Clinical Data Evaluation – A Holistic Approach to Risk Management

2014 BSI Healthcare Roadshow

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Clinical Data Evaluation

• Review Requirements from Directives on Medical Devices & State-of-the-art Guidance (MEDDEV 2.7.1)
  o Linkage to Risk Management (EN ISO 14971:2012)
• Practical Example / Group Discussion
• Panel Discussion
EU Directives on Medical Devices
EU Directives on Medical Devices

**MDD & AIMD** modified by Directive 2007/47/EC, effective 21 Mar 2010

- **MDD:** ER 6a – Demonstration of *conformity with the essential requirements* must include a clinical evaluation in accordance with Annex X
- **AIMD:** ER 5a - Demonstration of *conformity with the essential requirements* must include a clinical evaluation in accordance with Annex 7
Annex X (MDD) / Annex 7 (AIMD)

• As a general rule, **confirmation of conformity with the requirements concerning the characteristics and performances** ... under the normal conditions of use of the device, **and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio** ... **must be based on clinical data**.
EU Commission Guidelines on the Clinical Evaluation of Medical Devices
EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE GENERAL

Consumer Goods
Cosmetics and Medical Devices

MEDDEV. 2.7.1 Rev.3
December 2009

GUIDELINES ON MEDICAL DEVICES

CLINICAL EVALUATION:
A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES
When is clinical evaluation undertaken?

- Clinical evaluation is an **ongoing process** conducted throughout the life cycle of a medical device.
- It is **first** performed **during the conformity assessment** process leading to the marketing of a medical device and then **repeated periodically** as new clinical safety and performance information about the device is obtained **during its use**.
- This information is fed into the ongoing risk analysis and may result in **changes to the Instructions for Use**.
• It is expected that the manufacturer has demonstrated the **device achieves its intended performance** during normal conditions of use and that the **known and foreseeable risks, and any adverse events, are minimized and acceptable when weighed against the benefits** of the intended performance, and that any **claims** made about the device’s performance and safety (e.g. product labelling and instructions for use) are **supported by suitable evidence**.
MEDDEV 2.7.1

• CER must be thorough & objective
  o Consider both favorable and unfavorable pre- and post-
    market clinical data relevant to the intended use
  o Needs to be informed by and cross-referenced to the risk
    management documents
  o Risk documents should identify all known risks associated
    with device and how such risks have been addressed
• Often possible to draw on experience of “equivalent” devices
• May be possible to use compliance with recognized standards
• Depth of evaluation commensurate with classification,
  intended use, claims, and risk of device in question
Annex X (MDD) / Annex 7 (AIMD)

- **The clinical evaluation** must follow a defined and methodologically sound procedure based on:

  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.
Clinical Investigations:

• **MDD:** In the case of implantable devices and devices in Class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.

• **AIMD:** Clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.
CER Updates:

- CER must be actively updated with data obtained from the post-market surveillance.
- Where post-market clinical follow-up (PMCF) as part of the post-market surveillance (PMS) plan for the device is not deemed necessary, this must be duly justified and documented.
Where demonstration of conformity with ERs based on clinical data is not deemed appropriate:

- Adequate justification for any such exclusion has to be given based on risk management output and under consideration of the specifics of the device/body interaction, the clinical performances intended, and the claims of the manufacturer.

- Adequacy of demonstration of conformity with the essential requirements by performance evaluation, bench testing and pre-clinical evaluation alone has to be duly substantiated.
Harmonized Standard on Risk Management for Medical Devices
BS EN ISO 14971:2012

Medical devices — Application of risk management to medical devices (ISO 14971:2007, Corrected version 2007-10-01)
Evaluation of Risk / Benefit (EN ISO 14971:2012)

• Annex ZA (MDD) / Annex ZB (AIMD) Deviation 4
  o The manufacturer **must undertake the risk-benefit analysis** for the individual risk and the overall risk-benefit analysis (weighing all risks combined against the benefit) in all cases.

• Annex D
  o Those involved in making risk/benefit judgments have a responsibility to understand and take into account the technical, clinical, regulatory, economic, sociological and political context of their risk management decisions.
  o 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**.
Review
Practical Example / Group Discussion
Hypothetical Scenario

• **Device:** Non-absorbable polypropylene mesh (class IIb device)

• **Indication:** **P-MESH** is used for the repair of hernias, uterovaginal prolapse, and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result. It can be used in open or endoscopic procedures.

• **Use:** Device is extensible in both directions and can be cut to size without unraveling.

• **Market Introduction:**
  - 1994 (Devices A – C) for all indications except uterovaginal prolapse
  - 2009 (Device D) for uterovaginal prolapse
Hypothetical Scenario

- **Hernia**: A hernia occurs when the contents of a **body cavity bulge out of the area** where they are normally contained. These contents, usually portions of intestine or abdominal fatty tissue, are enclosed in the thin membrane that naturally lines the inside of the cavity.
  - May be asymptomatic or cause slight to severe pain.
  - Nearly all have a potential risk of having their blood supply cut off (becoming strangulated).

