

15th Medical Device Quality Congress
April 4, 3:00-4:30 pm

Panel Discussion:
MEDDEV 2.7/1 revision 4 and Clinical
Evaluation Reporting (CER)

Moderator:

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Panel Discussion: MEDDEV 2.7/1 revision 4 and Clinical Evaluation Reporting (CER)

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- Presentation [45 min]
- Q&A [45 min]



the **and** means more

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MEDDEV 2.7/1 revision 4 and Clinical Evaluation Reporting

- Challenges surrounding demonstration of equivalence
- Considerations for grouping devices for process efficiencies
- Challenges with legacy products with limited clinical data

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CHALLENGES WITH EQUIVALENCE

DEFINITIONS



MEDDEV 2.7/1 Rev. 4 :

- **Clinical data:** the safety and/or performance information that is generated from the clinical use of a device. Clinical data are sourced from:
 - clinical investigation(s) of the device concerned; or
 - clinical investigation(s) or *other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated*; or
 - published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.
- **Equivalent device:** a device for which equivalence to the device in question can be demonstrated.

EQUIVALENCE - BASICS

MEDDEV 2.7/1 Rev 3

Equivalence means:

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

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 in contact with the same human tissues or body fluids.

MEDDEV 2.7/1 Rev 4

Clinical, technical and biological characteristics shall be taken into consideration:

Clinical: used for the same clinical condition (including when applicable similar severity and stage of disease, same medical indication), used for the same intended purpose, and used at the same site in the body, and used in a similar population (this may relate to age, gender, anatomy, physiology, possibly other aspects), and not foreseen to deliver significantly different performances (in the relevant critical performances such as the expected clinical effect, the specific intended purpose, the duration of use, etc.).

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

Biological: Use the 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 of devices...

EU MDR Annex XIV

The following technical, biological and clinical characteristics shall be taken into consideration:

Clinical: the device is used for the same clinical condition or purpose, including similar severity and stage of disease, at the same site in the body, in a similar population, including as regards age, anatomy and physiology; has the same kind of user; has similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.

Technical: the device is of similar design; is used under similar conditions of use; has similar specifications and properties including physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and software algorithms; uses similar deployment methods, where relevant; has similar principles of operation and critical performance requirements;

Biological: the device uses the 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;

EQUIVALENCE – ADDITIONAL CONSIDERATIONS



- MEDDEV 2.7/1 Rev 4 has additional considerations for “Demonstration of equivalence”
 - Only based on single device (*may use several devices)
 - All three characteristics need to be fulfilled (more details)
 - Similar means that no clinically significant difference in the performance and safety of the device
- Notified bodies assessing more critically:

“The notified body should also assess and document the level of access to the technical and clinical data from an Equivalent device that the manufacturer has...**The notified body should challenge the ability of the manufacturer to access information that are relevant to the demonstration of equivalence.** Demonstration of equivalence might be difficult or impossible in cases of limited access to the technical documentation of the devices.”

EQUIVALENCE – ADDITIONAL CONSIDERATIONS



EU MDR Article 61 (5)

If different manufacturer, in order for clinical investigation to not be performed for Class III or implantable devices due to demonstrated device equivalence:

- Manufacturers must have **contract** in place explicitly allowing **full access to technical documentation** on ongoing basis
- Original clinical evaluation performed in compliance with MDR requirements
- Clear evidence of this provided to notified body

*Does this apply to all devices

EQUIVALENCE – CASE STUDY



Class IIb, Implantable with Different Material

- Manufacturer's own device used for equivalence
- Safety profile and performance requirements/characteristics of device type well known
- Clinical and technical characteristics the same
- Subject device used a material new to the specific application but established for other, similar applications
- Equivalence rejected since it was not the same material

EQUIVALENCE – CASE STUDY



Class IIb (not implantable) with Same Materials, Similar Technology

- CER submitted using two equivalence devices from other manufacturers
- Well established technology and treatment
- Significant information available for equivalent devices and detailed comparisons provided in CER
- Equivalence accepted

