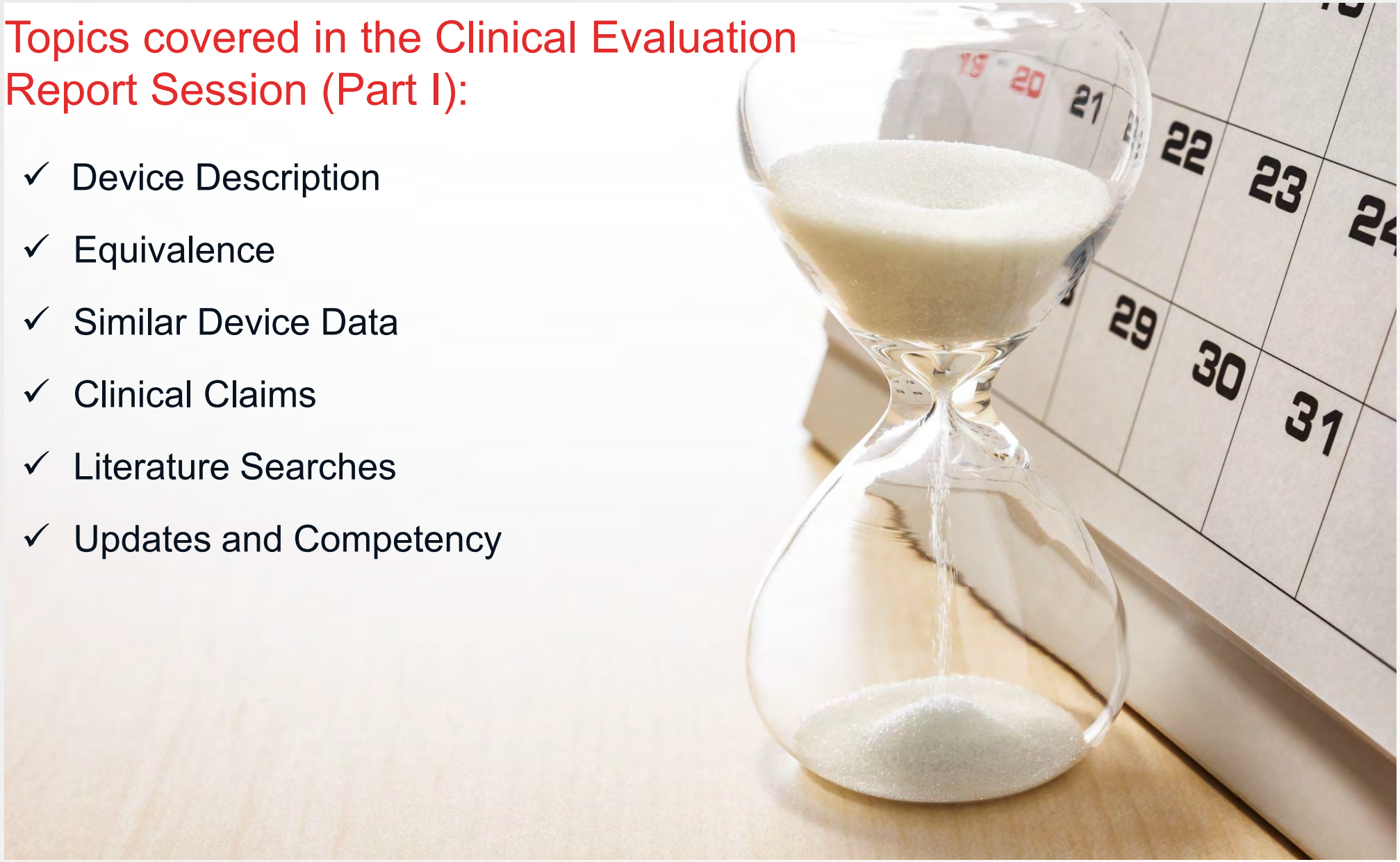
The Clinical Evaluation Report (Part I)

BSI Clinical Masterclass 2023
Session 2

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

- ✓ Device Description
- ✓ Equivalence
- ✓ Similar Device Data
- ✓ Clinical Claims
- ✓ Literature Searches
- ✓ Updates and Competency



Documenting the Device Description

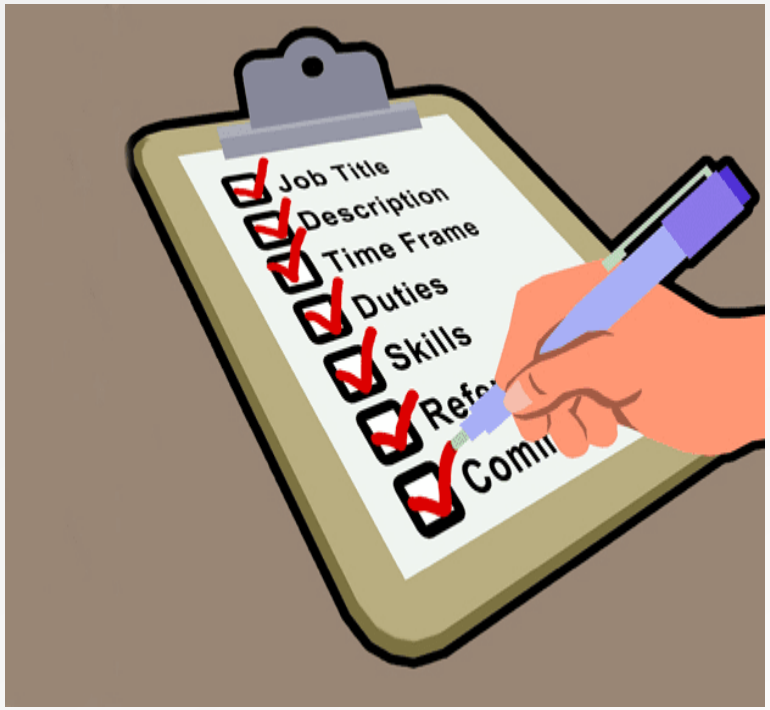
Documenting the Device Description

Documenting a clear and comprehensive description is critical not only to help the assessor understand your device but also a good description of the device will help the assessor verify that you have been able to retrieve meaningful literature data.

