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Practical Guide to CER Preparation

Mary Beth Henderson, Ph.D., MBA

VP Regulatory Affairs and Quality Systems & Senior Principal Advisor

February 18, 2014

Thank you for joining us!

We will begin at Noon Central Time.

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Type in any questions you have in the Questions box.

We'll have Q&A at the end of the presentation.

For technical difficulties, please call 952-746-8080.

Agenda

1. General Background
   - Regulatory Requirement
   - Options
   - MEDDEV 2.7.1
   - Product Life-Cycle

2. Planning and Preparation Considerations
   - SOP
   - Literature Searches
   - Summary Strategies
   - Format
   - Inputs

3. Maintenance

4. Notified Body Review
   - Common Deficiencies

5. Take-Aways

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General Background

WHY?

Demonstrate Compliance with Essential Requirements

- Device is safe
- Performs as intended
- Known and foreseeable risks and AEs minimized and acceptable when weighed against benefits
- Claims supported by evidence
- Device state-of-the-art

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General Background

Regulatory Requirement

MDD: Demonstration of Conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.

AIMD: Demonstration of Conformity with the essential requirements must include a clinical evaluation in accordance with Annex 7.

As a general rule, *confirmation of conformity with the requirements concerning the characteristics and performances …* must be based on clinical data.

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General Background

Options

The Clinical Evaluation:

1.1.1 either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, the design characteristics and the intended purpose of the device, where:

- there is demonstration of equivalence of the device with that to which the data relates and,
- the data adequately demonstrate compliance with the relevant Essential Requirements;

1.1.2 or a critical evaluation of the results of all clinical investigations made;

1.1.3 or a critical evaluation of the combined clinical data provided in 1.1.1 and 1.1.2 above.

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General Background

MEDDEV 2.7.1 Key Contents

Sections:

5. General principles of Clinical Evaluation
6. Sources of data / documentation (Stage 1)
7. Appraisal of clinical data (Stage 2)
8. Analysis of clinical data (Stage 3)
9. The CER
10. Role of the Notified Body (NB)

Appendices:

A – E: Sample formats / methodologies

F: NB Clinical Evaluation Checklist

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General Background

Product Life-Cycle (and CERs)

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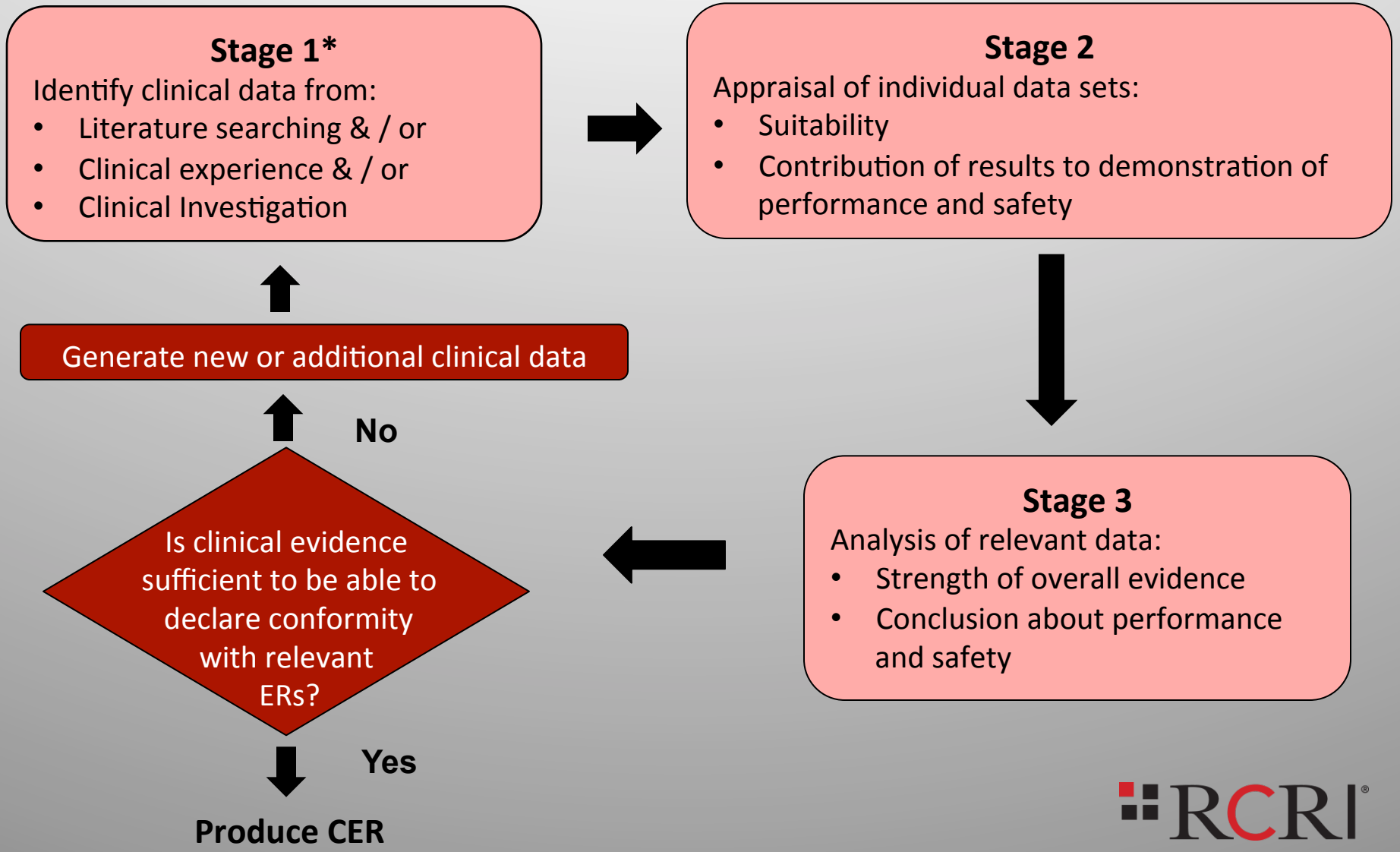
Planning and Preparation Considerations