EQUIVALENCE – CASE STUDY



Class III, Implantable with Modified Materials, Technology

- CER submitted for change to device
- Previous version of device used for equivalence
- Significant bench-top, animal studies and biocompatibility testing performed to support the design change
- Equivalence will likely be rejected

EQUIVALENCE - CONCLUSIONS



- Equivalence still possible under the MDD but Rev 4 makes establishing equivalence more difficult
 - Need sufficient technical data for comparison
 - Pay attention to same materials (if implantable) and similar technology
- Equivalence to other manufacturers products is currently a temporary measure until EU MDR



CONSIDERATIONS FOR GROUPING DEVICES FOR PROCESS EFFICIENCIES

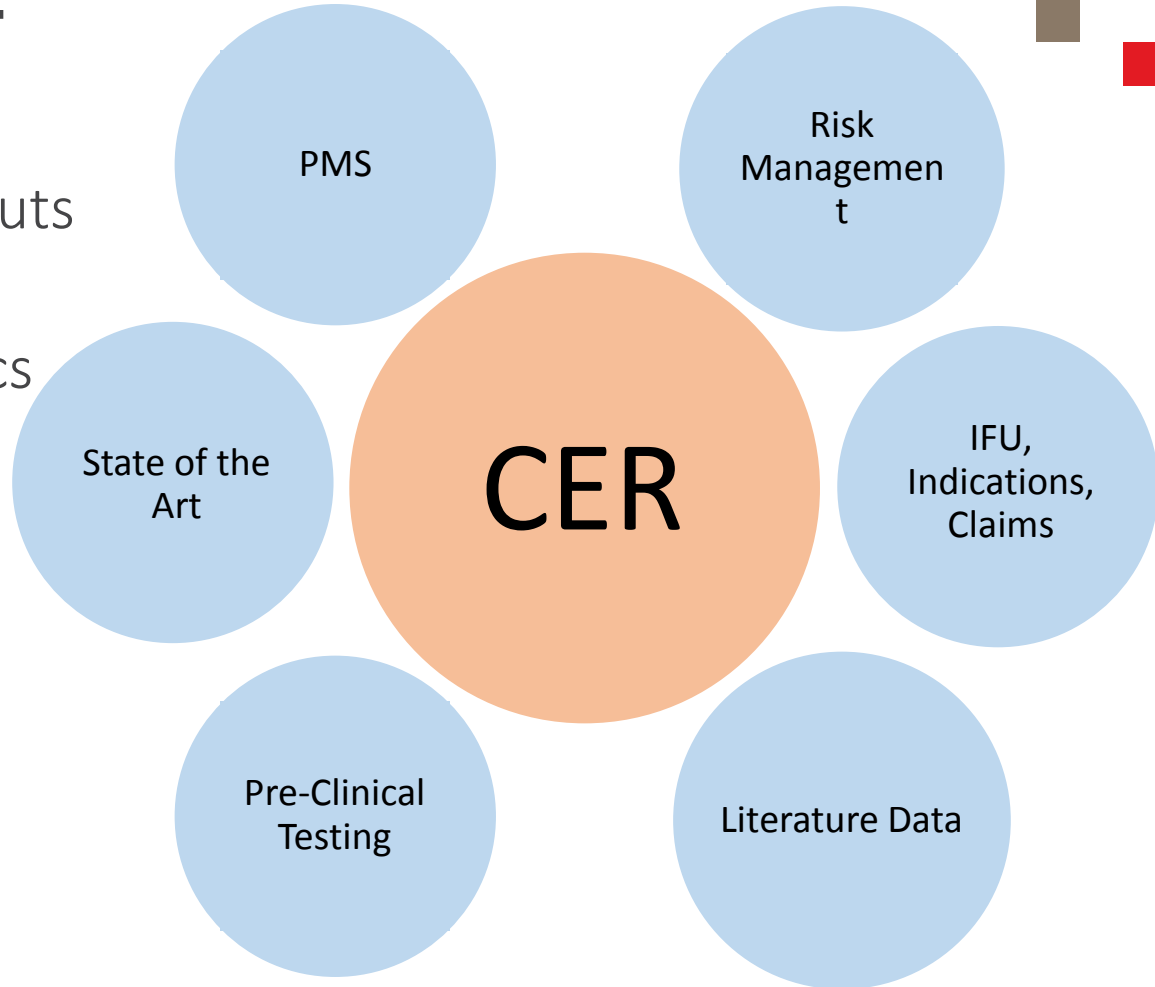
CER WORKLOAD AND ORGANIZATION



- CERs historically inconsistent and updated prior to audits (e.g., 3 years) or at the time of changes to or extensions of EC certificates
- MEDDEV 2.7/1 Rev 4 provides more details for content and updates to the CER:
 - at least annually if the device carries significant risks or is not yet well established; or
 - every 2 to 5 years if the device is not expected to carry significant risks and is well established
- This, along with more scrutiny on CERs, has resulted in an increased workload and desire to reorganized files

CER ALIGNMENT

- Multiple sources of inputs
- Clinical, Biological, and Technical Characteristics should align:
 - Indications
 - Benefits/risks
 - Design and device type
- Special considerations



CASE STUDY



- Large number of technical files/design dossiers
- Technical file / design history file structure developed organically based around new product development
- Organization of files reconsidered to merge similar files and combine CERs
 - Decreased number of CERs
 - Decreased submissions and costs

*A single State of the Art may also be used across similar product lines



CHALLENGES WITH LEGACY PRODUCTS WITH LIMITED CLINICAL DATA



CERS AND LEGACY PRODUCTS

- The requirements for clinical evaluation apply to all classes of medical devices (Class I to Class III)
- The evaluation should be appropriate to the device under evaluation, its specific properties, and its intended purpose
- Two common scenarios with limited clinical data
 - Well established devices
 - Accessories

SCOPING



MEDDEV 2.7/1 Rev. 4 :