Meddev Section A3 is still valid under the Medical Device Regulations (MDR) via MDCG 2020-6 and provides a good basis for the device description, but there are new considerations that need to be considered in the description for the purposes of the MDR.

Whilst the device description should reflect the current version/model of your device, it is equally important to give due consideration to the device's history in your device description. This includes both regulatory history and design history.

Including images in your device description is essential. Where appropriate, images should include the steps required to use the device.



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Device Description – Names, Models, Sizes Components including Software and Accessories.

The CER should list the name of the device along with all available sizes, variants of the device.

The CER should list all the devices in the scope of its use that form part of the evaluation. This includes accessories and software.

Each UDI-DI should be listed alongside the device and variants/accessories. This allows the assessor to quickly cross check against other documentation such as the Summary of Safety and Clinical Performance (SSCP). If such a section is mirrored in your SSCP then this improves efficiency.

The Basic UDI-DI should also be listed for the combination of devices within the CER.

If you claim that the device is compatible with other manufacturer devices these devices should be listed, alongside other critical information such as the legal manufacturer and regulatory status of those devices.

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Device Description – Accessories

The assessor is required to list all accessories as part of the evaluation so it is critical that these are listed with an image and description of their interaction with the main device.

Please avoid listing accessories intended to be used with the main device in a separate CER.

The importance of accessories should not be underestimated, often the device is not functional without such accessories.

The purpose of the clinical evaluation is to consider the interaction of the device **and its accessories** – It is difficult and time consuming to review the clinical data without the full picture.

Device Description – Regulatory History

Providing clear information of the regulatory history of the device gives confidence to the assessor about it's past use and a better understanding of your overall device history.

If your device is a legacy device, consideration should be given to:

- ❑ The date of first CE marking
- ❑ The most recent CE certificate number
- ❑ Classification/Rules and any changes associated with classification.
- ❑ Number of units placed on the market to date.
- ❑ Justification for any gaps in the history where the device was not CE marked.

If your device is *new to EU* device, consideration should be given to:

- ❑ Description of where the device has been approved and the regulatory authority that approved e.g. UKCA, TGA, FDA
- ❑ Date of first regulatory approval.

It is also helpful to provide the status on any regulatory issues such as FSN, open FSCA to aid the assessor understand current regulatory compliance.

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Device Description - Intended Purpose & Indications

Intended Purpose

The device description should provide a clear intended purpose of the device and where appropriate a list of all indications.

If the device has changed its intended purpose/Indications, providing some context around the history of this can help the assessor understand the history of the device.

A clear list of all contra-indications, warnings/precautions should also be provided.

Ensure that this information is consistent across the technical documentation.

(See CEP Masterclass Series 2 Session 1 for more information)

Device Description – Considerations

General description of the medical device including

- ✓ a concise physical and chemical description
- ✓ the technical specifications, mechanical characteristics
- ✓ sterility
- ✓ radioactivity
- ✓ how the device achieves its intended purpose
- ✓ principles of operation
- ✓ materials used in the device with focus on materials coming in contact (directly or indirectly) with the patient/ user, description of body parts concerned
- ✓ whether it incorporates a medicinal substance (already on the market or new), animal tissues, or blood components, the purpose of the component
- ✓ other aspects

Section A3 Meddev 2.7/1 rev 4 provides a good list of contents to cover within the device description.

When considering these points thinks about:

- Would images support the description?
- Is a justification needed?
- What is the history of the device in relation to this point?/Have there been changes?

Device Description – New Considerations under the MDR – Lifetime

Lifetime

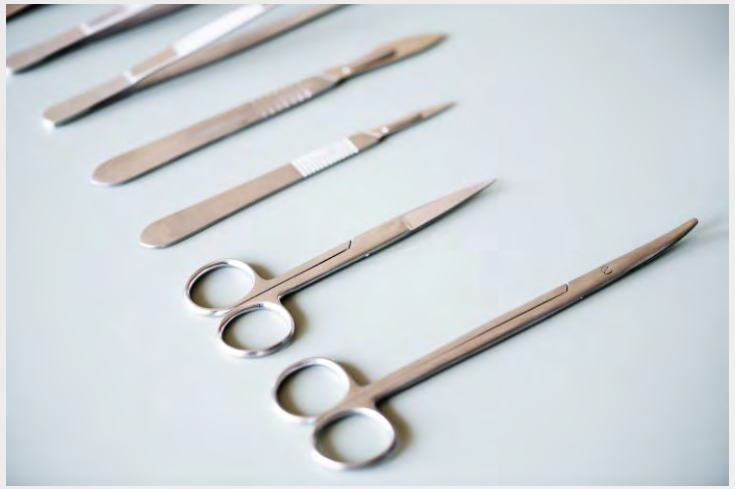
It is essential you define a lifetime for your device. This allows the assessor to ensure that the clinical data and/or PMCF plan is appropriate to meet the requirements of Annex XIV.

