IMPACT OF THE UPCOMING CHANGES TO THE IVDR: MEETING NEW CLINICAL EVIDENCE REQUIREMENTS

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✓ IVD regulation changes
✓ Impact on clinical evidence
✓ CER Best Practices
Pending changes in regulation

IVD Directive
- 24 Articles
- 10 Annexes

IVD Regulation
- 10 chapters
- 90 articles
- 14 annexes
Implementation timeline

ENVI
- Parliament approved the ENVI report

Plenary Vote

Council

Second Reading

Adoption

Implementing Acts

Transition

Enforced

IVDR 2016

5 Years

IVDR must be applied 2021
Classification changes

**Regulation**

- **D**: Blood screening, HIV, Hepatitis
- **C**: Companion dx, genetic tests, cancer, infectious disease, etc.
- **B**: Not D, C or A
- **A**: Controls without an assigned value
- **A**: Instruments, specimen receptacles

**Directive**

- Annex II List A
- Annex II List B
- Self test/ home use
- General
Major changes resulting from regulation

- Device classification
- Conformity assessment
- Clinical requirements
Notified Body reviews will increase

80-90% WILL require a NB review

80-90% DO NOT require a NB review

Slide content from: Sue Spencer, Head of IVD, BSI
### Clinical Evidence

#### Scientific validity
- Refers to the association of an analyte to a clinical condition or physiological state
- For established analytes this may be from literature, but for companion dx or novel analytes this needs to be established

#### Analytical performance
- Refers to the ability of an IVD medical device to correctly detect and measure a particular analyte
- Performance requirements similar to IVDD

#### Clinical performance
- Refers to the ability to yield results that relate to a particular clinical condition physiological state for the intended use and in accordance with target population and where applicable to the intended user
- Data to support dx accuracy compared to reference test; information related to expected values

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Slide content from: Sue Spencer, Head of IVD, BSI
Are CERs coming to IVDs?

BSI says, “Yes!”
BEST PRACTICES FOR
CLINICAL EVALUATION REPORTS (CER)
‘Clinical evaluation’ is the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device.

Guideline outlines content of the Clinical Evaluation Report used by a manufacturer to demonstrate conformity with the Essential Requirements.
Who prepares the CER?

Evaluation should be conducted by a “suitably qualified individual(s)”, knowledgeable about:

- Device technology and application(s)
- Clinical research methodology (investigation design and biostatistics)
- Diagnosis and management of the conditions intended to be treated or diagnosed by the device
  - Includes review by medical/clinical expert
Data/documentation sources

- Clinical Investigation
- Literature Searches
- Clinical Experience
General CER outline

1. Title Page
2. Scope
3. Device Overview
4. Assessment of Equivalent (Similar) devices
5. Pre-clinical Summary
6. Clinical Data Summary
7. Post-Market Surveillance
8. Clinical Literature Review
9. Benefits vs Risk Analysis
10. Conclusion
11. Appendices
Define scope of CER

Scope

- Scope and objective – include table of all products and accessories
- Timeframe to be covered in review - published literature and post-market surveillance information

Device Overview

- Device Description and Intended Use
- Indications for use
- Contraindications
- Product Development and Market History
Pre-clinical data

Summary of key data (bench, animal, human) demonstrating performance and safety of the device:

- Biocompatibility testing
- Material and mechanical performance testing – durability, strength, chemical properties
- Design Validation
- Usability
- List of applicable Product safety and EMC standards
- Animal studies to evaluate intended use
Identify clinical data

- Clinical investigation
- Clinical experience
- Literature search

Clinical Data
Clinical data summary

- Review pre-market and post-market study reports
- Summarize studies to assess the efficacy and safety of the device
- Perform critical appraisal of clinical data
- Include copies of clinical report in Appendices
Clinical experience

Post Market Surveillance

- Summarize of product complaints and worldwide sales
- Review recalls, Field Actions and Safety Notices
- Review Adverse Event Reports –
  - MAUDE (FDA),
  - IRIS (TGA),
  - Health Canada,
  - MHRA (UK)
- Sort into appropriate categories to allow cross reference with Warnings and Precautions in device labelling
“Literature searching can be used to identify published clinical data that is not in the possession of the manufacturer that may assist the manufacturer to establish acceptable performance and safety of a medical device. The data generated through literature searching may relate directly to the device in question or to equivalent devices.”

MEDDEV 2.7.1, Rev 3
Other medical device(s) on the market which have the same characteristics (Clinical, Technical, and Biological) as the subject device OR are justified as being sufficiently similar to the subject device. (per MEDDEV 2.7.1)

- Justify use of and selection of equivalent device in CER
- Key factors
  - Clinical use
  - Biological equivalence
  - Technical equivalence
Evaluation of equivalent (similar) device

Determine if the new and comparator device are......

Clinically equivalent
- Have same intended use
- Are used for the same clinical condition or purpose
- Used in similar patient populations
- Have similar relevant critical performance according to the expected clinical effects

Biologically equivalent
- Biocompatibility of materials
- In contact with the same body tissues/fluids for similar durations

Technically equivalent
- Design
- Specifications
- Physiochemical properties including energy intensity
- Sterilization method
- Critical performance requirements
- Principles of operations
- Conditions of use
Clinical literature review

...is not simply a list of the literature articles retrieved from the search.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Citation</th>
</tr>
</thead>
</table>
Conducting the literature search...