- Considerable diversity in the types and history of technologies used in medical devices and the risks posed by them
 - Equivalence may be appropriate for devices that are not completely novel and developed by increments
 - Compliance with harmonised standards may be used to satisfy the clinical evidence requirements for devices based on technologies with well established safety and performance characteristics

CLINICAL DATA NOT DEEMED APPROPRIATE



MEDDEV 2.7/1 Rev. 4 Section 10.3:

- Where demonstration of conformity based on clinical data is not deemed appropriate, adequate justification for any such exclusion has to be given
 - Be based on the output of the risk management process,
 - Include an evaluation of the background clinical literature data and appraisal of its relevance to the subject device
 - Consider the device/body interaction, the clinical performances intended and the claims.
 - Reasoning for the adequacy performance evaluation, bench testing and pre-clinical evaluation*
- A clinical evaluation is still required

*Common specifications may be available under EU MDR

CASE STUDY



Class 1 Instruments

- Specific and general standards were available for the device
- Limited number of complaints and adverse event reports relative to sales
- Approach 1 - Instrumented associated with a system
 - Moved under the scope of the system CER
 - System data and conclusions assumed to apply to the instruments
- Approach 2 - General instruments
 - Included in a separate CER
 - Provided justification that clinical data was not needed and it was acceptable to rely on pre-clinical testing and reliance on standards
 - Performed clinical evaluation per MEDDEV 2.7/1 Rev 4



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Panel Presentation: MEDDEV 2.7/1, revision 4 and Clinical Evaluation Reporting (CER)

15th Medical Device Quality Congress
Bethesda, MD
4 April 2018

State of the Art Best Practice Suggestions

State of the Art and MDD



Council Directive 92/43/EEC

I. General Requirements

2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged **state of the art**.

Directive 2007/47/EC

Clause (20)

Taking account of the growing importance of software in the field of medical devices, be it as stand alone or as software incorporated in a device, validation of software in accordance with the **state of the art** should be an **essential requirement**.

