patient numbers.
- Objectives and endpoints.
- Length of follow up and intervals.
- Study locations.

Section 2.2. and 2.3 of Annex XV of the MDR discusses the need for the research methodologies and procedures to be appropriate to the device under evaluation. Consideration should be given to the follow-up methods and intervals between data collection.

- The length of follow up should be appropriate to capture the correct data at the correct timepoints.
- The study length should also be sufficient to reflect the device under investigation.
- A justification should be considered alongside the results as to why the data intervals were conducted at the chosen time periods.

What does the notified body focus on…

Considerations

(Pre-Market Study)

- Ethics
- Study design.
- Patient population.
- Patient numbers.
- Objectives and endpoints.
- Length of follow up and intervals.
- Study locations.

Section 2.4, Annex XV of the MDR requires that clinical investigations are conducted in a clinical environment that is represented of the intended normal conditions of use of the device in the target population.

- Always provide details of the clinical investigations sites, not just locations, but the type of environment, theatre vs a day surgical room on a ward, tertiary centre vs secondary care.
- Consider differences in patient populations between sites - even within the EU there can be significant differences in patients.
- Consider differences in surgical techniques or post operative clinical differences between countries
- Is there any national/society guidance that confirms the location/skill set/post operative care for such procedures?
- If the device is novel how will you address roll-out if CE marked, do your require a staged roll-out to allow for adequate training?

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Clinical Investigations – Accompanying Documentation.

When submitting clinical investigation data the notified body is also required to verify the following supporting documentation as a minimum;

- ✓ Clinical Investigation Plan(s)
- ✓ Completed Clinical Investigation Reports – Signed by Principal Investigator
- ✓ Evidence of communication and no objections with the ethics committee.
- ✓ All regulatory approvals of the clinical investigation (from all countries, including outside of EU).
- ✓ Investigator's brochure.
- ✓ Sample of the informed consent.
- ✓ Statistical analysis Plan
- ✓ Evidence of public registration (if applicable)

If any deviations to the protocol have been applied, then justifications/acceptance of these deviations should be provided with copies of original and changed protocols.

If there is missing or incomplete information, always provide an explanation.

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Article 61 (7)

Cases in which paragraph 4 is not applied by virtue of paragraph 6 shall be justified in the clinical evaluation report by the manufacturer and in the clinical evaluation assessment report by the notified body.

This requirement is often overlooked by manufacturers. If you are a manufacturer of a Class III or Implantable device and have chosen not to perform clinical then you should provide a clear justification within the CER.

Consider pointing to this clause in the CER to acknowledge the justification.

Tips when documenting clinical investigations

- ✓ Provide comprehensive information for each of your clinical investigations considering the 7 points discussed:
  - Ethics
  - Study design.
  - Patient population.
  - Patient numbers.
  - Objectives and endpoints.
  - Length of follow up and intervals.
  - Study locations.

- ✓ When considering these areas be clear in your rationalisation for choice/process and how it reflects the intended purpose and indications.

- ✓ Always provide the list of documents mentioned in slide 14 for each investigation. For any missing or incomplete information provide a clear explanation.

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Stratification of Data & Analysis

What is the notified body looking for?

Does the data cover all device variants?

Does the data consider all indications?

What is the data source/quality of the variant?

Does the data cover the entire lifetime of the variant?

Are all clinical and non-medical claims supported?

How does the device compare to SoTA?

Is there data supporting the variant with compatibility of other devices?

Does the data introduce any additional risks for the variant?

Does the data suggest any performance concerns with the variant?