- **Uterovaginal Prolapse**: A vaginal prolapse is a condition in which **structures** such as the uterus, rectum, bladder, urethra, small bowel, or the vagina itself may begin to prolapse, or **fall out of their normal positions**. Without medical treatment or surgery, these structures may eventually prolapse farther and farther into the vagina or even through the vaginal opening if their supports weaken enough.
  - Symptoms commonly affect sexual function as well as bodily functions such as urination and defecation.
  - Pelvic pressure and discomfort are also common symptoms.
  - Many women do not seek medical help because of embarrassment.
Hypothetical Scenario

Latest Device Released in 2009
• May not meet MEDDEV 2.7.1 or EN ISO 14971:2012

PMS Review: 2009 - 2014
- Lit / State of Art Review
- Complaint / Vigilance Analysis
- Risk Analysis
- IFU Analysis

Updated CER
Updated Risk Analysis
Updated IFU
Hypothetical Scenario

- **Conclusions Drawn After PMS Review:**
  - No new risks associated with use.
  - Data sufficient to demonstrate compliance with the ERs covering safety and performance.
  - Benefits outweigh risks.
  - No new clinical data is required.

Canned Language → Watch Out!
Hypothetical Scenario

• Detailed Review:
  o Ensure CER / Risk meet today’s requirements
    ➢ Review impact of incremental design / indication changes
    ➢ Assess quality of clinical data
    ➢ Determine if clinical data representative (i.e. for subject or equiv. devices)
  o Each component (CER, IFU, Risk, PMS) delivers consistent message
  o Conclusions are supported by data
    ➢ Any Unknown AEs were identified
    ➢ AEs rates consistent with risk unless justifiable
    ➢ Risk controls (including IFU) are sufficient
    ➢ Device still state-of-the-art
    ➢ Sufficient data collected for each indication
Hypothetical Scenario - Literature Review

- Objective, search strategy, databases, inclusion/exclusion criteria clearly stated.
- Identified 57 articles to be pertinent to review out of 182 uncovered in search. Reasons for exclusion documented and consistent with criteria.
- 2 Equivalent Devices Identified with justification for equivalence
- Summary of each article provided (typical of abstract)
- No discussion of weighting of papers
- F/U periods not routinely reported
- No analysis done to critically evaluate outcomes

• High-level methodology seems generally consistent with MEDDEV 2.7.1 but statements raise the following concerns:
  - **No weighting may** indicate quality/suitability not assessed
  - **Lack of documenting F/U periods and detailed analysis** may indicate only abstracts reviewed
## Hypothetical Scenario - Equivalence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P-Mesh (Subject Device)</th>
<th>X-Mesh (Equivalent Device)</th>
<th>Y-Mesh (Equivalent Device)</th>
<th>Potential Clinical Impact of Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Repair of hernias, uterovaginal prolapse, and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.</td>
<td>For reinforcement of soft tissue, where weakness exists, in procedures involving soft tissue repair, such as groin hernia defects</td>
<td>For repair of hernias and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result.</td>
<td>Subject device specifically indicates uterovaginal prolapse where others don’t but as this is still due to soft tissue deficiencies which require reinforcing, indications are considered equivalent.</td>
</tr>
<tr>
<td><strong>Material</strong></td>
<td>Polypropylene</td>
<td>Polypropylene</td>
<td>Polypropylene</td>
<td>Equivalent</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Flat square &amp; rectangular meshes 3 Sizes (10 cm x 5 cm to 15 cm x 15 cm) Can be cut to size</td>
<td>Flat rectangular meshes and Mesh Plug Flat: 2 Sizes (14 cm x 7 cm and 9 cm x 5 cm) Can be cut to size Plug: 2 Sizes (3 cm dia / 5 cm and 3.5 cm dia x 4 cm) Can be cut to size</td>
<td>Flat square &amp; rectangular meshes 4 Sizes (5 cm x 5 cm to 15 cm x 15 cm) Can be cut to size</td>
<td>All the devices can be cut to size for the particular application. Since the subject device includes the largest available mesh, differences in size and shape do not matter.</td>
</tr>
<tr>
<td><strong>Burst Load</strong></td>
<td>703 ± 87 N</td>
<td>525 N</td>
<td>589 N</td>
<td>Subject device is a stronger construction relative to others so considered clinically superior</td>
</tr>
</tbody>
</table>
Hypothetical Scenario – IFU / CER Review

IFU Indications

Repair of hernias, uterovaginal prolapse, and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result. It can be used in open or endoscopic procedures.

CER Indications

Repair of hernias, uterovaginal prolapse, and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result. It can be used in open, laparoscopic, and endoscopic procedures.

- CER also identifies “laparoscopic” procedures.
- Are devices knowingly being used outside of approved indications?
  - Is this misuse or other appropriate use?
  - Is this considered in risk analysis?