Article 81 European Reference Laboratories

- To provide scientific advice regarding the **state of the art** in relation to specific devices, or a category of devices

Annex I

1.Devices shall achieve the performance intended by the manufacturer and be designed and manufactured in such a way that, during normal condition of use, they are suitable for their intended purpose, taking into account the generally acknowledged **state of the art**.
2. Solutions adopted by the manufacturer for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged **state of the art**.

State of the Art and MEDDEV



Cited 39 times

Section 6 General Principles of Clinical Evaluation (2 times)

Section 7 Definition of the Scope of the Clinical Evaluation (2 times)

Section 8 Definition of the Scope of the Clinical Evaluation (2 times)

Section 9 Appraisal of pertinent data (3 times)

Section 10 Analysis of the clinical data (4 times)

Section 11 The clinical evaluation report (2 times)

A.2 When should clinical investigations be carried out? (2 times)

A 4 Sources of literature (once)

A.5 Literature search and literature review protocol, key elements (2 times)

A.7 Analysis of the clinical data - compliance to specific Essential Requirements (7 times)

A.9 Clinical evaluation report – proposed table of contents, examples of content (6 times)

State of the Art and MEDDEV



The current knowledge/ **state of the art** in the corresponding medical field, such as applicable standards and guidance documents, information relating to the medical condition managed with the device and its natural course, benchmark devices, other devices and medical alternatives available to the target population.

Data on the safety and performance of other devices and alternative therapies, including benchmark devices and equivalent devices, should be used to define **the state of the art** or identify hazards due to substances and technologies. This will allow the clinical data requirements to be established more precisely in relation to the intended purpose of a device. Precision in this analysis and the choice of selected medical indications and target populations may reduce the amount of clinical data needed from additional clinical investigations.

State of the Art and MEDDEV



The current knowledge/ **state of the art** therefore needs to be identified and defined, possibly also relevant benchmark devices and medical alternatives available to the target population. Typically, documentation of the clinical background shall include the following information:

- clinical background
 - information on the clinical condition(s) to be treated, managed, or diagnosed
 - prevalence of the condition(s)
 - natural course of the condition(s)
- other devices, medical alternatives available to the target population, including evidence of clinical performance and safety
 - historical treatments

State of the Art and MEDDEV



- Sufficient detail of the clinical background is needed so that the **state of the art** can be accurately characterised in terms of clinical performance, and clinical safety profile. The selection of clinical data that characterises the **state of the art** should be objective and not selective of data on the basis of being favourable for the device under evaluation. Information should be provided on alternative approaches that have been used or considered and their benefits and drawbacks. Deficiencies in current therapies should be identified from a critical and comprehensive review of relevant published literature. The literature review should demonstrate if the device addresses a significant gap in healthcare provision. Where there is no such clinical need, the design solution needs to show an improved or at least equivalent benefit/risk profile compared to existing products or therapies.
- If or when treatment comparability versus accepted therapy is not available at the time of placing on the market, this should be clearly described in the device IFU.
- Even if a device cannot compete with an agreed first-line treatment or the best in class, it may add to the portfolio of acceptable treatments, as even a first-line treatment will likely have contraindications or non-responders.
- Devices, that might not be best-in-class, might provide sufficient clinical evidence for an

SOA – Best Practice Suggestions



Look to:

- Standards
- Guidance documents
- Info relating to the medical condition
- Benchmark devices
- Other devices and medical alternatives available to target population

as a basis for your SOA

SOA must:

- Describe the clinical background and identify the current medical knowledge
- Identify potential clinical hazards
- Justify the validity of criteria used for demonstration of equivalence (if appropriate)
- Justify surrogate (clinical) endpoints (if appropriate)

SOA – Best Practice Suggestions



SOA discussion should address:

- Clinical Background
 - Clinical condition
 - Prevalence of condition
 - Natural course of the condition
- Other Devices/Medical Alternatives
 - Target population
 - Historical treatments
 - Available medical options

What does that mean for the writer?