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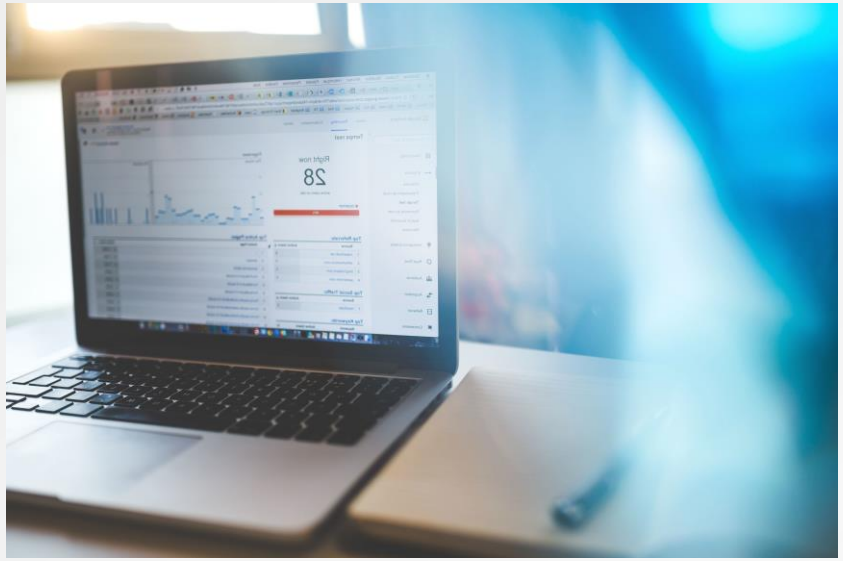
Stratification of Data within the CER

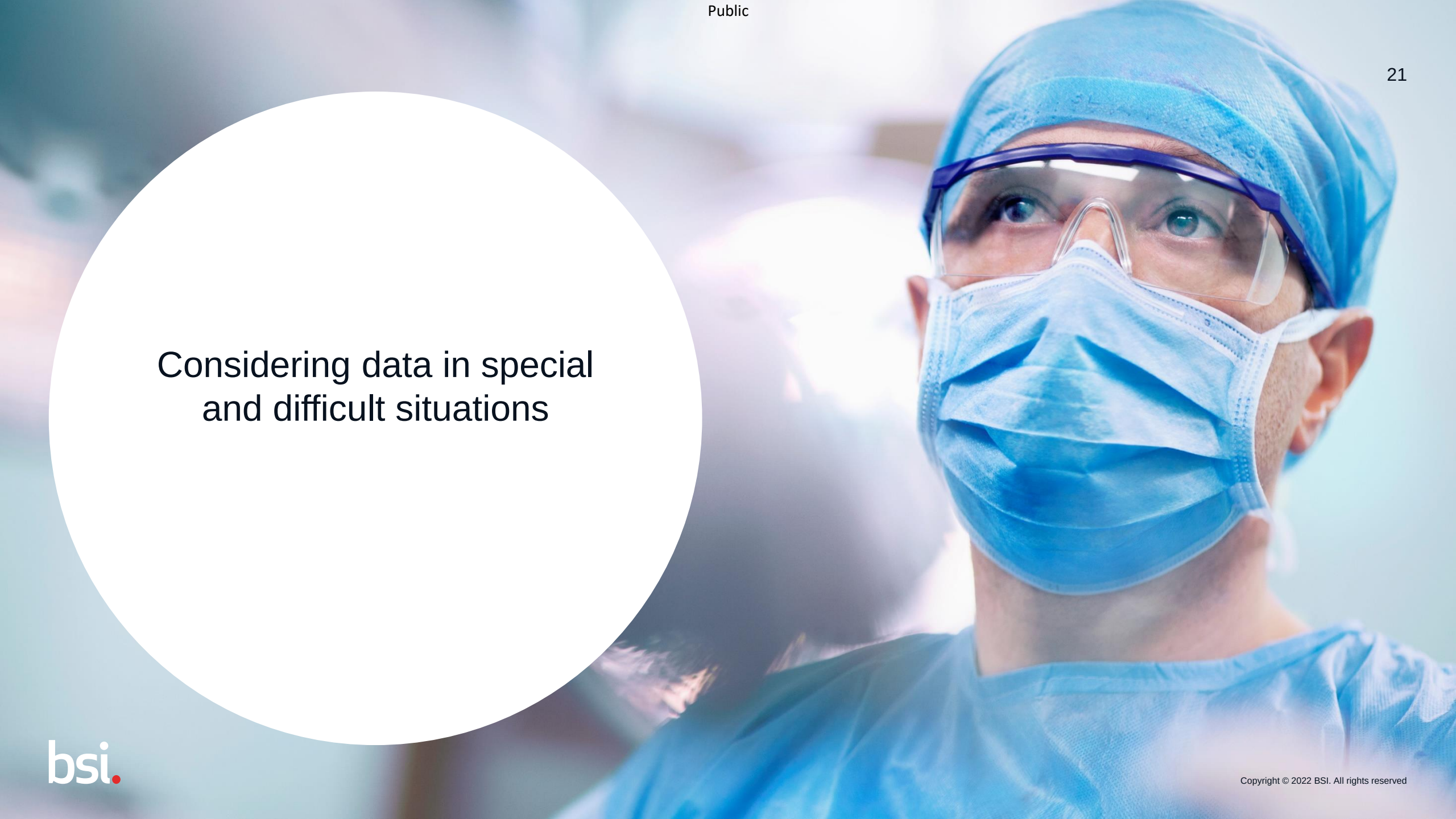
- ✓ Stratification of data within your CER can help provide clear transparency between the reviewer and the manufacturer.
- ✓ This often results in fewer questions from the notified body and a more efficient conformity assessment.
- ✓ Stratification of data can be applied to all variants for all classifications.
- ✓ The reviewer can immediately see where there are areas of data that may need to be supported by PMCF activities.
- ✓ When presented in a table format/excel sheet this is beneficial to the reviewer.