Claims of indefinite lifetime are not acceptable.

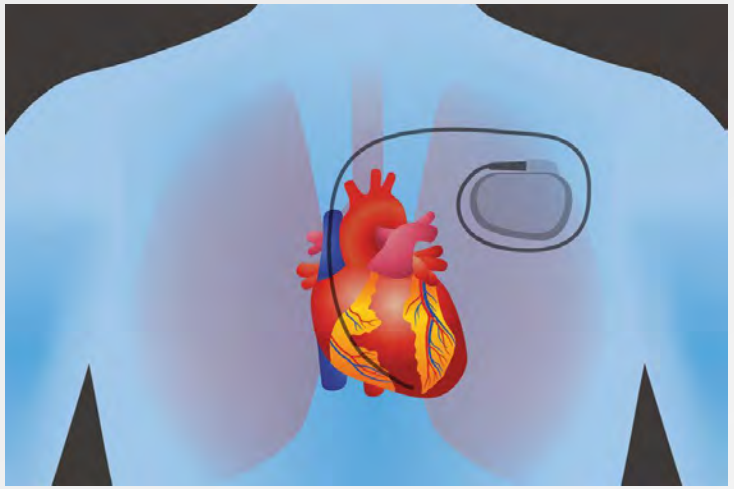
Device Description – New Considerations under the MDR – Lifetime

How is Lifetime defined?

There is an EU taskforce looking at the definition of ‘lifetime’



This could be the number of sterilisation reprocesses before the device loses is it optimal function



This could be the ‘mean’ battery performance based on technical considerations.

This could be the lifetime of the shortest component before replacement. Note: Ability to continuously service is not a way of claiming an indefinite lifetime.

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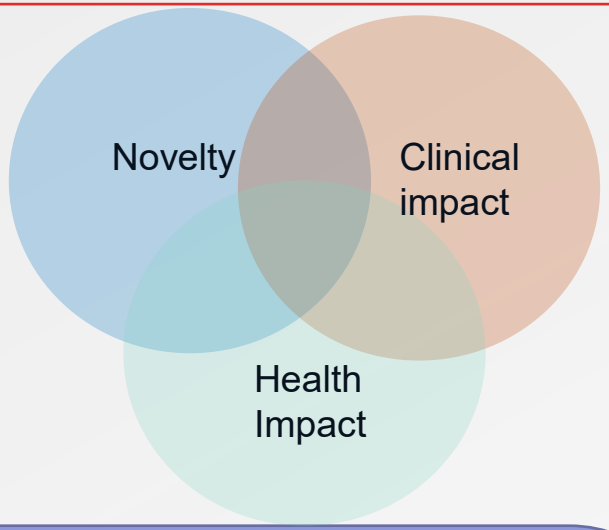
Device Description – New Considerations under the MDR – Novelty



Clinical or Surgical Procedure Novelty Dimensions

- Mode of Use or Treatment Option
- Device-Patient Interface
- Interaction and Control
- Deployment Methods

Device Related Novelty Dimensions

- Medical Purpose
- Design
- Mechanism of Action
- Materials
- Site of Application
- Components
- Manufacturing Process

It is critical that manufacturers address **ALL** these aspects in a section of the CER, indicating if the device has any novelty in relation to these areas.

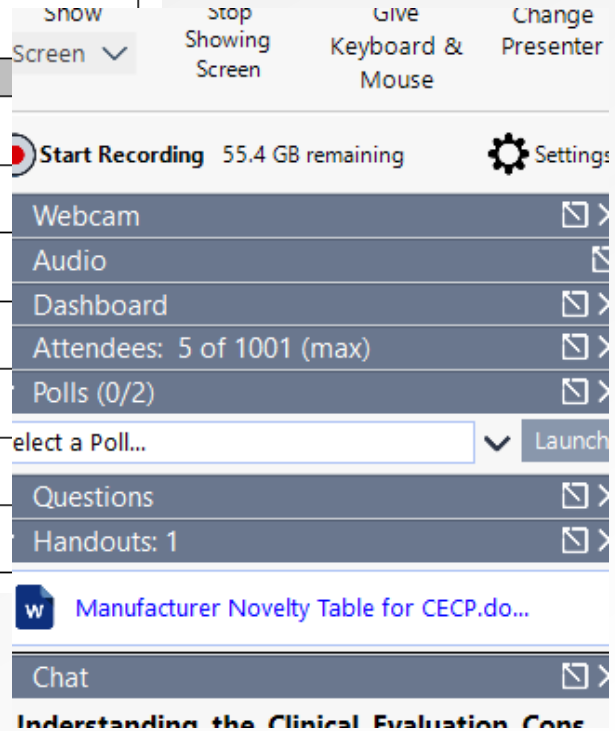
If the device has these novel features it is paramount the manufacturer adequately describes with scientific justification why there would be no impact to safety or performance and overall benefit/risk.

Failure to address these aspects in the CER/CEAR may trigger an unnecessary CECP Opinion for Class III Implantable and Class IIb Rule 12 ARMS.