Planning and Preparation Considerations

SOP needs to:

1. Follow MEDDEV 2.7.1
2. Include your:
   - Literature search strategy
   - Literature evaluation criteria
   - Format/template

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Planning and Preparation Considerations

Literature Searches

1. Define your sources
    - **Published original peer-reviewed research work:**
        - PubMed, Medline, EMBASE, SciSearch, Pascal, Biosis, TGG Health & Wellness Database, General Science Abstracts …
    - **Systematic reviews:**
        - Cochrane Database of Systematic Reviews
    - **Registries:**
        - National, Mfr. Sponsored
2. Define your selection criteria
    - **MEDDEV Appendix D**
    - **Centre for Evidence-Based Medicine, Oxford, UK Chart**

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Planning and Preparation Considerations

Literature Searches – Considerations

- Database(s) used must be able to search a broad cross-section of journals.
- If only looking at papers in English, regional differences may be missed.
- Reliance on abstract vs. full citation – abstract may not allow evaluator to assess quality of study / bias or get sufficient details.
- Use of inappropriate comparators (non-equivalent devices) or narrow search criteria (insufficient data).
- No comparison to state-of-the-art.
- Literature search terms ill-defined.

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Planning and Preparation Considerations

Analysis Strategies

- Consider ALL data per weighting characterization and document key parameters.
- Evaluate reasons for different outcomes.
- Consider any undue safety concerns.
- Consider whether performance demonstrated over lifetime for ALL indications.
- Consider whether data demonstrate benefits outweigh risks in light of state-of-the-art / alternate treatment options.
- Evaluate whether labeling consistent with data and risks.

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Planning and Preparation Considerations

Analysis Strategies – Considerations

- Only favorable data included.
- Positive results are more likely to be published.
- Under-coverage of subgroups.
- Citations lack sufficient detail to draw equivalence or understand outcome.
- Summary of data not clear (missing weighting, study design, device ID, suitability assessment, sample size, outcome, complications).

Planning and Preparation Considerations

Analysis Strategies – Considerations

- Literature only route used inappropriately – CI warranted.
- New / emerging risks not discussed or considered in risk analyses.
- Citations do not identify devices used or other key info.
- Data do not cover (sufficient portion of) lifetime.
- Conclusions not supported by data.
- Suitably qualified individuals not involved.
- Risk / Benefit analysis does not consider all risks.
- Data do not support safety and / or performance for ALL INDICATIONS.

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Planning and Preparation Considerations

Format

- Outline scope & context of evaluation
  - Objectives – demonstrating compliance with Essential Requirements
  - Justification of equivalency
- Inputs (clinical data)
- Appraisal and analysis
- Conclusions (on basis of documented justification)
  - risks acceptable when weighed against intended benefits
  - relevant Essential Requirements met
  - justification for not requiring Clinical Investigation (AIMD, implantable/class III MDD)
  - justification for not requiring further PMCF (may contain)
- Signature of evaluator(s) w/ justification of choice of evaluators

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Planning and Preparation Considerations

Format – Equivalency

Equivalent Devices

- Section 5.1:
  - Devices should have the same intended use and will need to be compared with respect to their technical and biological characteristics.
  - Characteristics should be similar to extent that there would be no clinically significant difference in the performance and safety of the device.
- Appendix F, Sec. 3.2.3
  - If differences are identified, an assessment must be done to demonstrate potential significance of differences on safety & performance.