Variant 1: name/add image, description

Data sources/quality/CER location	Name the source of data for the variant, Literature, clinical investigations or PMS/PMCF data and provide location of evidence within the CER.
Safety data summary	Provide a summary of safety information from all sources of clinical data.
Performance data summary	Provide a summary of performance information from all sources of clinical data.
Comparison to state of the art	Consider whether the clinical data gathered for the variant is aligned to the objective data gathered from state of the art search.
Claims supported	Provide information on any claims being made to the variant and whether the clinical data supports overall/individual clinical and non-medical claims.
Indications supported	Consider whether the clinical data on the variant covers all claimed indications.
Cohort/lifetime, Follow up appropriate	Provide the length of time period that the clinical data covers the device. Where this is insufficient data to cover the lifetime of the variant, consider reference to the type of PMCF activity to be conducted to capture this data.,
Compatibility considered	Clarify and demonstrate if the clinical data for the variant considers any claimed compatibility or configuration options.
New risks observed **AE's/complications considered into risk management**	Identify any new risks that may be associated with the variant and how these have been considered within risk management and where appropriate how such new risks will be considered as part of PMS/PMCF plans.

Considering data in special and difficult situations



Low Volume/Rare Indications/Populations

We understand it is unlikely that manufacturers would have a substantial amount of data for a device that has typically low use e.g. if it used in rare conditions or specific populations.

This can be a similar situation for certain variants of devices that are at the extreme end of the size range.

Therefore, careful consideration needs to be considered on the justification of sufficient data for such limitations.

Aligned to Article 61 (1) - always provide a robust justification such as evidence of demonstration of incidence, sales volumes.

Poll Question

Q: For a device with a broad indication such as a CT Scanner, is evidence required to support every possible indication?