Do Not Use the ANSM Card – Requested by EMA Secretariat

Novelty Table – Consider using this table

Clinical or Surgical Procedure Novelty Dimensions		
	Is there novelty? Yes /No	If Yes – Specifically describe novel features and any potential clinical or health impact. If No – provide evidence/justification to demonstrate non-novel features
Mode of Use or Treatment Option		
Device-Patient Interface		
Interaction and Control		
Deployment Methods		
Device Related Novelty Dimensions		
Medical Purpose		
Design		
Mechanism of Action		
Materials		
Site of Application		
Components		
Manufacturing Process		



You can download this from the Handouts section of the GoTo Webinar Taskbar

Listen back to the CECP webinar if you are a Class III Implantable or Class IIb Rule 12 – Administer or remove a medicinal substance manufacturer .

https://www.bsigroup.com/en-GB/medical-devices/resources/webinars/2022/mdr/article-54-understanding-cecp/

Tips when considering the Device Description

- ✓ Organise your CER so it reflects the device that is being evaluated. A CER that contains 20 different devices for which only one is being CE marked is not helpful and will slow down the assessment.
- ✓ Please ensure you have your Single Registration Number at time of submitting.
- ✓ Documenting the history of the device from both a regulatory perspective and design history is helpful to the assessor.
- ✓ Using Meddev 2.7/1 rev 4 section A3 is a good checklist for the device description but always consider identifying any additional information that may be needed for purposes of MDR.

Documenting Equivalence

Annex XIV Part A

MDCG 2020-5

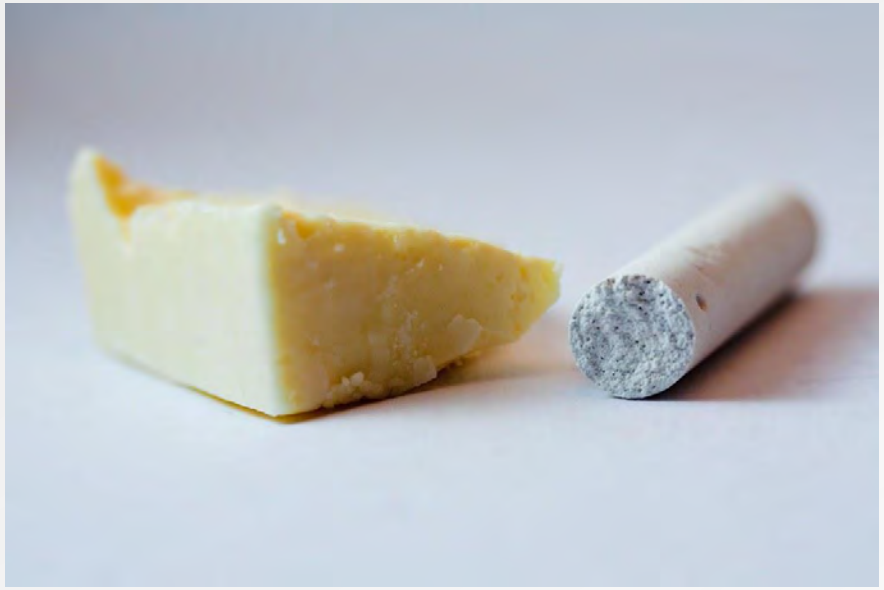
Documenting Equivalence

It is important to specifically identify the device you are claiming equivalence to.

There should be a clear description of the device for which you are claiming equivalence, including: name, models, sizes, settings components of the device presumed to be equivalent,
including software and accessories.

It is also important to consider the regulatory history and legal manufacturer of the equivalent device. The regulatory history information presented on Slide 7 should be considered for the equivalent device.

Whilst it is possible to claim equivalence to more than 1 device, all aspects of equivalence need to be considered with regards to Technical, Biological and Clinical Equivalence for **every device** presented. This is particularly time consuming for the assessor and will generate many questions, so when possible identify a single device.



Documenting Equivalence

Equivalence table for the comparison of a device with a presumed equivalent marketed device for the purpose of demonstrating equivalence			
1. Technical characteristics (add a separate row for each of the assessed characteristics)	**Device 1 (under clinical evaluation)** Description of characteristics and reference to specifying documents	**Device 2 (marketed device)** Description of characteristics and reference to specifying documents	**Identified differences or conclusion that there are no differences in the characteristic**
Device is of similar design			1.1
Used under similar conditions of use			1.2
Similar specifications and properties including physiochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and software algorithms			1.3
Uses similar deployment methods where relevant			1.4
Has similar principles of operation and			1.5

MDCG 2020-5 provides a equivalence template and when possible this should be used.

When providing scientific justifications to support differences, then be sure to include the evidence/articles with your submission and clearly reference them in this table.

Provide clear and comprehensive information - single word conclusions are not acceptable.

Top Tip – It is easier to justify differences where the requirement is ‘similar’ .

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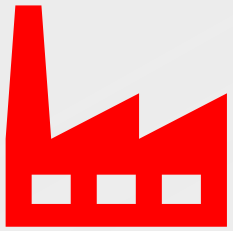
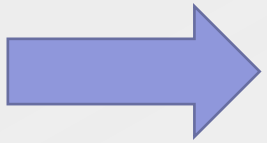
Class III and Implantable Devices
- *Different Manufacturer*

This includes subsidiaries where there is a different legal manufacturer



Different Legal Manufacturers



Device A Equivalent

Device B Device under Evaluation

For Equivalence to be claimed to a Class III and Implantable device of a **different** manufacturer the following conditions need to be met for the equivalent device ;

- *Valid CE Certificate **to MDR Only***
- *Contract in place allowing **full access** to technical documentation.*
- *PMCF plan **includes** Post Market Studies (Article 61 (4))*

New devices claiming Equivalence that are Class III Implantable still are subject to CECP

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Documenting Equivalence – Considerations for Class III and Implantable

What does BSI require to meet the requirements of Article 61 (5)?

- ✓ Copy of MDR certificate. (Until Eudamed is fully functional)
- ✓ A contract/agreement that explicitly states there is ongoing access to the technical documentation and is signed by **BOTH** parties.