- Establish the Literature search protocol
- Assemble the data sources/relevance/appraisal methods/inclusion and exclusion criteria.
- Prepare summary of the literature (high level; tabular form).
- Critically analyze the literature (detailed, paragraph form).
  - may simply split into safety and performance sections
  - OR
  - into main topic areas specific to the device or therapy type(s).
Establish the approach prospectively

- Determine key word strategy
- Identify literature sources
- Is use of an equivalent device applicable?
Literature Search Report

Includes:

- Device name/model
- Key word used to create search
- Methods
  - Date of search conducted
  - Name, qualification of researcher
  - Period covered (e.g. Jan 2010 through Jul 2015)
  - Sources (e.g. PubMed)
  - Search terms
  - Output numbers
Review of literature

Inclusion Criteria

- Peer-reviewed, published literature, follows scientific principles, appropriate endpoints and number of patients and inclusion/exclusion criteria
- Reflects generally acknowledged state of the art
- Randomized and non-randomized trials are eligible
- English language
- Discusses the subject device or equivalent
Exclusion Criteria

- General overviews; surgical technique descriptions
- Opinions, letters to the editor
- Lacking safety and performance outcomes
- Insufficient data (poster presentations, abstracts, vaguely written, etc.)
- Mere mention of the device (usually just in the Methods section) with no further safety or performance information provided.
- Non-equivalent device studies
- Isolated case reports
- Pre-clinical data or animal studies
- Off-label use
## Assessing quality of literature articles

<table>
<thead>
<tr>
<th>Level</th>
<th>Therapeutic Studies</th>
<th>Diagnostic Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High quality randomized trial</td>
<td>Testing consecutive patients; includes reference “gold” standard</td>
</tr>
<tr>
<td>II</td>
<td>Lesser quality randomized trial</td>
<td>Development of diagnostic criteria</td>
</tr>
<tr>
<td>III</td>
<td>Case control study</td>
<td>Testing nonconsecutive patients</td>
</tr>
<tr>
<td>IV</td>
<td>Case series</td>
<td>Case-control study or poor reference standard</td>
</tr>
<tr>
<td>V</td>
<td>Expert opinion</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

From Oxford Centre for Evidence-Based Medicine.
Screen and sort articles

Citations identified from search
N = 140

Excluded n=1
• Duplicate

Abstract Review
n=139

Excluded n=71
• Preclinical
• Technique
• Incorrect device

Full text review
n=68

Excluded n=3
• Preclinical
• Spanish

Included
n=65
## Literature summary

Create a table to summarize all included articles

- May include from 10 to 100 articles
- Consider contribution of results to demonstration of performance and safety

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Device</th>
<th>Study Type</th>
<th># Subjects/ Age</th>
<th>Safety Outcomes</th>
<th>Summary</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdellatif, 2014</td>
<td>GlideScope video laryngoscope, Flexible Fiberoptic bronchoscope</td>
<td>Prospective randomized trial</td>
<td>N=63&lt;br&gt;22 Male&lt;br&gt;41 Female&lt;br&gt;Morbidly obese patients&lt;br&gt;Age 18 to 60</td>
<td>Severe gagging and coughing with 1 of 63 patients&lt;br&gt;Both groups: post-operative hoarseness and throat pain&lt;br&gt;4 of 64 patients experienced oxygen saturation &lt;90%</td>
<td>Study showed GVL and FOB are comparable methods for awake intubation of morbidly obese patients with predicted difficult intubation. Study observed no significant difference in time to awake tracheal intubation, number of intubation attempts and glottis view.</td>
<td>1</td>
</tr>
</tbody>
</table>
Complete the CER

- Risk Management
- Conclusions
- Appendices
Risk Management Process

- Describe the risk management process
- Review current risk analysis
- Review benefits vs. risks
- Include Use Risk Assessment if applicable (e.g. for surgical techniques with surgical devices)
State Conclusions

- **Identify** those sets of data considered “pivotal”
- **Describe** how each dataset demonstrates the performance and safety of the device
- **Explain** how combined data show:
  - The device performs as intended by the manufacturer
  - The device does not pose any undue safety concerns to either the recipient or end-user
  - Any risks associated with the use of the device are acceptable when weighed against the benefits to the patient
- **State** the device continues to represent “state of the art”
The CER should include the statement:

“Clinical evidence is sufficient to declare conformity with the Essential Requirements of the MDD (Annex X) related to safety and performance”

The CER should be updated accordingly to reference applicable Chapter and/or Annex within new regulation for medical devices, implantable devices or IVDs.
Appendices

- References (standards, websites, internal documents/SOPs, etc.)
- Bibliography of all included literature articles
- Summary table of included articles ranked for relevancy
- Table of excluded references – full citations
- Copies of Clinical Study Reports
- CV(s)
  - Final medical reviewer
  - Author(s) (RCRI and/or internal)
Key points

The CER should contain sufficient information to be read as a stand alone document

▪ **Outline** technology on which device is based
▪ **Summarize** the clinical data that has been evaluated
▪ **Explain** how referenced information constitutes valid clinical evidence and demonstrates the safety and performance of the device
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