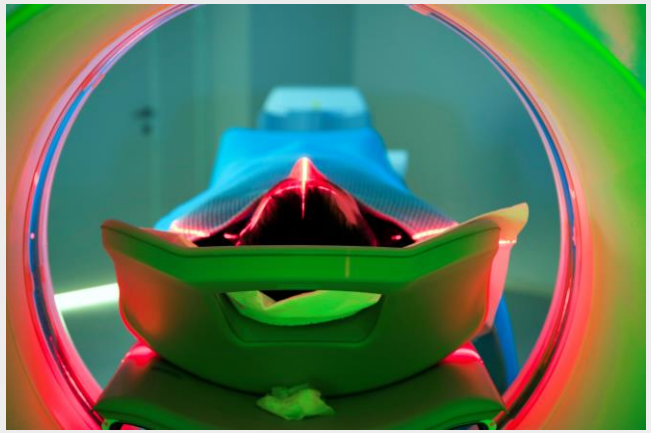
- **Yes**
- **No**

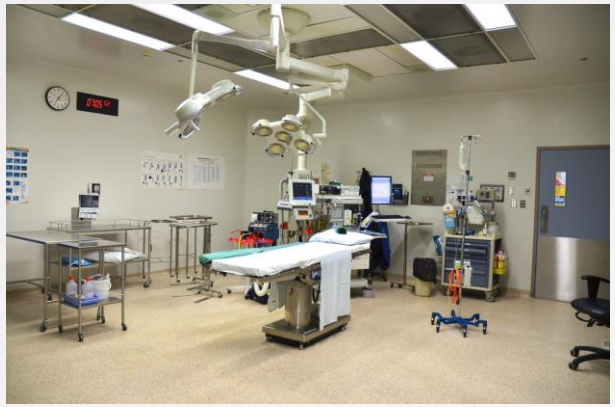
Poll Question

Q: For a device with a broad indication such as a CT Scanner, is evidence required to support every possible indication?

- **Yes**
- **No**

Broad Indication Devices





Broad Indication Devices

There are some medical devices that serve all populations and all anatomical areas. An example of this is an X-ray machine or CT Scanner. It would be impossible for a manufacturer to provide data for every population type and every anatomical location.

1.Examining Blood Vessels. ...
2.Diagnosing Abdominal Issues. ...
3.Examining Small Bones. ...
4.Investigating Tumours. ...
5.Guiding Cancer Treatment. ...
6.Examining Head and Brain Injuries or Issues. ...
7.Diagnosing Soft Tissue Damage.

Focus should be on the data for the most common use of a broad indication device, with reference to other situations with supporting low quality data.

N.B If these devices have claims focused on a specific condition/population then we would expect to see specific clinical data to support. E.g. Cardiac MRI

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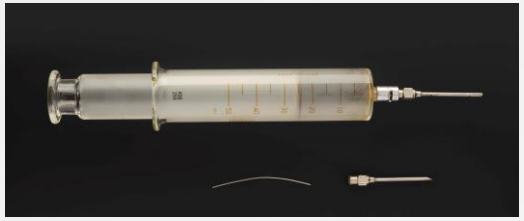
Tips when documenting equivalence

- ✓ Providing tabulated data for each variant covering the aspects mentioned in slide 20 will make the review process efficient and will likely reduce the number of questions issued.
- ✓ When there are devices/variants that are seldomly used consider supporting your justification with condition incidence or sales volumes to demonstrate the rarity of the use of the device.
- ✓ Article 61 paragraph 1 is clear that it is the manufacturer responsibility to justify the level of evidence to support the intended purpose of the device.

