MedDev 2.7.1 Rev 4
Medical Devices Regulation
Clinical Evidence Requirements

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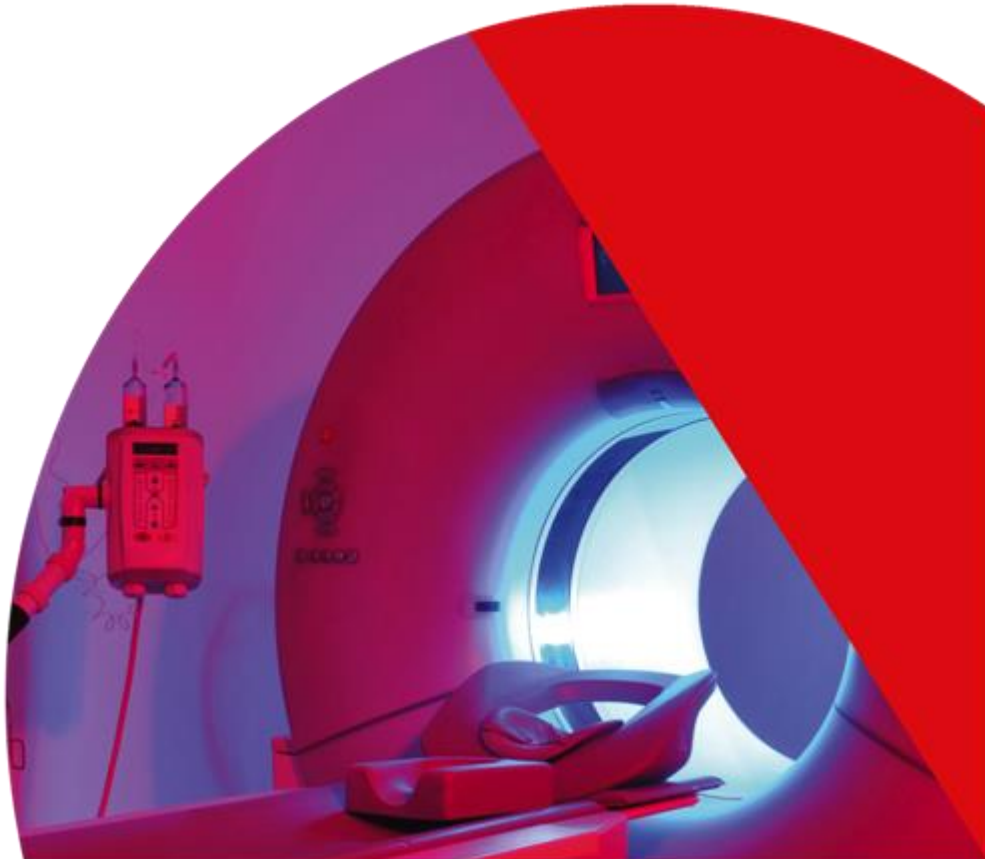
18 October 2016



Clinical Evidence Requirements - MedDev 2.7.1 rev 4

1. Frequency of updates to the Clinical Evaluation Report (CER)
2. Qualifications of report authors and evaluators
3. Specific and measurable objectives for the CER
4. Establishing the state of the art
5. Scientific validity of data

6. Equivalence
7. Access to data for equivalent devices
8. When is a clinical investigation required?
9. Risk-benefit
10. Post Market Surveillance (PMS) and Post Market Clinical Follow-up (PMCF)

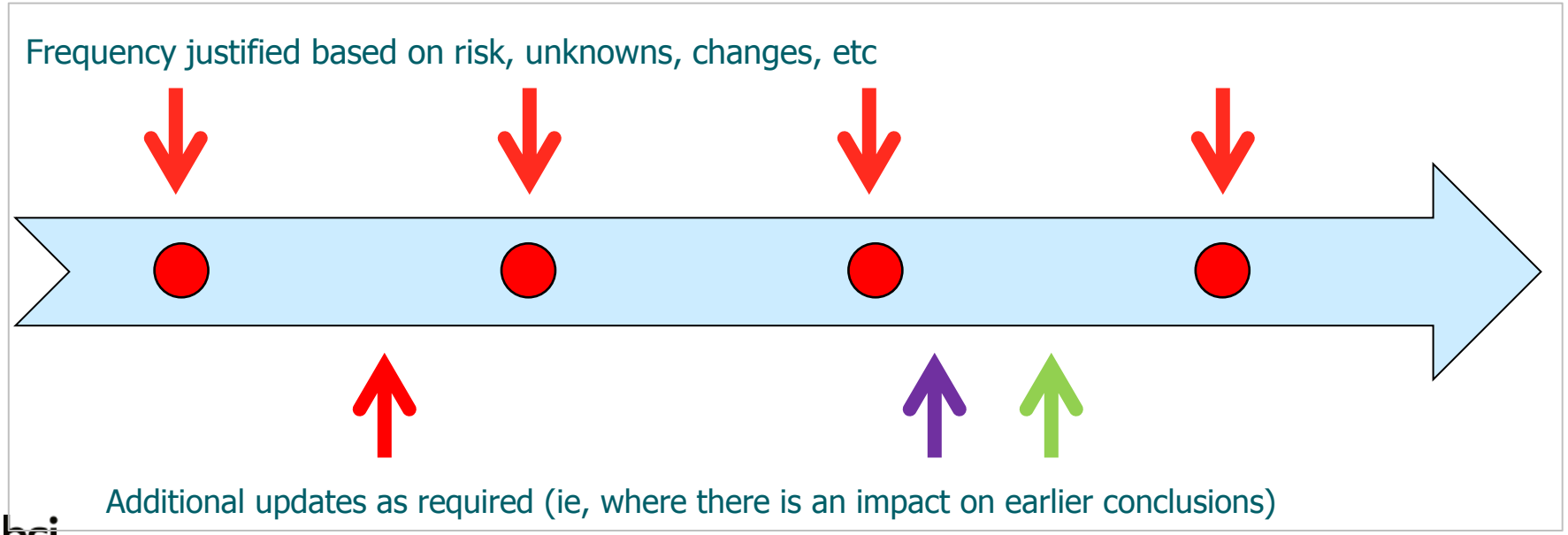
1. Section 6.2.3
2. Section 6.4
3. Section 7 + Appendix 5
4. Section 8.2
5. Section 9.3.1
   - Section 8 + Appendix 5
   - Section 9 + Appendix 6
   - Section 10 + Appendix 7
6. Appendix 1
7. Appendix 12.2.3
8. Appendix 2
9. Appendix 7
10. Appendix 12