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Tips when documenting equivalence

- ✓ When claiming equivalence, detail is key. You need to demonstrate to the assessor that you have a strong and clear knowledge of the equivalent device and that there are no unknowns for the device under evaluation.
- ✓ Claiming equivalence is allowing the clinical and technical data of another device to enter the clinical evaluation. Therefore sufficient access to the data is required, but the legal manufacturer of the claimed equivalent is still required to demonstrate conformity to the GSPRs
- ✓ Same is **not** Similar. There is a reason these are differentiated within the MDR.

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Poll Question

Q: Can similar device data be reported in your CER?

- Yes
- No

Poll Question

Q: Can similar device data be reported in your CER?

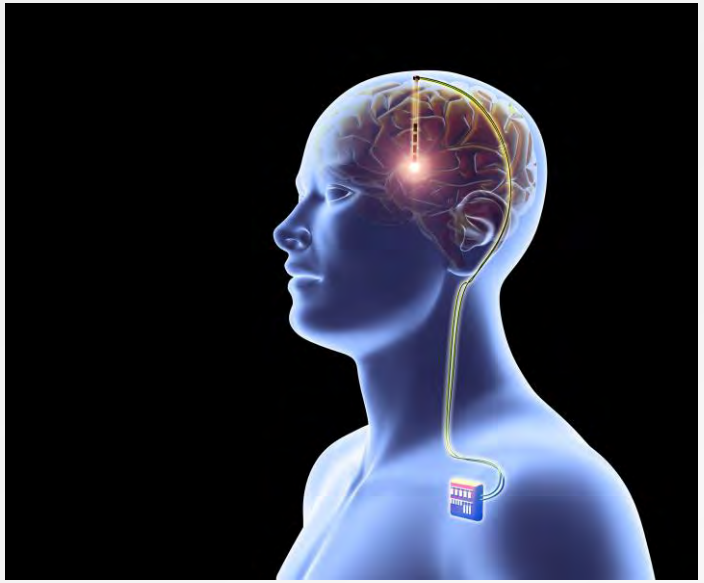
- **Yes**
- No

Documenting Similar Device Data

Understanding Similar Devices

‘**similar device**’: *devices belonging to the same generic device group. The MDR defines this as a set of devices having the same or similar intended purposes or a commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics.*

MDCG 2020-6



How can similar device data help the clinical evaluation… (MDCG 2020-5)

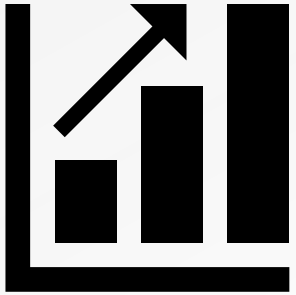
Ensuring that the risk management system is comprehensive by identifying relevant hazards and clinical risks.

Understanding the state of the art, the natural course of disease and alternative available treatment options

Helping to define the scope of the clinical evaluation, by identifying any design features in similar devices that pose special performance or safety concerns.

Provide input for clinical investigation design or post-market clinical follow-up design, and the post-market surveillance system.

Identification of relevant and specified clinical outcome parameters for the intended clinical benefits, based on the published clinical data pertaining to the similar device(s).



To define minimum requirements for a quantified clinical benefit that is considered clinically relevant, and/or to identify acceptable occurrence rates of risks and adverse events.

Why document similar devices in the CER?

Similar device data helps the assessor understand the availability of existing treatment/diagnostic options that exist for the clinical condition and other devices on the market.

This can be particularly helpful where there is an absence of data reported in the state of the art clinical literature search and could help support and explain why surrogate objectives/endpoints have been used.

Understanding similar devices and the performance and safety criteria can also help support activities mentioned in Annex III in relation to the PMS Plan:

(a) post-market surveillance plan shall address the collection and utilization of available information, in particular:

— publicly available information about similar medical devices.

Tips when documenting similar device data

- ✓ Don’t be hesitant to include this section in your clinical evaluation. It provides a wealth of insight for the assessor into the understanding of the clinical conditions and available diagnostic/treatment options that exist.
- ✓ Do not describe similar devices as ‘equivalent devices’ Equivalence has a completely different legal interpretation under MDR. Claiming a similar devices as equivalent will invite scrutiny from the assessor.
- ✓ Providing an overview of similar devices can help the assessor understand the relevance of the safety and performance objective data that has been used.
- ✓ Identify the sources of data when describing similar devices.

Documenting Clinical Claims

Claims & Evidence

MDR Article 7:

Prohibition of claims

- …ascribing functions and properties to the device which the device does not have, including creating false impressions
- …fail to inform about risks
- …suggesting misuse

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Clinical Claims

The clinical evaluation shall be thorough and objective, and take into account both favourable and unfavourable data. Its depth and extent shall be proportionate and appropriate to the nature, classification, intended purpose and risks of the device in question, as well as to the manufacturer's claims in respect of the device.

MDR Annex XIV Part A (2)

MDR Article 7- Example

Prohibition of claims ascribing functions and properties to the device which the device does not have.

This is not limited to clinical/medical claims. Non-Medical claims also require evidence.

Example:
Software as a medical device has a **non-medical** claim to ease a clinician's workload

-> Evidence is required to demonstrate this impact of reduced workload on the clinician.

Example:
Software as a medical device has a **medical** claim to be superior to detect cancerous cells
-> Clinical Evidence is required that cancer detection is superior to conventional methods.