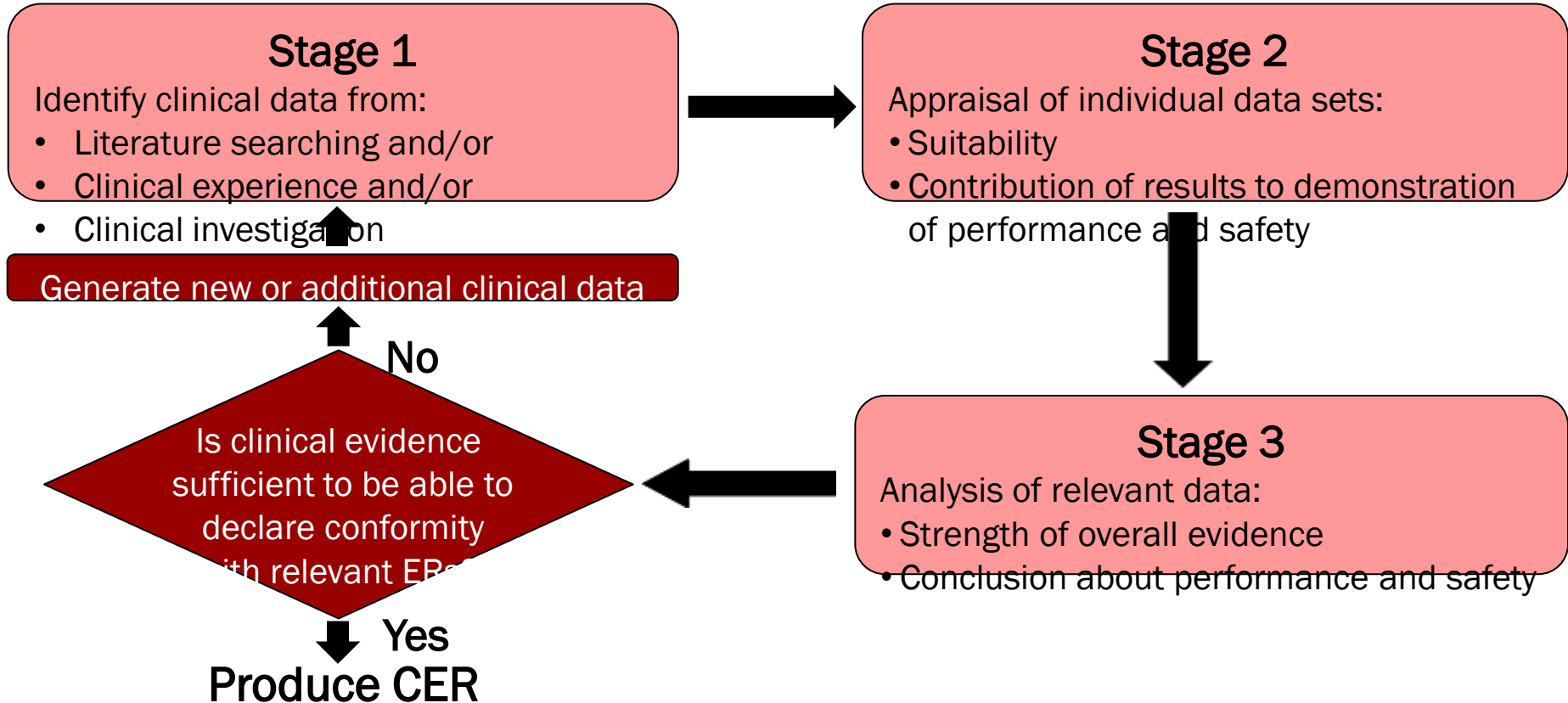
- Literature review
 - Consider risk/benefit
 - Deficiencies with other approaches
 - Does subject device address a gap?
 - If not, is the benefit/risk profile comparable
- Focus on **current** SOA
- Keep SOA high level, based on device indications for use and alternative therapies
- Analysis must be consistent and relate to device