1. Frequency of updates to the Clinical Evaluation Report

Clinical evaluation updates (MedDev 2.7.1 clause 6.2.3)

The clinical evaluation must be actively updated:

- At regular defined intervals
- Additionally, when new PMS information could impact the current evaluation



Clinical evaluation updates (MedDev 2.7.1 clause 6.2.3)

Frequency of updates must be:

- Defined
- Justified

high risk devices, patient populations or indications;

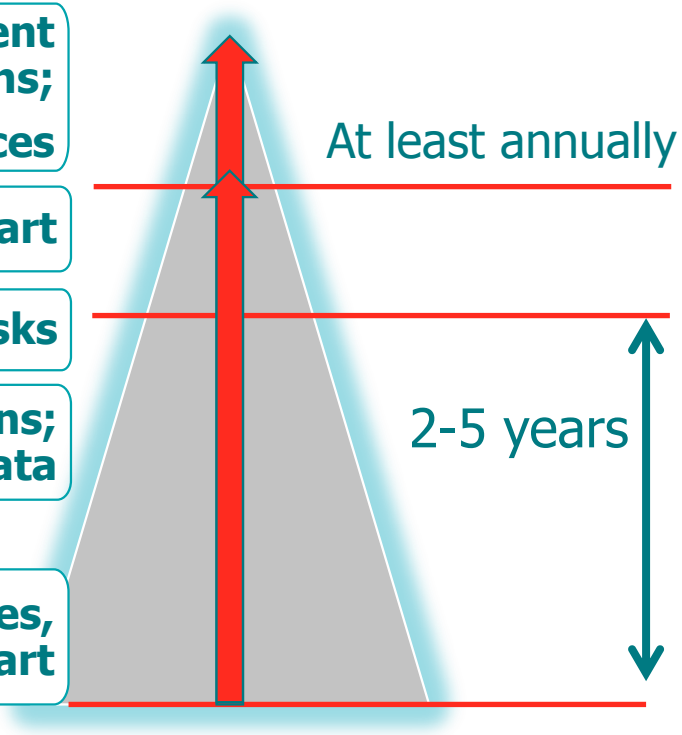
novel or not well established devices

rapidly evolving state of the art

medium to long term risks

uncertainties or unanswered questions; low volume of data

Very low risk, well established devices, little or no change in the state of the art



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MDR – Periodic Safety Update Report & Summary of Safety and Clinical Performance

Article 60c – PSUR: Summary and conclusions of PMS together with details of any associated CAPAs

- Conclusions of the benefit-risk determination
- Main findings of PMCF
- Volume of Sales, including
  - Estimate of the Population that use the device
  - Where practicable, usage frequency of the device

- Manufacturers of Class IIb and III devices ⇨ update <u>at least annually</u>
- Class III devices and implants ⇨ submit to the Notified Body via Eudamed
- Manufacturers of class IIa devices ⇨ update when necessary and <u>at least every two years.</u>

MDR – Periodic Safety Update Report & Summary of Safety and Clinical Performance

Article 26 – SSCP:

- Manufacturer + SRN
- Device + UDI
- Intended Purpose, Indications, Contra-indications
- Description, previous variant(s), differences, accessories, other products intended to be used in combination
- Possible diagnostic or therapeutic alternatives
- Harmonised Standards / Common Specifications
- Summary of the Clinical Evaluation Report + PMCF
- Suggested profile and training for users
- Information on residual risks, undesirable effects, warnings & precautions

- Required for Class III and implantable devices (except custom and investigational devices)
- Made available to users, and patients if relevant, via Eudamed
- Updated at least annually (Article 49.4) if warranted

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2. Qualifications of report authors and evaluators

MedDev 2.7.1 – 6.4 Who should perform the clinical evaluation?

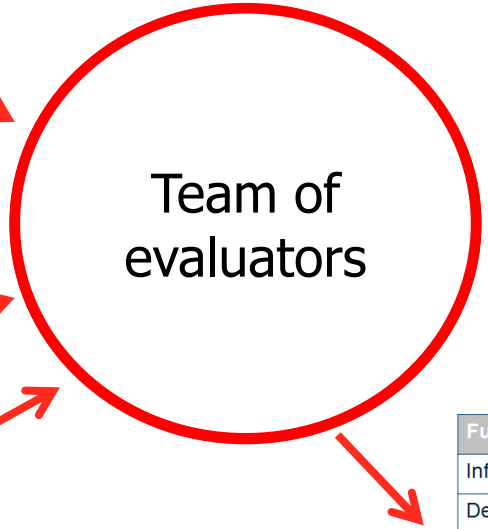
General requirements:

regulatory requirements

research methodology
(eg clinical investigation design and biostatistics)

medical writing
(eg systematic review, clinical data appraisal)

information management
(ie search strategies, databases, etc)



Device specific / risk-based requirements:

device technology
(eg engineers, materials scientists, toxicologists)

specialist clinical expertise

Functional Area	Signature	Date
Information Systems		11/October/2015
Development Engineer		11/October/2015
Research		11/October/2015
Clinical		12/October/2015
Marketing		11/October/2015
Regulatory		13/October/2015

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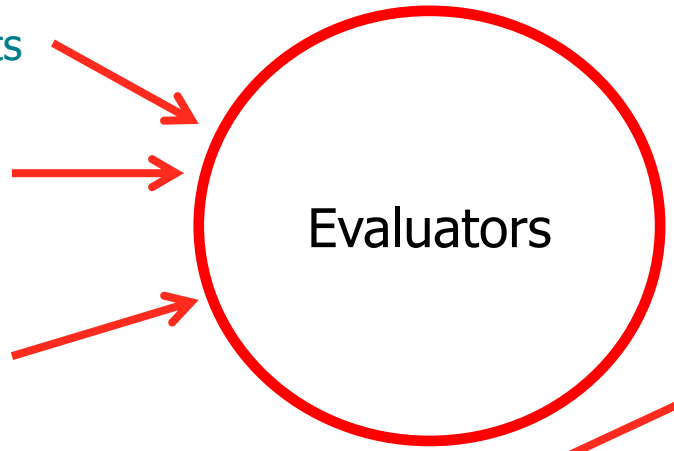
MedDev 2.7.1 – 6.4 Who should perform the clinical evaluation?