'***clinical claims'*** is not defined in the MDR but can be considered as claims made in relation to **clinical performance and/or clinical benefit.** These terms are defined by the MDR as;

*'**clinical performance'** means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a **clinical benefit** for patients, when used as intended by the manufacturer;*

*'**clinical benefit'** means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health;*

Claims established outside of these areas are not clinical claims and maybe considered '**marketing or non-medical claims**' or **more simply 'claims**'. Clinical claims made by a manufacturer would always need to be supported by '**clinical data**'.

A manufacturer who states their device has ***no clinical claims*** are confirming that they will not make any other conclusions from the clinical data presented for conformity assessment than those presented to support the intended purpose.

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Tips when documenting clinical claims

- ✓ Consider a section in the CER that lists both clinical and non-clinical claims.
- ✓ Consider tabulating the claims with a direct reference to the data that support this claim that can be verified.

Clinical Claim	Evidence
1. 99% of patients reported reduced pain at day 12	Davies, Thomas et al. 2017. Understanding Pain after a hip implant. (Page 78 of the Clinical Evaluation Report) Morgan, Freeman et al 2023 – Pain scoring post surgery, (Page 76 of the Clinical Evaluation Report)
2. Reduction in Hospital Stay	Liden, Thorn et al. 2022, a new method of hospitalization for Buoy (Page 89 of the Clinical Evaluation Report)

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Performing and Documenting Literature Searches

Poll Question

Q: What is the minimum number of searches of literature required for your CER?

- 1
- 2
- 3
- 4

Poll Question

Q: What is the minimum number of searches of literature required for your CER?

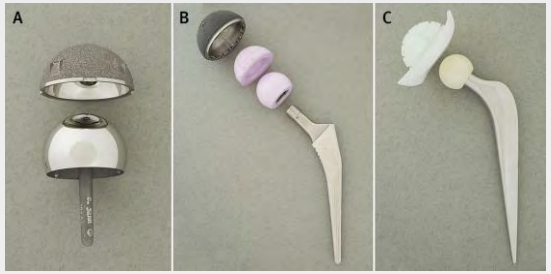
- 1
- **2**
- 3
- 4

Literature searches.

SoTA

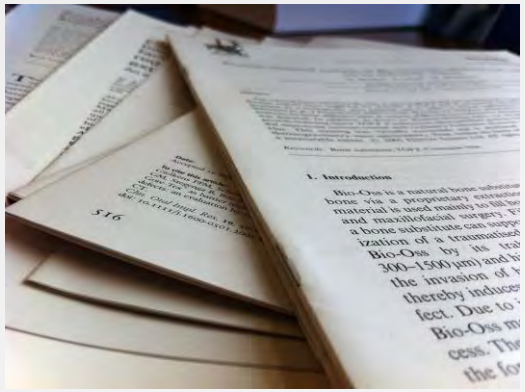
A literature search needs to be conducted to define the State of the Art for the clinical condition to be diagnosed/treated.

This will help formulate the safety and performance objectives required for the device under evaluation.



A second literature search needs to be conducted on the device (or equivalent) to identify existing favourable and unfavourable clinical data for all sizes/variants that is not held by the manufacturer.

This data will help you support the conformity assessment and ensure the data covers the scope of your devices.



Additional literature searches may be needed to specifically demonstrate safety/performance for other aspects of the device/complications associated with side-effects e.g. to confirm long-term outcomes from an undesirable side effect.

This supportive evidence can help build a stronger scientific argument of the device under evaluation.

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The Search Protocol

There is an expectation that the search protocol is comprehensive i.e. all effort should been made to retrieve all available data, and this provides confidence that bias is minimised.

Checklist

- ✓ Always use multiple databases as part of the search protocol and provide a clear justification as to the criteria for choosing those databases.
- ✓ The search protocol needs to be clear in its objective of the review with a validated method such as PICO or PRISMA
- ✓ Clear and exact search terms that are able to ensure appropriate identification of the data.
- ✓ Additional methods taken to identify literature such as internet searched and unpublished information such as competitor IFUs. The strategy should be defined and justified.
- ✓ Timelines of data searched and justification for ‘cut-off points’
- ✓ Clear exclusion and inclusion criteria and justification for these choices.
- ✓ A clear strategy for considering data already held by the manufacturer and supplication of returned results.
- ✓ the data collection plan that defines data management practices to ensure data integrity during extraction (e.g. quality control/second review of extracted data by additional reviewer)

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Appraisal Plan

The appraisal plan needs to be clear and applied consistently and take into consideration:

- **Suitability** - Is the data pre-clinical or actual clinical data as defined in the MDR Article 2 (48)?
- **Applicability** - Is this data on the actual device or the equivalent device?
- **Population** - Is the population reflective of the intended purpose of the device?
- **Quality** - Is the data **sufficient?**

Sufficient Data = Quality & Quantity.

MEDDEV 2.7.1 Rev. 4, Appendix 6 expects the manufacturer to consider the following in relation to sufficiency of data:

- A lack of information on elementary aspects, such as methods, patient population, side-effects, or clinical outcomes.
- Statistically insignificant data or improper statistical methods.
- A lack of adequate controls leading to bias or confounding.
- The improper collection of mortality and serious adverse events data.
- Misinterpretation of data by the authors, such as when the conclusions they draw are not in line with the results section of the report.
- Any illegal activities, such as clinical investigations that were not conducted in compliance with local regulations.

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Impact of minimising bias

- If a manufacturer can clearly demonstrate that the search protocol and appraisal plan is free from bias and has been screened appropriately for sufficiency, then this means greater trust in the results of the output of that search.
- This inevitably means that the data is reliable and trustworthy, and the assessor can be confident the manufacturer is presenting an accurate story and making the correct conclusions.
- Therefore it is essential the manufacturer provides a **strong and transparent** search protocol and appraisal plan.