Content of Clinical Evaluation Plans

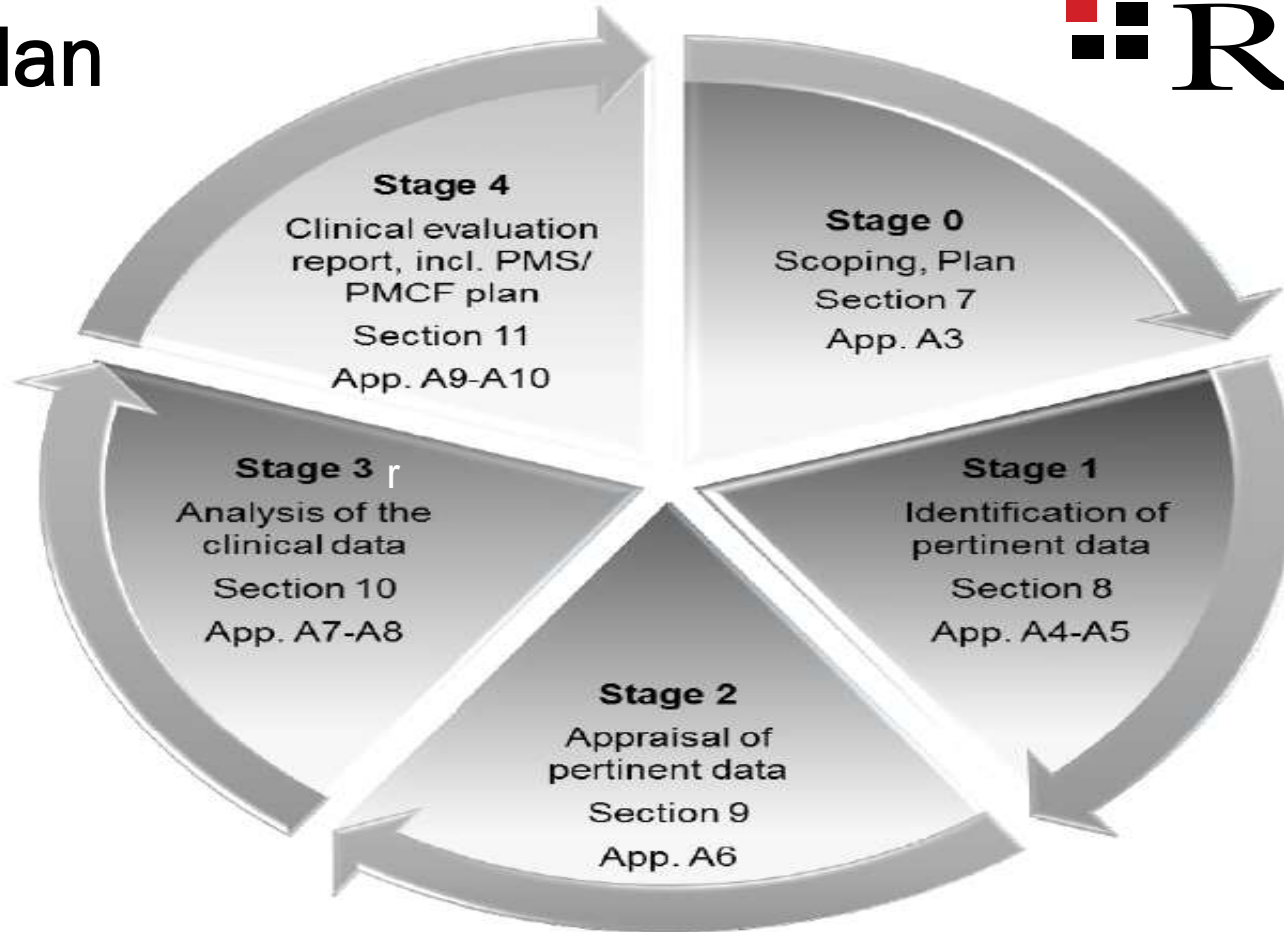
Resources for CER Preparation:

- Regulatory
- R&D (Design inputs/specs)
- Labeling
- Preclinical
- Clinical PMS/PMCF
- Risk Management
- Library Sciences
- Clinical (medical) expertise

CER Plan



CER Plan



Aspects to Consider for Plan:

- Device description, including areas that require specific attention
- Identify areas requiring special attention
- Time frame (for updates)
- Questions of equivalence
- Risk management documents
- State of the Art
- Data Sources
- Device Changes
- Clinical Concerns

Template or Checklist?