Manufacturer must:

- Define requirements
- Justify choice
  (CV, declarations of interest)
- Provide evidence of suitability
  (CV, declarations of interest)



Unless duly justified, evaluators should have at least:

- Degree + 5 years' relevant professional experience

or

- 10 years relevant experience if degree not required

- Document and justify if evaluators are less experienced

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3. Specific and measurable objectives for the CER

MedDev 2.7.1 – 7 Definition of scope of the clinical evaluation

Device specification (technology, intended use, design history, etc)

Essential Requirements requiring clinical evidence

Scope of clinical evaluation (ie products/models/sizes/settings, state of the art / benchmarks, conditions of and intended use, safety and performance requirements)

Specific and measurable objectives

MedDev 2.7.1 – A5. Literature search and review protocol, key elements

The literature search and literature review protocol should:

- Be objective, non-biased, systematic
- specify the literature review questions to be addressed

- **Cochrane Handbook for Systematic Reviews of Interventions**
- **PRISMA (The Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement**
- **MOOSE Proposal (Meta-analysis Of Observational Studies in Epidemiology)**

- **PICO (patient characteristics, type of intervention, control, and outcome queries)**

Research questions leading to specific and measurable objectives

The PICO criteria

- **P**opulation/Patient (what population the device is intended for)
- **I**ntervention/Indicator
- **C**omparator/Control
- **O**utcome (measurable & specific)

Appropriate to device, intended use, safety, performance, risks, etc

eg: pain scores, mortality, re-intervention, mobility, quality of life, size (of tumour / lesion / obstruction), flow rates, blood oxygen levels, etc

Research question(s): For (Patient population) should (Intervention) or (Control) be performed to achieve (Outcome)?

4. Establishing the state of the art

MedDev 2.7.1 – 8.2 Data retrieved from literature

Establishing the state of the art:

- Standards and guidance documents
- Data from benchmark devices
- Data from equivalent devices
- Safety and performance of other available treatment options

Used to determine:

- clinical safety and performance endpoints
- what the minimum acceptable outcomes for these endpoints should be
- Clinically acceptable vs. avoidable risks
- Validity of surrogate endpoints (if used)

5. Scientific validity of data

What *is* sufficient clinical evidence?

MedDev 2.7.1, 4. Definitions

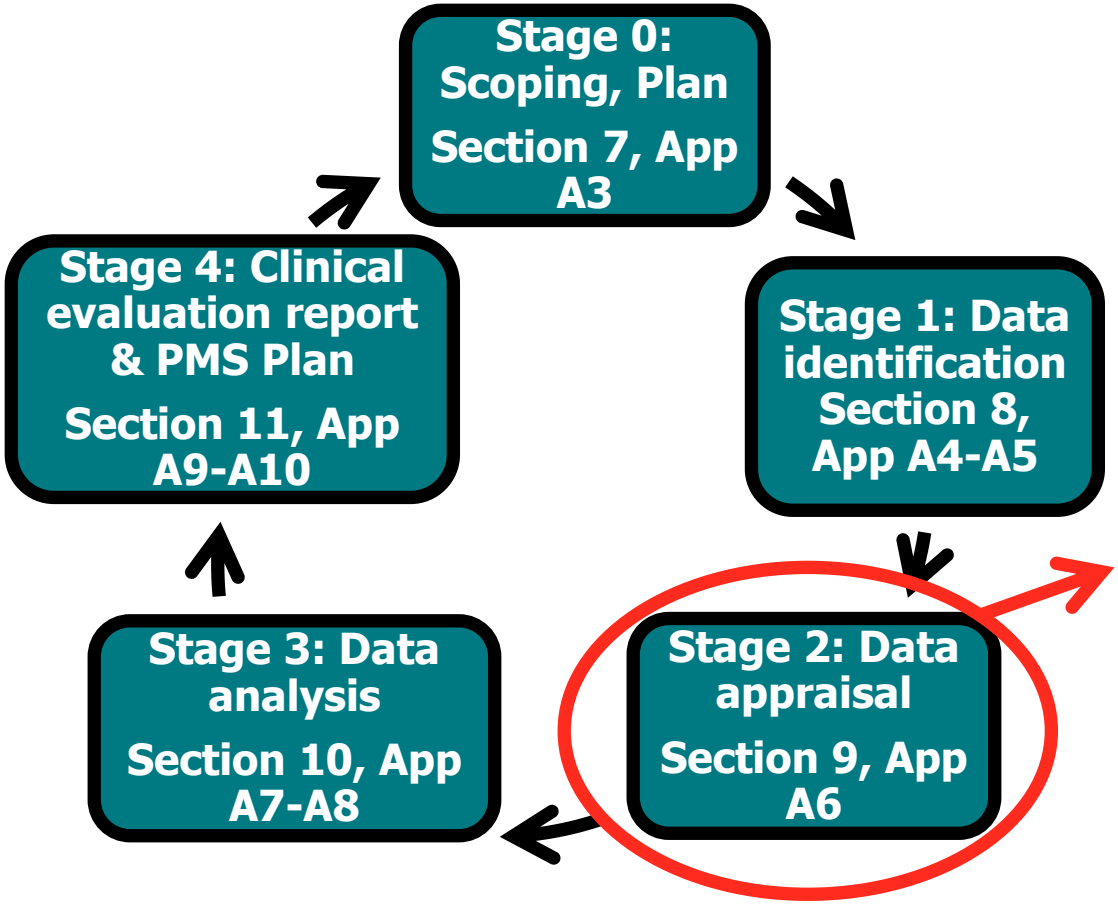
Sufficient clinical evidence:

an amount and quality of clinical evidence to guarantee the scientific validity of the conclusions.

Key sections of MedDev 2.7.1:

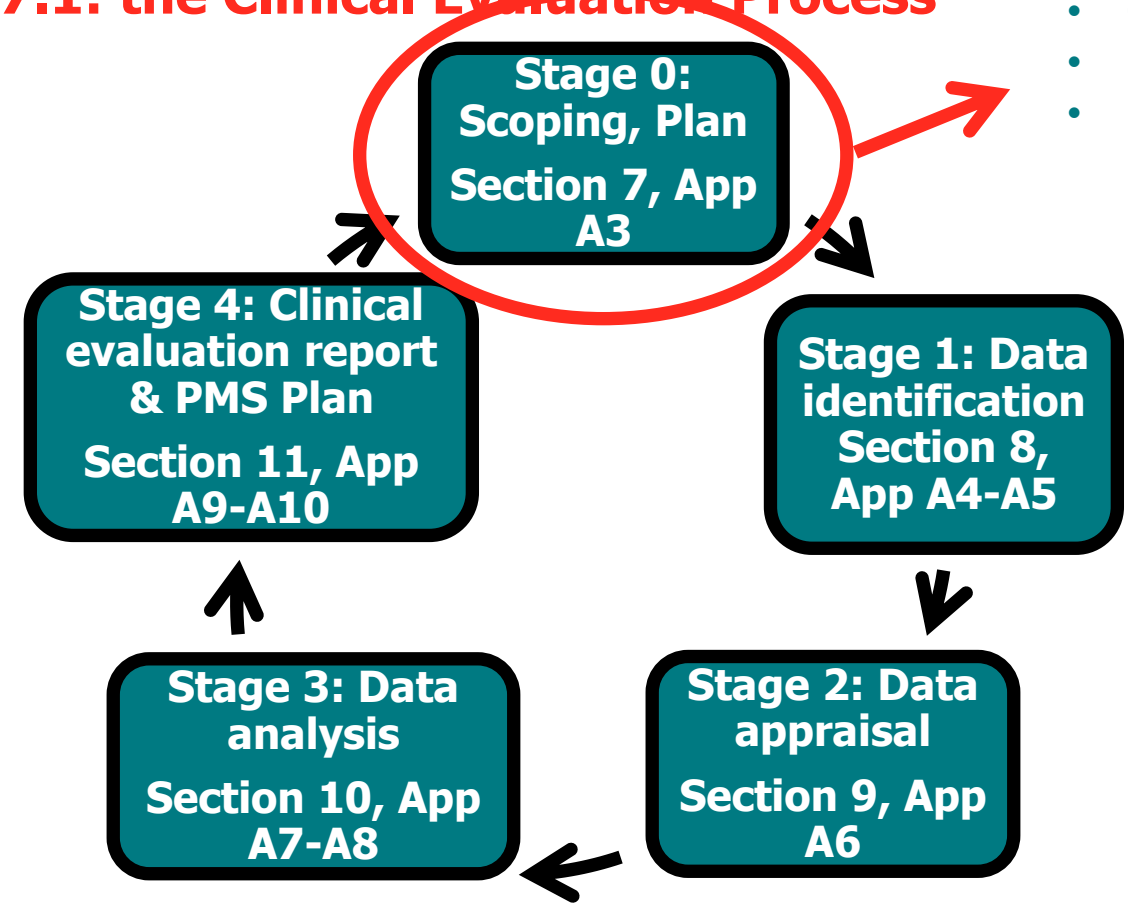
- 9.3.1: How to evaluate methodological quality and scientific validity
- A6: Appraisal of clinical data - examples of studies that lack scientific validity

MedDev 2.7.1: the Clinical Evaluation Process



- Quality of study or methodology
- Quality of data
- Volume of data
- Relevance
- Weighting
- Thoroughness
- Objectivity
- Sources of error
- Statistical methods
- …

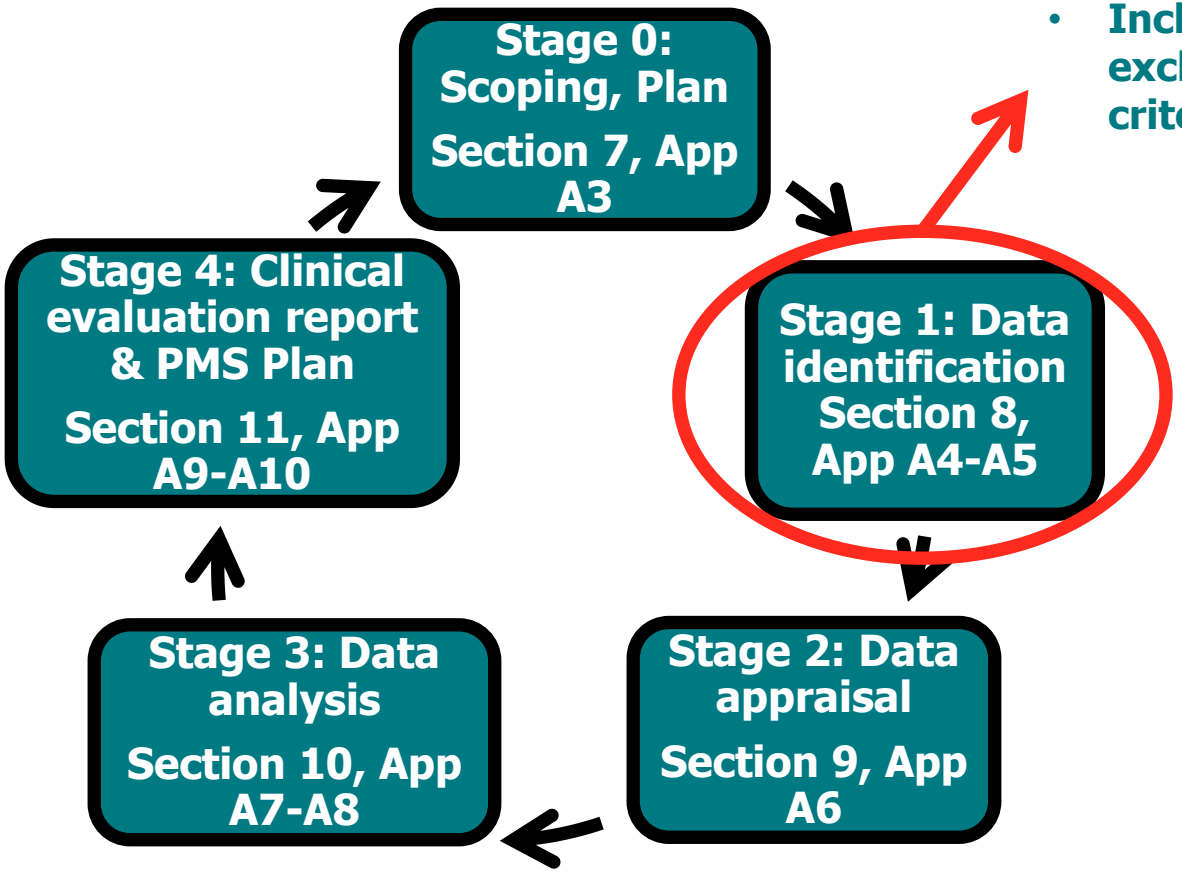
MedDev 2.7.1: the Clinical Evaluation Process