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Planning and Preparation Considerations

Format – Equivalency

Appendix F, Sec. 3.2.3 (Footnote)

Clinical:

–C1 - same clinical condition or purpose

–C2 - same site in the body

–C3 - similar population (including age, anatomy, physiology)

–C4 - similar relevant critical performance for specific intended use

Technical:

–T1 - similar conditions of use

–T2 - similar specifications and properties

–T3 - similar design

–T4 - similar principles of operation

Biological:

–S1 - same materials in contact with the same tissues or body fluids

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Planning and Preparation Considerations

Format – Data Analysis Summary Example

Author, Year (Biblio Ref)	Study Type / # Patients (Per Device)	Level of Evidence (Safety, Performance)	Study Objective / Follow-up Time	Performance Outcomes	Safety Outcomes	Conclusions
Smith, 2012 (1)	RCT 80 Device A 80 Device B	Level I / Both	Estimate effectiveness of the devices in XYZ procedure F/U = 6 mo			

Planning and Preparation Considerations

Format – Data Analysis Rejected Literature Table Example

Author, Year	Rationale for Rejection
Miller, 2009	Irrelevant; does not include actual or comparable device.
Johnson, 2008	Not originally published in English.

Planning and Preparation Considerations

Format – Data Analysis – Benefit

- **No standardized approach** to **estimate benefit.**
- The decision as to whether risks are outweighed by benefits is essentially a matter of **judgment by experienced and knowledgeable individuals**.
- An important consideration in the acceptability of a residual risk is **whether** an anticipated clinical **benefit can be achieved through the use of alternative** design **solutions** or therapeutic options that avoid exposure to that risk or reduce the overall risk.
- Benefit is related to the **likelihood and extent of improvement of health** expected from its use.

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Planning and Preparation Considerations

Format – Data Analysis – Benefit (cont)

- Estimate from knowledge of things such as:
  - the performance expected during clinical use.
  - the clinical outcome expected from that performance.
  - factors relevant to the risks and benefits of other treatment options.
- Also need to consider:
  - Difficulty in comparing different outcomes (e.g. pain vs. loss of mobility).
  - Difficulty in accounting for non-stable outcomes (e.g. long-term effects).

Planning and Preparation Considerations

Format – Example

1. Introduction
2. System Description
3. Background Info on therapy/indication
4. Summary of preclinical testing
5. Clinical Evaluation
6. Risk Management (Including Clinical/Risk Benefit Analysis)
7. Post-market Clinical Follow-Up
8. Conclusion
9. Authorship
10. References

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Planning and Preparation Considerations

Format – Inputs

Internal Information

- Risk/Hazard Analyses
- Complaint/MDRs/Vigilance reports
- Unpublished manufacturer's reports
- Reports of clinical investigations
- Customer feedback on device use
- Post-market studies
- Sales information

Planning and Preparation Considerations

Format – Inputs

External Information

- Literature review of devices that can be demonstrated to be equivalent
- Database review
- Standard of care review

Maintenance

Post Market Surveillance Plan

- Frequency and duration of updates
- What will be included
  - literature – subject & comparative devices, state-of-the-art
  - complaints/vigilance
  - PMCF – surveys, cohort studies, etc.
    - # patients, end points, outcome measures
  - Design Changes

Notified Body Review

Most Common Deficiencies

1. Insufficient safety and performance data for each indication.
2. Data on devices that are not equivalent.
3. Inadequate comparison to 'state of the art.'
4. Limited search terms or databases to be searched – anything missing?
5. No assessment of quality / no weighting of papers included.
6. Poor rationales for no clinical investigation.
7. Poor rationales for no PMCF.
8. Inadequate risk benefit analysis.
9. Unsubstantiated conclusions.
10. Unsuitably qualified people.

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Take-Aways

1. Develop robust CER SOP(s) and template(s).
2. Use them for all CERs – establish a common voice.
3. Use MEDDEV 2.7.1 and your Notified Body for guidance.
4. Standardize the literature review process and output format.
5. Train staff on analysis of relevant information.
6. Develop a process and schedule for ongoing CER updates.

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Questions?

Type any Questions in the “Questions” Box.

Thanks for joining us!

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