CER Plan

Develop stand alone template



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CER Plan



Develop stand alone template

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CER Plan



Develop stand alone template

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CER Plan



Develop a list of required materials

Description and Intended Use Information

- Marketing Brochures
- Technical File
- Instructions for Use
- Claims
- Standards
- Promotional Literature
- Website Information
- Patient Guides
- Videos
- Training Materials

Data and testing and design changes

- Hazard Analysis
- Pre-Launch testing
- Post-Launch Testing
- Design changes

Post market surveillance data:

- A Three Year Review of complaints
- MDR's
- MDV's
- Recalls
- CAPAs

Commercial Data

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- Competitor Device Information

Questions

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MDR – Clinical Evaluation Panel

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April 4th 2018



INVESTORS
IN PEOPLE

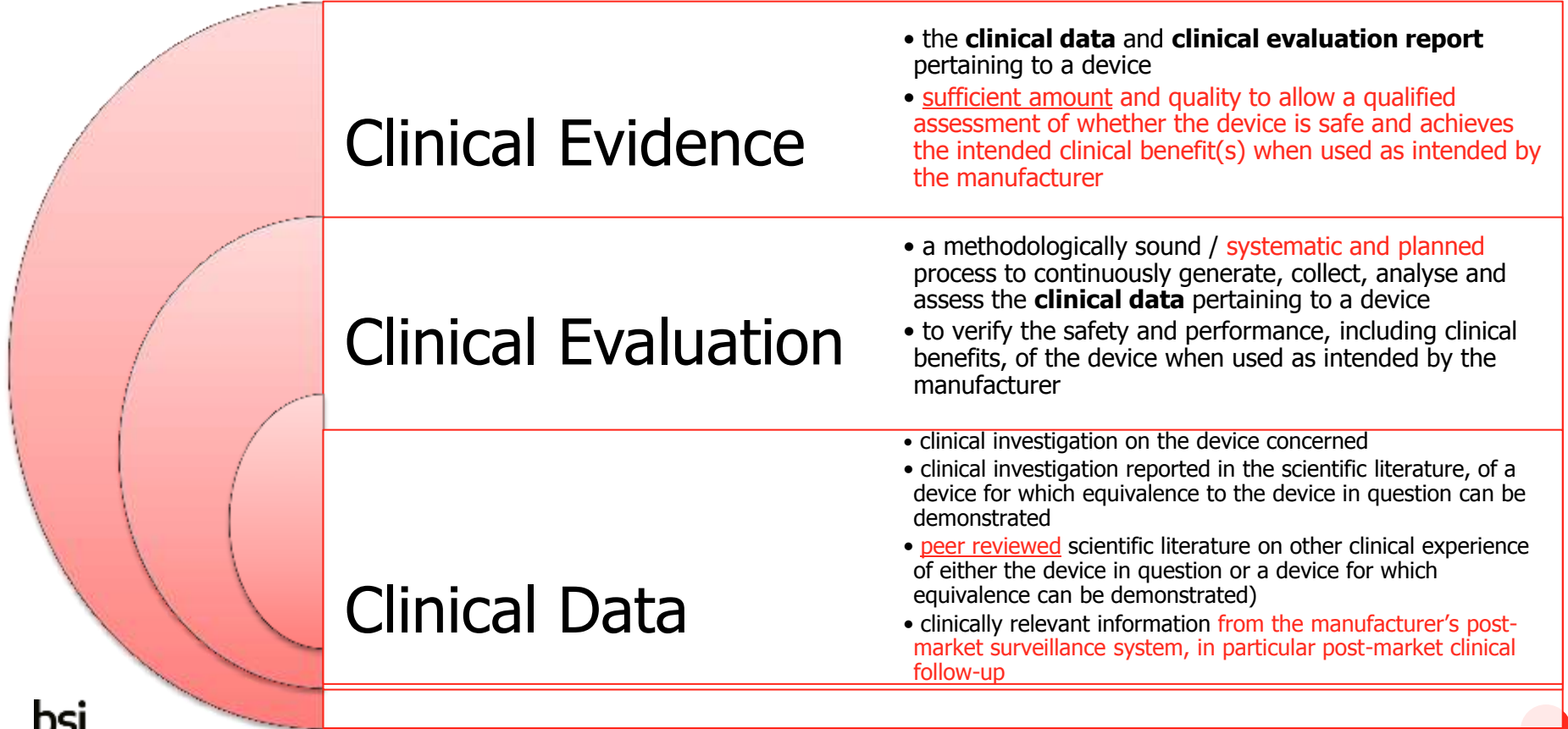


By Royal Charter

Overview

- MDR Clinical Data - Definitions
- Most common CER deficiencies
- What does “proactive clinical evidence” mean from a Notified Body (NB) perspective for low risk ~~legacy~~ products?

Clinical Evidence – MedDev 2.7.1 & MDR



MedDev 2.7.1 Rev 3 / MedDev 2.7.1 Rev 4 / MDR (Annex XIV) – Equivalence

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 intended purpose (including similar severity and stage of disease, medical indication, therapy)
- 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

MDR requirements for Equivalence

Each device with which equivalence is claimed must fulfil all clinical, technical, biological characteristics

Any differences shall be similar such that there would be no clinically significant difference in the safety and clinical performance of the device.

Overall, the equivalence criteria is narrower and the requirements more explicitly defined

- Includes many aspects of EN ISO 14155 (clinical investigation)
- MedDev 2.7/1 rev 4 provides greater detail (clinical evaluation)
- More publicly available information via Eudamed (eg SSCP, clinical investigation status, etc)

Article 61(4) & (5)

For implants and Class III devices, equivalence can only be claimed with:

- Manufacturer's own device
- Other manufacturer's device if contract is in place allowing full access to data on on-going basis
- For other device classifications, must demonstrate "sufficient levels of access to data"

Annex IX

NB must substantiate equivalence claims