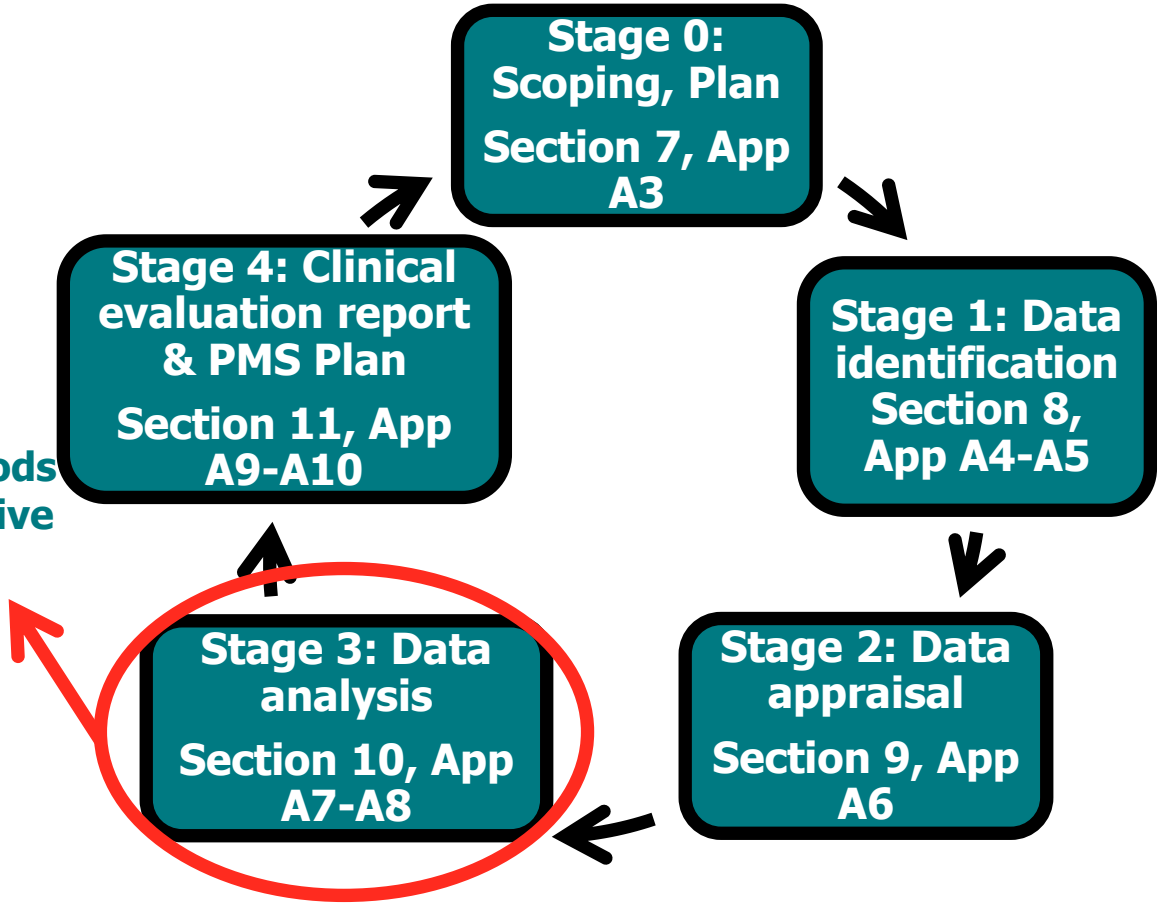
- Objectives
- Benchmarks
- Equivalence rationales

MedDev 2.7.1: the Clinical Evaluation Process

- Sources of data
- Search protocols
- Inclusion & exclusion criteria



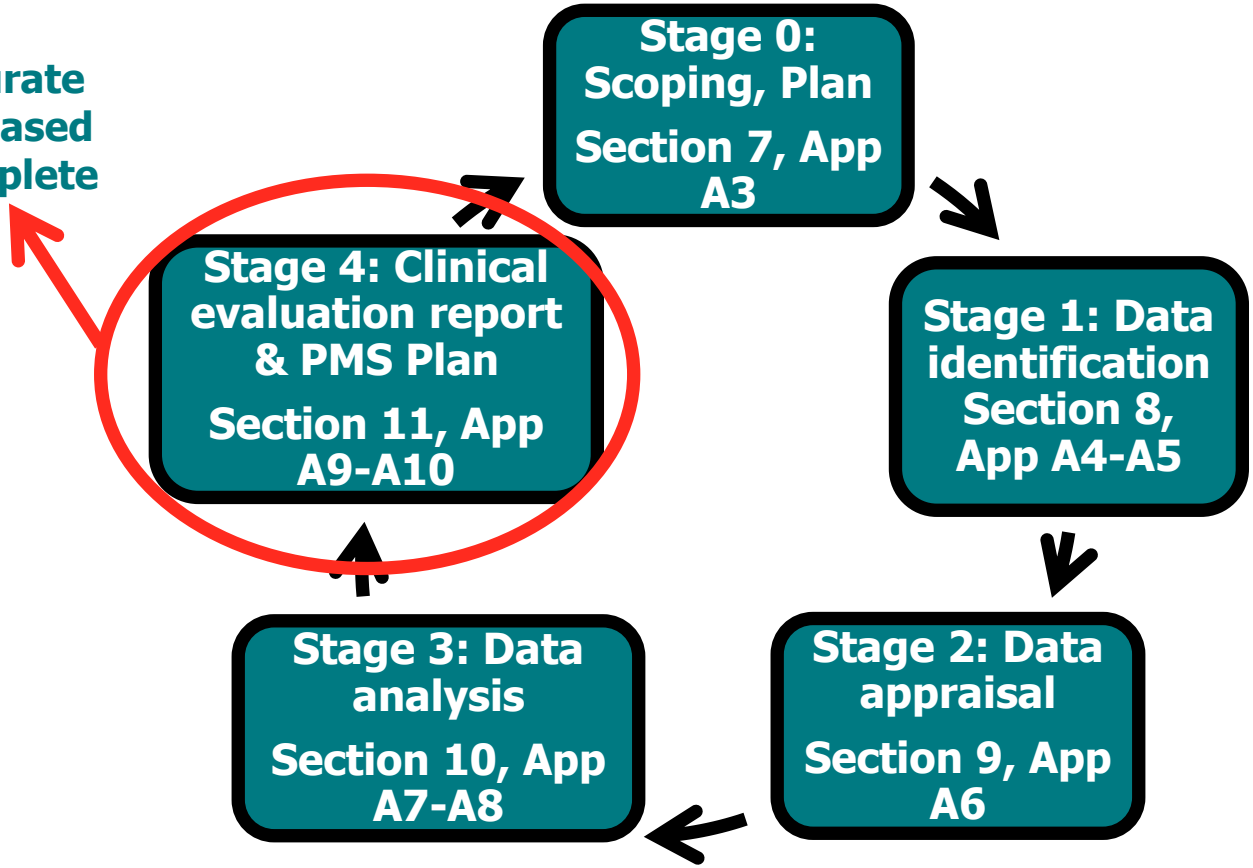
MedDev 2.7.1: the Clinical Evaluation Process