Benefit-Risk Assessment

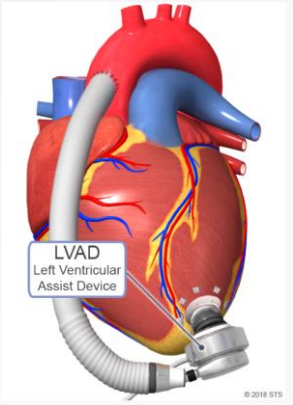
Benefit Risk Statements

Benefit | Risk

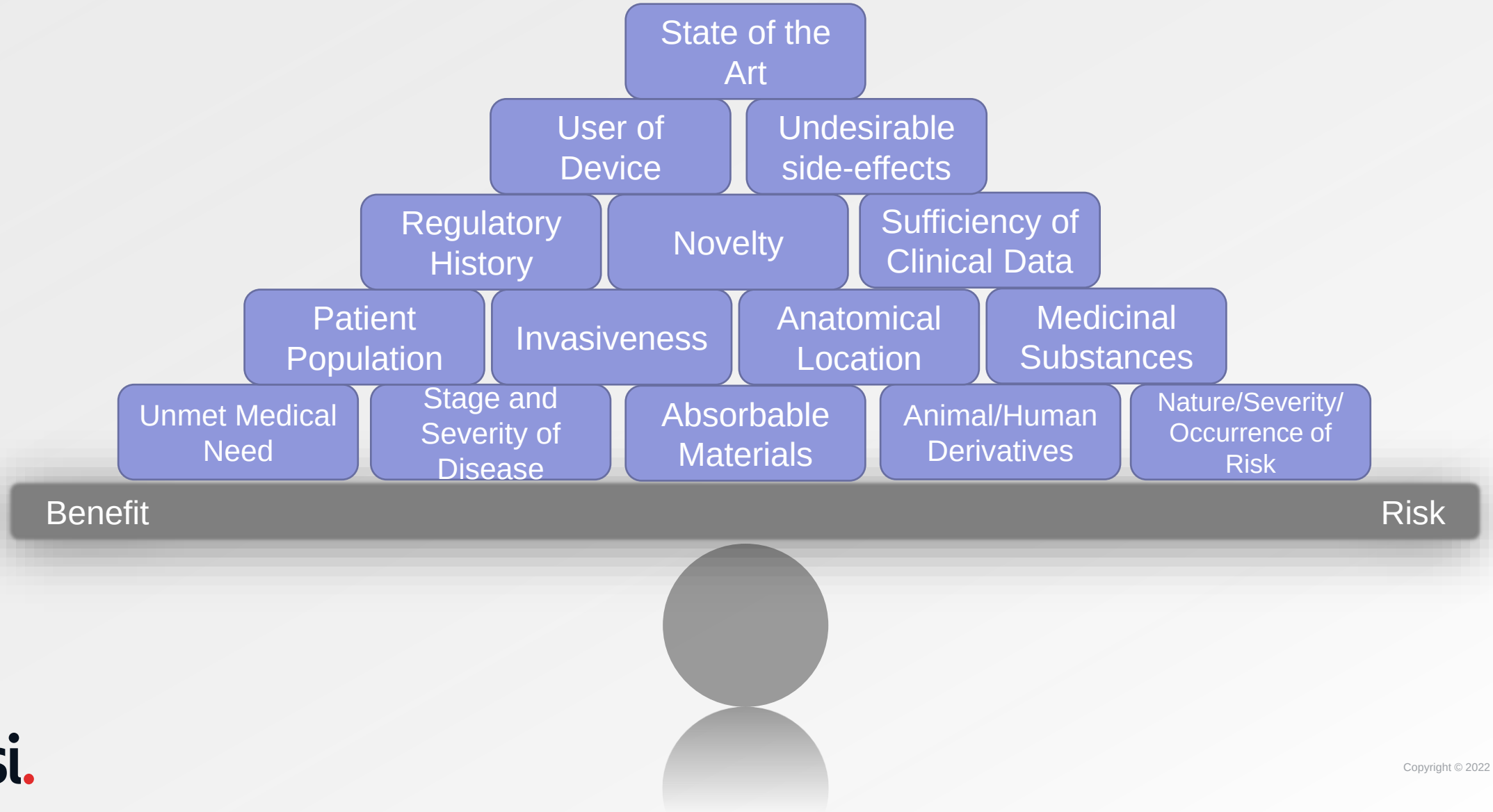


Benefit | Risk

Benefit | Risk



Benefit Risk Statements



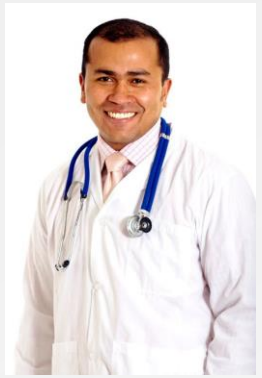
MDR Submissions – Benefit Risk Statements

- Brief/benefit risk statements that do not consider all the available evidence are not acceptable.
- The purpose of the benefit/risk assessment is to pull in all areas of the assessment and clinical data and confirm that there is in fact benefit over all risks.
- Consideration should be given to SoTA and how the device compares as a treatment/diagnostic option and any additional risks identified can be acceptable when given the devices measured and meaningful clinical benefit.

What do Notified Bodies require in a Benefit/Risk?

Describe the benefit/risk per indication. Benefit/risk will be different for every indication.

Tell the story and consider all the data in the your CER to develop a benefit/risk conclusion.



Benefit/risk should conder the users of the device as well as the recipient.

Benefit-risk assessments are required for all devices and are proportionate to the classification of the device .