Most common CER deficiencies

- CERs are not often ratified by appropriately qualified physicians
- The Declaration of intent from the authors is almost never there.
- Lit reviews don't have critical analysis and appropriate weightage
- Critical analysis of competitor devices is often missing
- In case of well-established devices which have only PMS data (sales/complaints info, only), most often there is no device performance data. This will be a big issue as we move forward => MDR.
- PMCF studies are not started in a timely manner after receipt of CE mark
- In depth data analysis with statistical justifications for PMCF data is missing
- Assessment of risk-benefit is seldom quantified
- The CER groups several devices and pools the data for all but does not outline and establish equivalence between these devices.



Most common CER deficiencies

- The CER is updated annually, and each year the literature search window is only one year. The old data is “thrown away” and not considered in the analysis and discussion. Therefore the CER does not stand alone as the data is not analyzed together unless 5 annual reports are read. Each CER should be comprehensive and stand alone and is not a “top-up” or appendix to a previous CER (the previous version would not be provided in a device review!)
- The data does not clearly support all indications.
- The demonstration of equivalence outlines similarities and differences but does not give any comment on the differences noted and their impact to the clinical outcomes. Differences observed should be honestly disclosed and discussed as to why these do not impact the ability to leverage device data – this may be supplemented by head to head testing or design validation, etc.
- The CER does not include a rationale for whether continued PMCF is needed
- Missing clinical investigators’ signatures from report.
- Clinical investigation conclusions not aligned with study Objectives.



What does “proactive clinical evidence” mean from a Notified Body (NB) perspective for low risk legacy products?

Proactive clinical evidence could take a number of forms:

- Going back to key accounts to collect some retrospective case data.
- Conducting some limited performance surveys that are not quite a “full blown” PMCF.
- Conducting full PMCF.
- Clinical investigation reported in the scientific literature, of a device for which equivalence to the device in question can be demonstrated
- Peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence can be demonstrated

Ultimately it is up to a manufacturer to make the case why it is sufficient!



Questions

Thank You!