- Sound methods
- Comprehensive
- Complete
- Consistent

MedDev 2.7.1: the Clinical Evaluation Process

- Accurate
- Unbiased
- Complete



6. Equivalence

Equivalence - MedDev 2.7.1 Rev 3

Technical

- be of similar design
- used under similar conditions of use
- have similar specifications and properties (e.g. tensile strength, viscosity, surface characteristics)
- use similar deployment methods (if relevant)
- have similar principles of operation

Biological

- use same materials or substances in contact with the same human tissues or body fluids

Clinical

- used for the same clinical condition or purpose at the same site in the body
- in a similar population (including age, anatomy, physiology)
- have similar relevant critical performance according to the expected clinical effect for a specific intended purpose

Equivalence - MedDev 2.7.1 Rev 3 / MedDev 2.7.1 Rev 4

Technical

- be of similar design
- used under similar conditions of use
- have similar specifications and properties (e.g. tensile strength, viscosity, surface characteristics, wavelength, surface texture, porosity, particle size, nanotechnology, specific mass, atomic inclusions such as nitrocarburising, oxidability)
- use similar deployment methods (if relevant)
- have similar principles of operation and critical performance requirements

Biological

- use same materials or substances in contact with the same human tissues or body fluids

Exceptions can be foreseen for devices in contact with intact skin and minor components; in these cases risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material. Evaluators should consider biological safety (e.g. ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference

Clinical

- used for the same clinical condition or purpose (including when applicable similar severity and stage of disease, same medical indication),
- at the same site in the body
- in a similar population (including age, gender, anatomy, physiology)
- not foreseen to deliver significantly different performances
- have similar relevant critical performance according to the expected clinical effect for a specific intended purpose

Equivalence - MedDev 2.7.1 Rev 3 / MedDev 2.7.1 Rev 4 / MDR

Technical

- be of similar design
- used under similar conditions of use
- have similar specifications and properties (e.g. physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, software algorithms, porosity, particle size, nanotechnology, specific mass, atomic inclusions – nitrocarburising, oxidability)
- use similar deployment methods (if relevant)
- have similar principles of operation and critical performance requirements

Biological

- use same materials or substances in contact with the same human tissues or body fluids
- for a similar kind and duration of contact and similar release characteristics of substances
- including degradation products and leachables
- Exceptions can be foreseen for devices in contact with intact skin and minor components; in these cases risk analysis results may allow the use of similar materials taking into account the role and nature of the similar material. Evaluators should consider biological safety (e.g. ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference.

Clinical

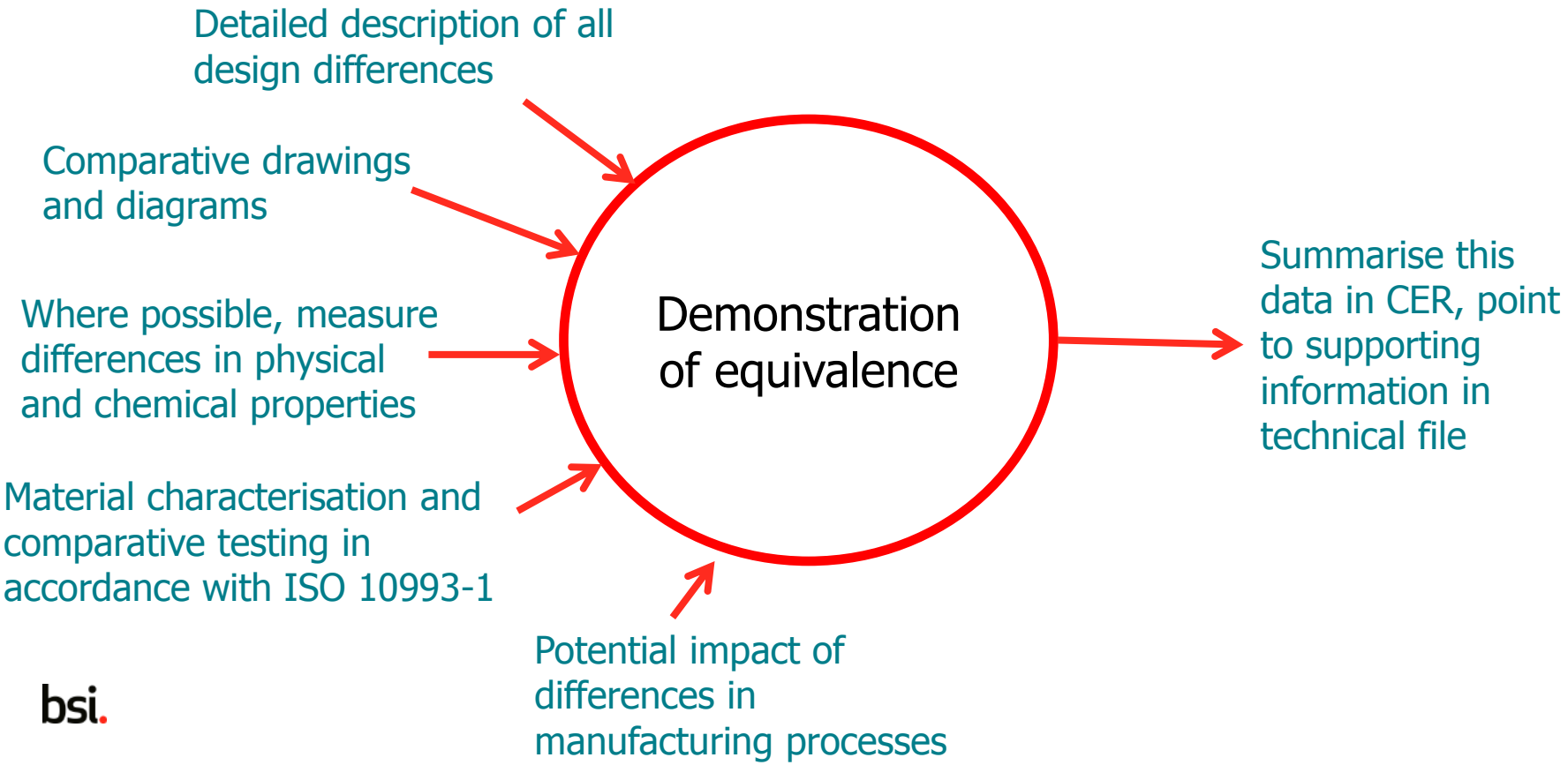
- used for the same clinical condition or purpose (including when applicable similar severity and stage of disease, same medical indication),
- at the same site in the body
- in a similar population (including age, gender, anatomy, physiology)
- have same kind of user
- not foreseen to deliver significantly different performances
- have similar relevant critical performance according to the expected clinical effect for a specific intended purpose