Describe the patient pathway and the context of the device when considering alternative options. Think magnitude of benefits.

Tips when documenting benefit/risk assessment

- ✓ The best benefit/risk assessments are typically performed by those with a medical qualification.
- ✓ Benefit/risk assessments should consider the magnitude and duration of benefit and risks over the lifetime of the user/patient/device.
- ✓ Typically devices with a higher classification will have more risks and more direct benefit and this should be evidenced by the data collected.
- ✓ The benefit/risk assessment should consider all aspects of the device and all data.
- ✓ Avoid one-line statements.

Article 61 (10)

Poll Question

Q: Do devices following Article 61 (10) require a CER?

- Yes
- No

Poll Question

Q: Do devices following Article 61 (10) require a CER?

- **Yes**
- **No**

General Considerations

The notified body assessment of article 61 (10) devices will rely heavily on technical and pre-clinical data. This should be reflected in the technical assessment.

The notified body is still required to produce a clinical evaluation assessment report (CEAR) for all devices including Article 61 (10) that undergo conformity assessment. This is documented in Annex IX. Section 4.9

> 4.9. The notified body shall provide the manufacturer with a report on the technical documentation assessment, including a clinical evaluation assessment report. If the device conforms to the relevant provisions of this Regulation, the notified body shall issue an EU technical documentation assessment certificate. The certificate shall contain the conclusions of the technical documentation assessment, the conditions of the certificate's validity, the data needed for identification of the approved design, and, where appropriate, a description of the intended purpose of the device.

The manufacturer should provide a clear logical justification and rationale for following article 61 (10).

Manufacturers of Article 61 (10) devices are still required to provide the following:

- Clinical Evaluation Plan
- Clinical Evaluation Report
- PMCF Plan
- PMS Plan

Nobody Performs Clinical Investigations on these devices… after all they are Accessories!

Our Literature Search returned 0 Results!

Our device performs as intended as we have only 1% of complaints

Absence of evidence is not evidence of absence.

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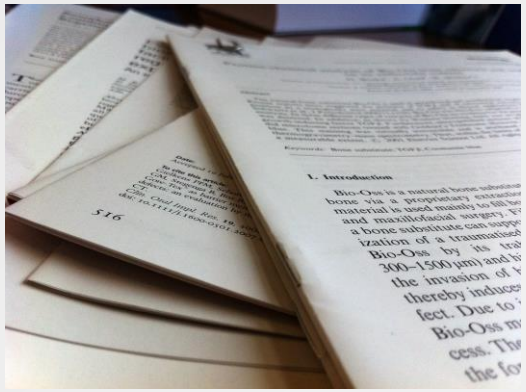
What data is expected in the CEP/CER for article 61 (10)?

SoTA

A literature search needs to be conducted to define the State of the Art.

In the absence of evidence a justification/explanation needs to be put forward as to why the devices can still be considered SoTA.



A literature search of the device under evaluation should also be conducted to demonstrate there is no clinical data available.

A summary of the type of pre-clinical data conducted to demonstrate conformity to the GSPRs with reference to the supporting technical documentation.

There is a still a requirement for a clinical evaluation plan and clinical development plan. It is understood these will be limited and will discuss how the GSPRs can be met in the absence of clinical data.

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What data is expected in the PMCF Plan for article 61 (10) ?

- PMCF under the MDR contains both general and specific activities.
- Given the nature of the device it is unlikely that specific activities will be conducted as part of the PMCF plan.
- General activities include feedback from users of the device and this is an activity that could be appropriate for article 61 (10) devices.
- The PMCF plan should consider:

✓ General PMCF activities

✓ A robust justification for not conducting specific PMCF activities.

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Article 61 (10)

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What if clinical data has been identified for an Article 61 (10) device…

- Article 61 (10) discusses where the demonstration of conformity with general safety and performance requirements based on clinical data is not deemed appropriate - even if there is clinical data present it could still be inappropriate to demonstrate conformity to the GSPRs.
- This will need a clear statement as to why you are still pursing article 61 (10) even though clinical data has been identified.
- If the clinical data is sufficient (quality/quantity) it may be the moment to use that clinical data to support conformity to the GSPRs.
- It is not acceptable to ignore any clinical data in the evaluation.