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Hypothetical Scenario – IFU/CER/PMS Review

IFU Adverse Events

Typical of surgical implant matls:
- Inflammation
- Seroma formation
- Adhesion formation
- Fistula formation
- Erosion
- Extrusion
- Infection
- Scarring / contraction

CER Outcomes

- P-Mesh had significantly lower rates of recurrence and pain at 3 years when using laparoscopic technique (n=349) vs. open technique (n=300) for inguinal hernia repairs.
- Comparison study of P-Mesh (n=280) to Y-Mesh (n=242) – no significant difference in post-op pain, return to work, QoL
- Post-op pain and visual analog scales reported to be significantly higher in P-Mesh group than in X-Mesh and Y-Mesh when used in inguinal hernia repair – n=90
- Significant pain and sexual impairment noted in P-Mesh group for uterovaginal prolapse from 4th – 12 wk post op. – n=180
- Significantly more men in P-Mesh group (22.6%) felt mesh in groin after inguinal hernia repair and experience pain on rising from lying to sitting (14.7%) – n=590
- P-Mesh caused complications such as seroma (8.3%, mesh infections (8.3%), chronic discharging fistula (4.17%) mesh removal (4.17%), recurrence (8.3%) – discomfort at abdominal wall very common complaint w/ P-Mesh – n=49
- P-Mesh used for paravaginal repair of anterior wall prolapse (n=33) - 39% develop stage 2 prolapse, 1 (3%) symptomatic, no erosions or mesh rejection @ 18 mo

Complaints

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernia Recurrence</td>
<td>2.0000%</td>
</tr>
<tr>
<td>Pain</td>
<td>1.0000%</td>
</tr>
<tr>
<td>Infection</td>
<td>1.0000%</td>
</tr>
<tr>
<td>Adhesion formation</td>
<td>0.5000%</td>
</tr>
<tr>
<td>Recurring prolapse</td>
<td>0.5000%</td>
</tr>
<tr>
<td>Seroma formation</td>
<td>0.2500%</td>
</tr>
<tr>
<td>Migration / Erosion</td>
<td>0.0800%</td>
</tr>
<tr>
<td>Mesh wrinkling/folding</td>
<td>0.0750%</td>
</tr>
<tr>
<td>Extrusion</td>
<td>0.0300%</td>
</tr>
<tr>
<td>Mesh Tears</td>
<td>0.0250%</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>0.0100%</td>
</tr>
</tbody>
</table>
Hypothetical Scenario – IFU/CER/PMS Review

• Complaints do not appear to be consistent with literature results
  o Seroma
  o Infection
  o Pain
• IFU does not address multiple CER AEs with high %
  o Sexual Impairment
  o Mesh sensation
  o Prolapse progression
• IFU does not identify a rate of expected AEs
• IFU seems to be based primarily on complaints
• Raises question as to whether QMS or PMCF is sufficient
• Is P-Mesh still state-of-the-art? P-Mesh performed more poorly than other devices (n=90).
Hypothetical Scenario – PMS / Risk Review

Complaints

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Hernia Recurrence</td>
<td>2.0000%</td>
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Complaints: 127
Sales: 429,319 units
Rate: 0.03%

Risk Analysis

**Pain, Seroma, Recurrence:**

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Cause</th>
<th>SEV</th>
<th>OCC</th>
<th>Control</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixation insufficient</td>
<td>wrong shape / fixed too loosely</td>
<td>Severe</td>
<td>0.01% - 0.02%</td>
<td>state-of-art, simulated use, IFU warning</td>
<td>Acceptable - ALAP Justified</td>
</tr>
<tr>
<td>Device tears post-op</td>
<td>structure incorrect, fixed under tension, low strength</td>
<td>Moderate</td>
<td>0.01% - 0.02%</td>
<td>animal study, mech testing</td>
<td>Acceptable - ALAP Justified</td>
</tr>
<tr>
<td>Device folds / wrinkles</td>
<td>Wrong shape / size</td>
<td>Severe</td>
<td>0.01% - 0.02%</td>
<td>cut to size, pre-defined shape</td>
<td>Acceptable - ALAP Justified</td>
</tr>
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Unacceptable risks:
Death/Permanent Disability: > 0.1%; Severe Injury: > 0.2%

- Risk rates not consistent with complaints
- Risk analysis does not appear to be updated by PMS
- Questionable Acceptability Criteria:
  - Death / permanent disability → 429 people in last 5 yrs
  - Severe injury → 858 people
“There is a risk of complications that can cause significant mortality”

“Although rare, these complications can have serious consequences”
Hypothetical Scenario

- **Conclusions Drawn After PMS Review:**
  - No new risks associated with use.
  - Data sufficient to demonstrate compliance with the ERs covering safety and performance.
  - Benefits outweigh risks.
  - No new clinical data is required.
Questions / Panel Discussion
...making excellence a habit.