MedDev 2.7.1 – A1 Demonstration of equivalence

For assuming equivalence:

- each device with which equivalence is claimed must fulfil all three equivalence characteristics (clinical, technical, biological)

MedDev 2.7.1 – A1 Demonstration of equivalence



MedDev 2.7.1 – A1 Demonstration of equivalence

For clinical data to be considered relevant, the equivalent device must be:

- CE-marked
- used in accordance with its intended purpose as documented in the IFU

"Note: Exceptions can be considered.

When the equivalent device is not a CE-marked device, information concerning the regulatory status of the equivalent device and a justification for the use of its data should be included in the clinical evaluation report. The justification should explain if the clinical data is transferrable to the European population, and an analysis of any gaps to good clinical practices (such as ISO 14155) and relevant harmonised standards."

7. Access to data for equivalent devices

MedDev 2.7.1 – A12.2.3 – Clinical data from an equivalent device and other products

- Notified Body should **assess and document the level of access** to the technical and clinical data from an Equivalent device.

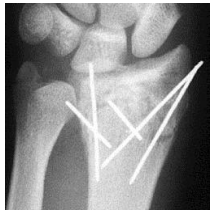
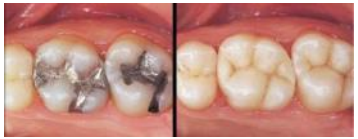
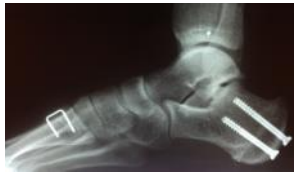
Clinical Evaluation and Investigation – Article 49 (MDR) – Clinical Evaluation

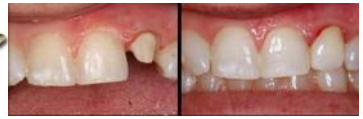
Equivalence can only be claimed for:

- Design modifications of manufacturer's own CE-marked devices
- Where there is a contract in place with the other manufacturer allowing full access to the data on an ongoing basis

There will be exceptions: "Clinical investigations need <u>not</u> be performed in the following cases – **sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors** for which the clinical evaluation is based on sufficient clinical data and is in compliance with the relevant product-specific **common specification**, where such a common specification is available"

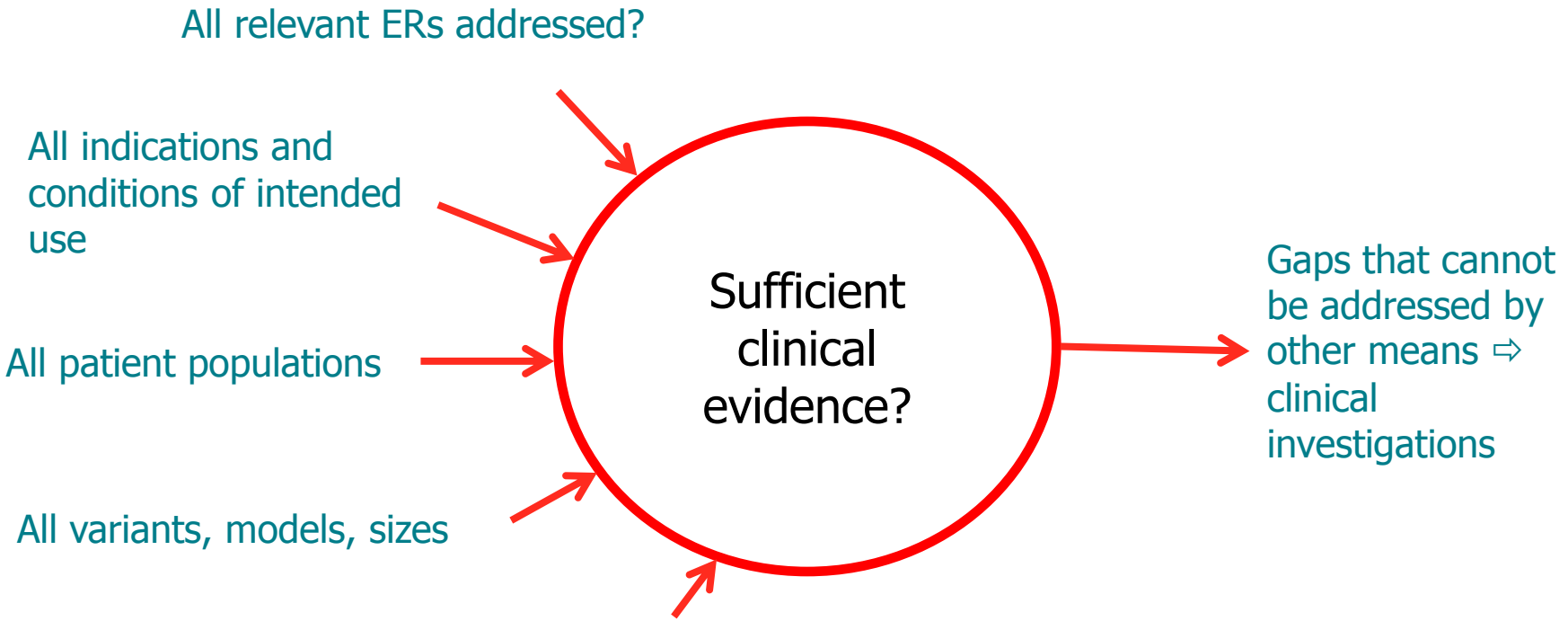
… in view of similar well-established technologies – Delegated Act – add or remove to this list …