Excellent search protocol performed with minimal bias → Trusted Results/Appraisal

Documenting the results of the clinical literature

- ✓ Focus your analysis on the data that holds the highest sufficiency (quality and quantity). These are the articles that your appraisal plan has identified as the heaviest weighting. Therefore these articles should support your overall conclusions.
- ✓ The data should be clear and reported in a scientific manner, avoiding any bias from the medical writer. (Or marketing department!)
- ✓ Consider stratifying the data in a table format with consideration to the indications, populations and variants.
- ✓ The analysis of the literature should be based on full text articles and the notified body may request a copy as part of the conformity assessment process.

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Remember the purpose of this activity…

As the literature data is reported consider how each article considers the intended purpose and indications of the device and how this information impacts/strengthens the below points.

- ✓name of disease or condition/ clinical form, stage, severity/ symptoms or aspects to be
- ✓treated, managed or diagnosed
- ✓patient populations (adults / children / infants, other aspects)
- ✓*intended user (use by health care professional / lay person)*
- ✓organs / parts of the body / tissues or body fluids contacted by the device
- ✓duration of use or contact with the body
- ✓repeat applications, including any restrictions as to the number or duration of reapplications
- ✓contact with mucosal membranes/ invasiveness/ implantation
- ✓contraindications
- ✓precautions required by the manufacturer
- ✓single use / reusable
- ✓other aspects

Tips when documenting Literature Searches

- ✓ A literature search on SoTA **and** the device under evaluation (or equivalent is always required)
- ✓ Focus efforts on documenting a strong and transparent search protocol and appraisal plan.
- ✓ Think of your intended purpose and indications of the device when reviewing the outputs of the literature search and describe each aspect of the intended purpose in your analysis.

Updates and Competency

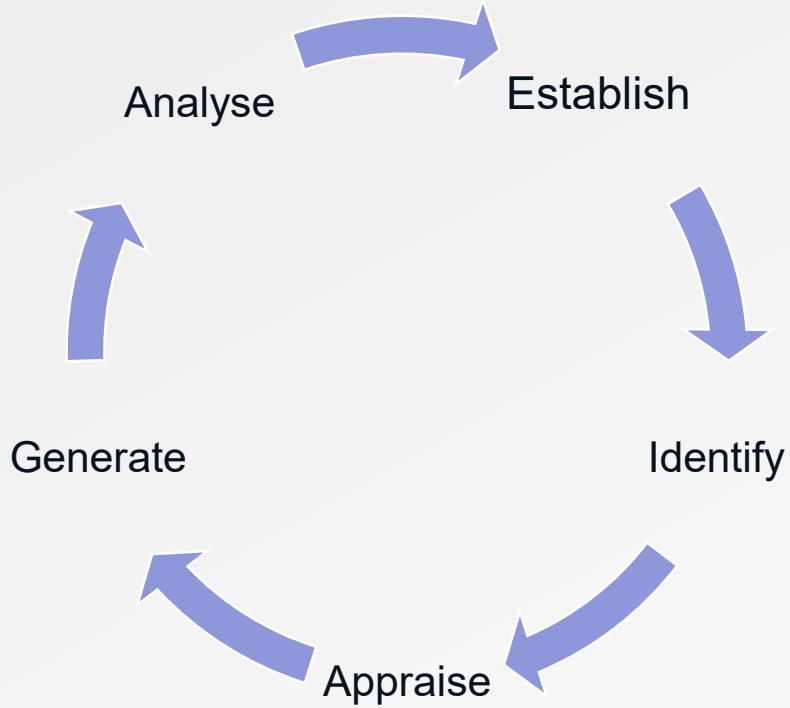
Expected updates to the CER

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.

Ensure your CER has a clear section and justification for your update frequency and a clear revision history.

As part of these updates it is expected that the manufacturer repeats the literature searches to look for new data on the device under evaluation but also to verify that they are still ‘state of the art’. This is also considered part of your overall PMS plan per Annex III.



Article 61 (11)

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.

Class III and Implantable devices require at least an annual update to the CER based on interpretation of Article 61 (11). What about Class IIa/IIb Non-Implantable devices?

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Competence

The evaluators should check the clinical evaluation report, provide verification that it includes an accurate statement of their analysis and opinions, and date and **sign the report**.

Provide an updated CV and signed/dated declaration of interests for **each** evaluator.

Ensure all matters in A11 of Meddev 2.7/1 rev 4 have been considered in the DOI.