Tips when considering clinical documentation for Article 61 (10)

- ✓ Provide a robust justification as to why you are following article 61 (10) taking note on the criteria mentioned within the clause.
- ✓ A CEP is always required alongside a CDP. A CER is also always required.
- ✓ A literature search on SoTA **and** the device under evaluation to demonstrate there is no clinical data on the device.
- ✓ A summary and reference to the supporting pre-clinical data is required in the CER
- ✓ A PMCF plan is always required but will typically only mention general activities with a justification for not conducting specific activities.
- ✓ If clinical data has been identified then this should not be excluded. Article 61 (10) may still be possible depending on the sufficiency of the data and the device under evaluation.

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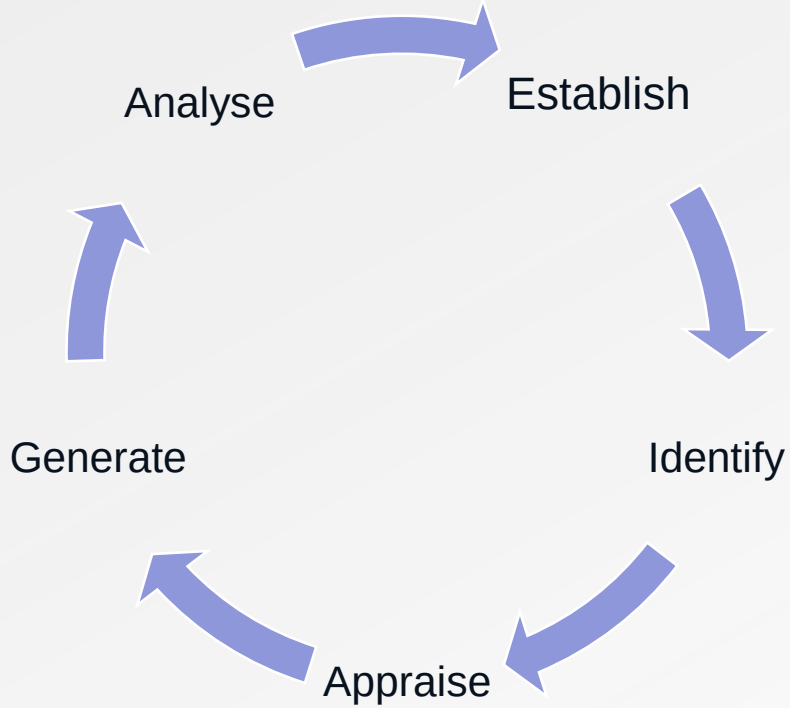
Consideration of other activities to the updates of the CER