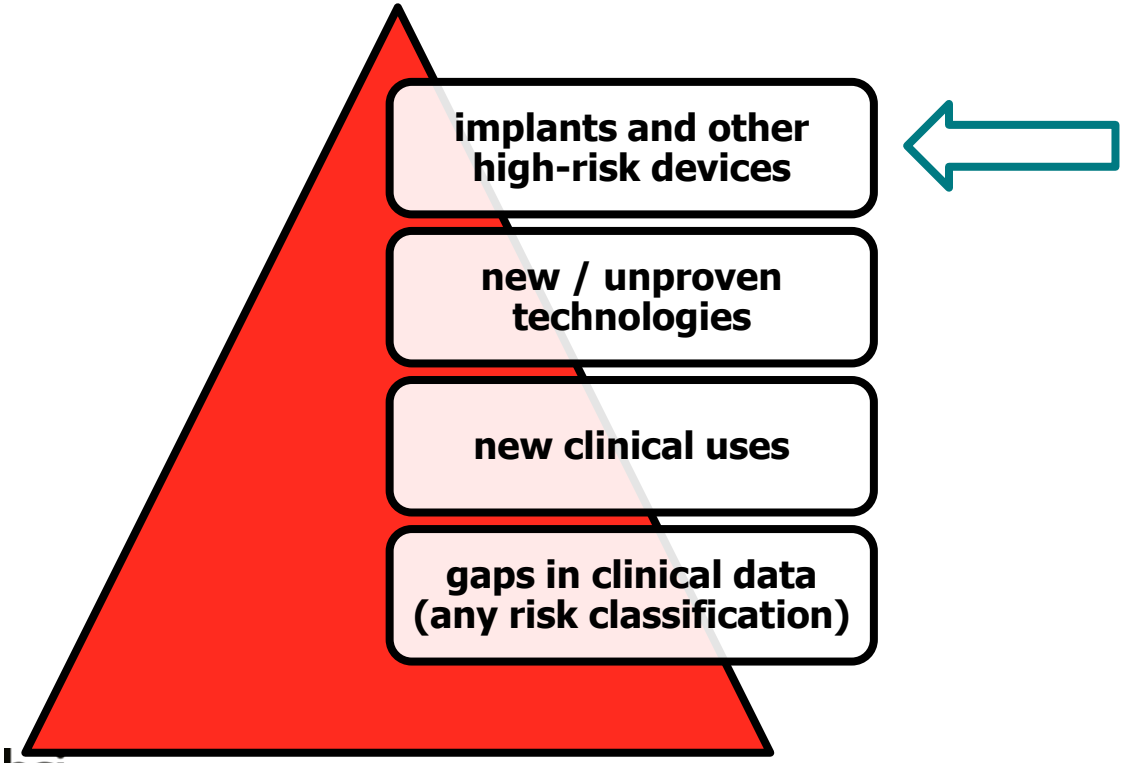



8. When is a clinical investigation required?

MedDev 2.7.1 – A2 When should clinical investigations be carried out?



MedDev 2.7.1 – A2 When should clinical investigations be carried out?



clinical investigations with the device under evaluation are required for implantable and class III devices unless it can be duly justified to rely on existing clinical data alone

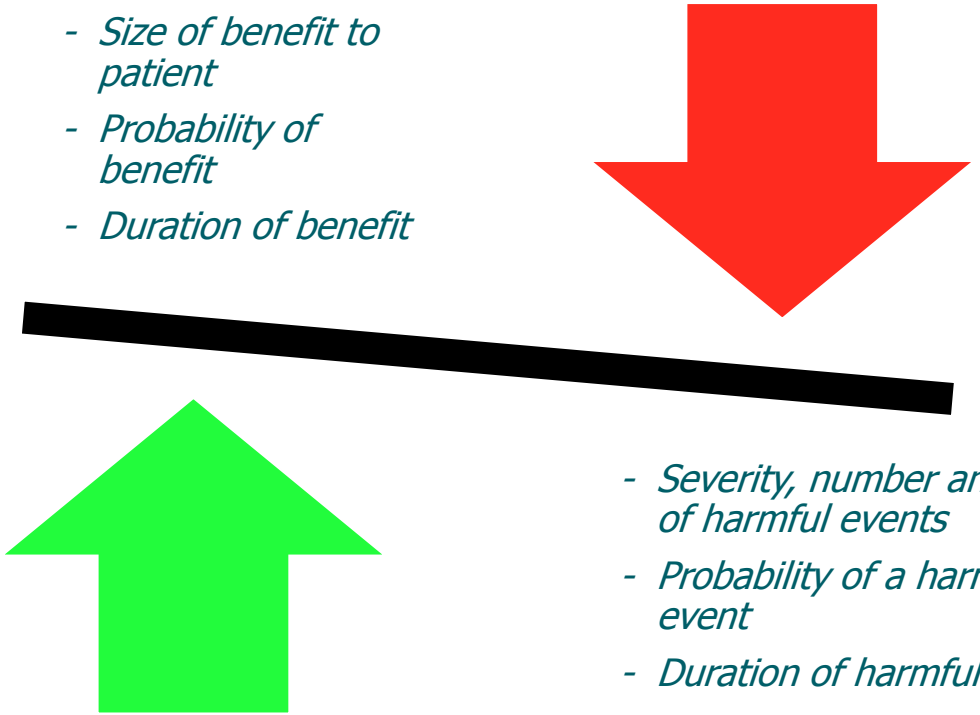
* guidance recognises that some data are not amenable to clinical investigation.

9. Risk-benefit

MedDev 2.7.1 – A7.2 Requirement for acceptable benefit/risk

Evaluation of clinical benefits

- *Size of benefit to patient*
- *Probability of benefit*
- *Duration of benefit*



- *Severity, number and rates of harmful events*
- *Probability of a harmful event*
- *Duration of harmful events*

Evaluation of clinical risks

10. Post Market Surveillance (PMS) and Post Market Clinical Follow-up (PMCF)

MedDev 2.7.1 – A12. Activities of notified bodies

QMS certificates

Notified Body assesses:

- the manufacturer's procedures for clinical evaluation, PMS and PMCF
- Representative sample of Class IIa and IIb devices (sample based on risk and novelty)

Design or type examination certificates

Notified Body assesses:

- data presented in the clinical evaluation report, validity of the conclusions drawn by the manufacturer, and conformity of the device to relevant Essential Requirements

NB confirms

- appropriateness and adequacy of the device specific PMS plan;
- PMCF is appropriate and aligned to gaps identified in by the clinical evaluation

- Class IIa and IIb samples must be assessed in full in accordance with this guidance document
- Review team must include relevant clinical experience (eg, doctor, nurse or other relevant medical practitioner)

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Questions & Answers

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Whitepaper – MedDev 2.7.1 Rev 4

http://www.bsigroup.com/meddev/LocalFiles/en-GB/Documents/MedDev-brochure.pdf