Common Issues

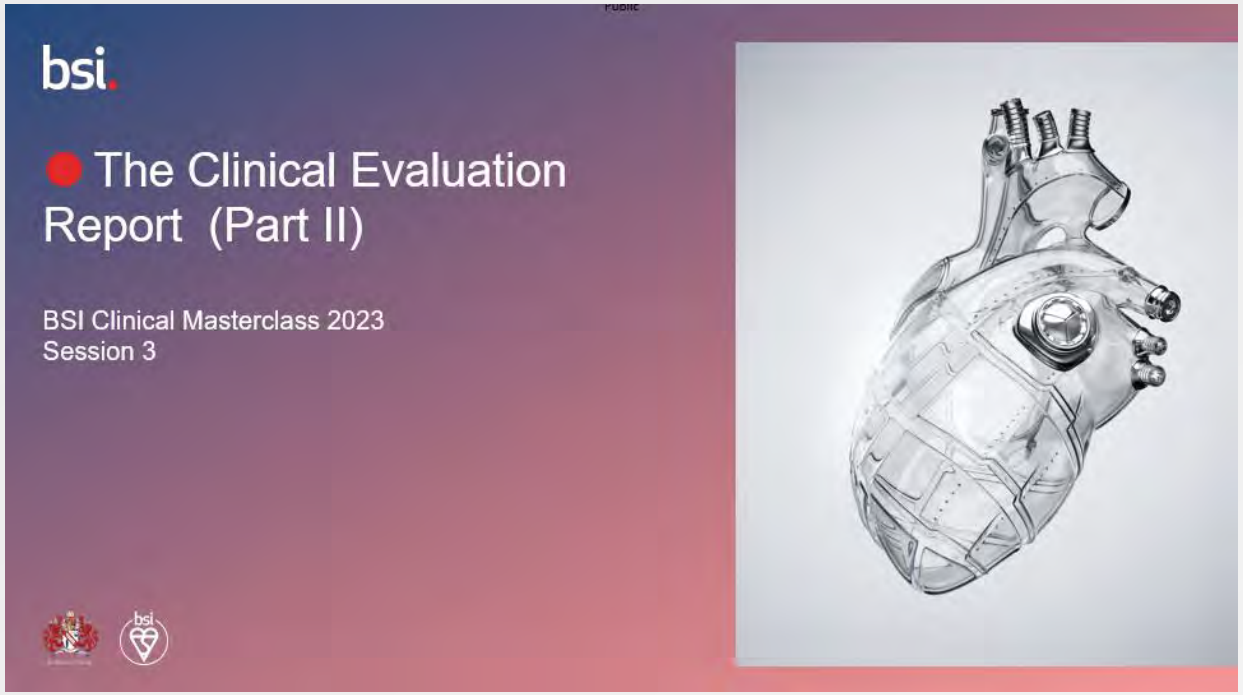
The evaluator has little experience of the device or intended patient population. It may be justifiable for lower risk devices that are standard of care but high risk devices need appropriate competence demonstrated.

CERs with an evaluator who has also been involved in the clinical evaluation studies presents an issue in relation to bias. Consider alternative clinical experts to approve the Clinical Evaluation Report than those who are also clinical trial investigators.

Tips when documenting frequency of updates and competence

- ✓ Ensure the frequency is appropriate to the device classification and a strong justification is provided if the timelines are longer than other output activities.
- ✓ Ensure the CER is signed and dated by the evaluator and an updated CV and DOI is provided for each author.
- ✓ Consider adding a list of the current version number/date of the information materials supplied by the manufacturer (label, IFU, SSCP available promotional materials in the CER.

Next Session Slide:



Next Session: **Wednesday 8th February 2023**
Clinical Evaluation Report Part II

How to document:

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

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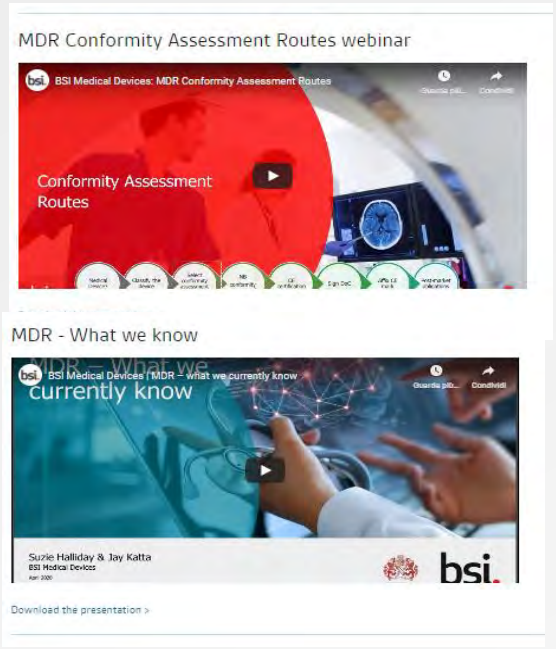
BSI Medical Devices – Use Our Resources

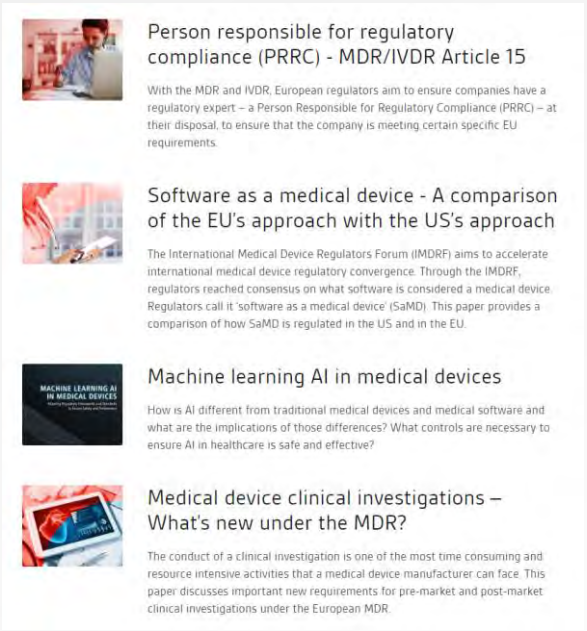
https://www.bsigroup.com/en-GB/medical-devices/resources

Brochures, Guides and Documents

Webinars



White Papers and Articles



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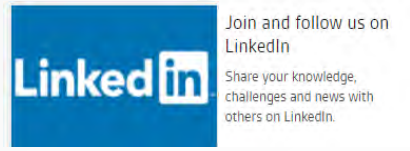

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