Consideration of other activity updates to the CER

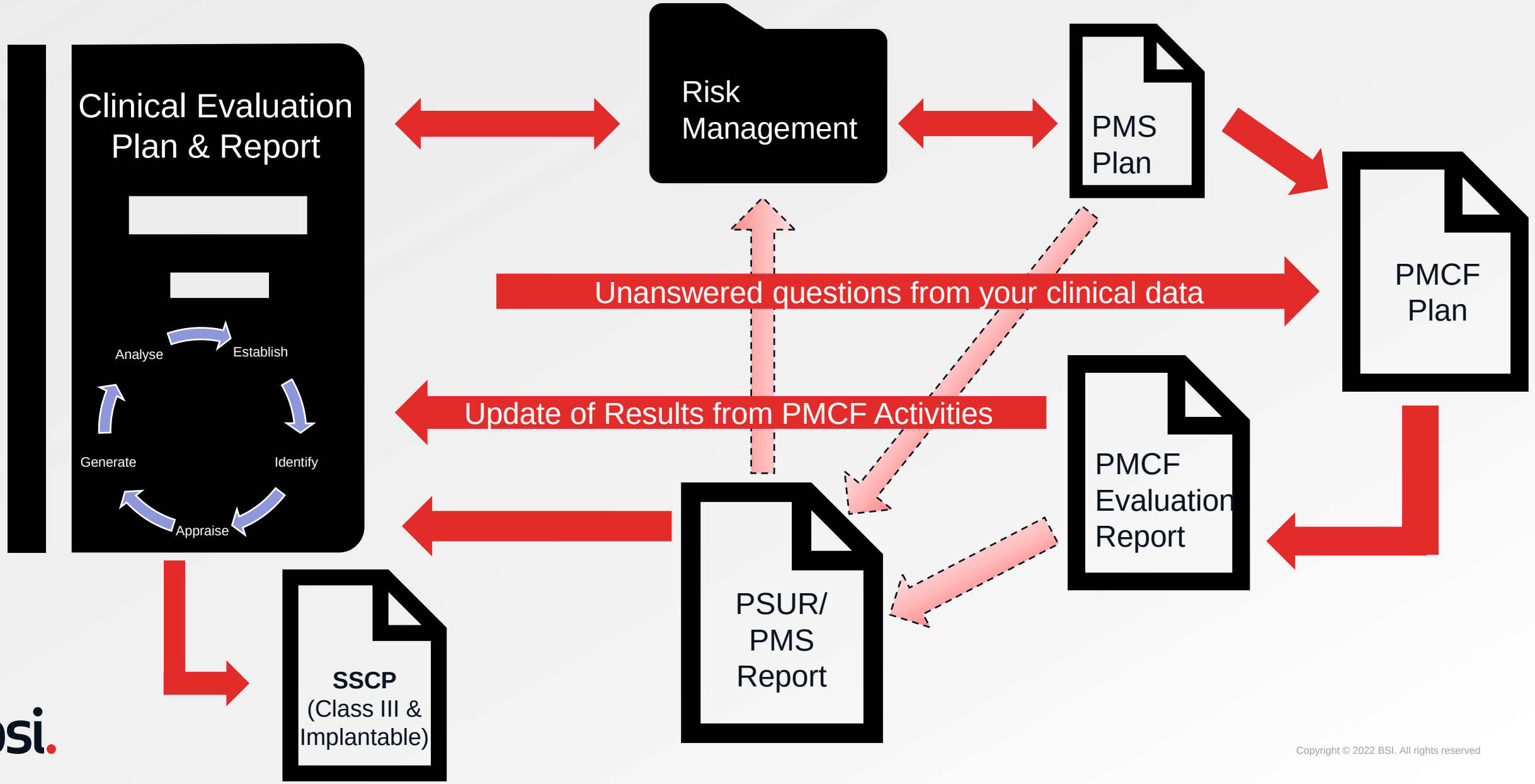
The Clinical Evaluation Process is continuous and the CER is the output of the process.

There will be many outputs of other activities such as PMCF Evaluation Reports and Periodic Safety Update Reports that will require updates to your CER.

The documentation needs to demonstrate a clear and strong link between the clinical evaluation, risk management and post market surveillance.



The Perfect Process



Tips when considering the interaction of other activities with clinical evaluation

- ✓ Always consider the inputs and outputs of the clinical evaluation process. These should be formalised within your QMS procedures.
- ✓ Consideration to updates of documentation should be considered in terms of important that new information is and the impact it will have to patients and users of the device.
- ✓ The MDR provides some consideration about expected timelines.
- ✓ There can sometimes be acceptable reasons to delay updates to the outputs of the clinical evaluation such as SSCPs, PSURs. For any duration/delay this should be justified within your procedures.
- ✓ More information will follow as part of the SSCP/PSUR sessions scheduled this year.

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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.

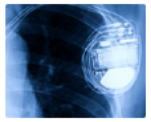
Watch on demand webinar

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/

Next Session Slide:

How to document:

- ✓ PMS Plans
- ✓ PMCF Plans
- ✓ PMCF Evaluation Reports

Next Session: **Wednesday 22nd February 2023**
PMS & PMCF

BSI Medical Devices – Use Our Resources

https://www.bsigroup.com/en-GB/medical-devices/resources

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

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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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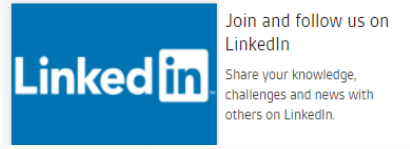

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