Clinical evaluation –
Latest development in expectations EU
BSI clinical strategy review service

Medical Devices: staying ahead of regulatory developments
Gert Bos – BSI Shanghai Medical Device Forum – 17 May 2013
EU Regulatory Requirements for Clinical Evaluation

MDD, AIMDD and IVDD
‘clinical data’ means the safety and/or performance information that is generated from the use of a device (GHTF SG5/N1R8).

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- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated;

**EQUIVALENCE SERIOUSLY CHALLENGED OPTION IN CLASS III / AIMD**
Where are Regulatory Requirements for Clinical Evaluation Specified?

Medical Devices Directive, 93/42/EEC
- Annex I, Essential Requirements (6a)
- Annex X, Clinical Evaluation

Active Implantable Medical Devices Directive, 90/385/EEC
- Annex 1, Essential Requirements (5a)
- Annex 7, Clinical Evaluation

In Vitro Diagnostics Directive, 98/79/EC
- Annex III, EC Declaration of Conformity (Section 3)
Annex X – Clinical Evaluation

- Significant rewrite
  - Critical evaluation of relevant literature (equivalence)
  - Critical evaluation of clinical studies

- Need for clinical investigation for high risk devices (implantables and class III)

- Clinical evaluation must be actively updated with PMS; Need for PMCF must be justified and documented

- Where demonstration of conformity based on clinical data is not deemed appropriate, compliance to ERs must be justified through risk management output, performance evaluation, bench testing and preclinical evaluation
IVD Differs from MDD / AIMD

• IVD Annex III:
  "... adequate performance evaluation data showing the performances claimed by the manufacturer and supported by a reference measurement system (when available), with information on the reference methods, the reference materials, the known reference values, the accuracy and measurement units used; such data should originate from studies in a clinical or other appropriate environment or result from relevant biographical references."

• MDD Annex I, Essential Requirement 6a:
  "Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X"

• AIMD Annex I, Essential Requirement 5a:
  "Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex 7"
Annex X, Clinical Evaluation, Section 1.1

“As a general rule, confirmation of conformity with the requirements of concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I, 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 referred to in Section 6 of Annex I, must be based on clinical data.”
Annex X, Clinical Evaluation, Section 1.1a

• “1.1a 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.”
“The clinical evaluation and its outcome shall be documented. This documentation shall be included and/or fully referenced in the technical documentation of the device.”

“The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.”
Annex X, Clinical Evaluation, Section 1.1d

“Where demonstration of conformity with essential requirements 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.”
Annex X, Clinical Evaluation, Section 2.1

“The objectives of clinical investigation are:
— to *verify* that, under normal conditions of use, *the performance of the devices* conform to those referred to in Section 3 of Annex I, and
— to *determine* any undesirable side-effects, under normal conditions of use, and *assess* whether they constitute risks when weighed against the intended performance of the device.
Annex X, Clinical Evaluation, Section 2.2

**Ethical considerations**

Clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.
Annex X, Clinical Evaluation, Section 2.3.1 – 2.3.4

- Clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer’s claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions.

- The procedures used to perform the investigations must be appropriate to the device under examination.

- Clinical investigations must be performed in circumstances similar to the normal conditions of use of the device.

- All the appropriate features, including those involving the safety and performances of the device, and its effect on patients must be examined.

- **DUAL PURPOSE and PRE/POST CE SPLIT TRIALS HEAVILY CHALLENGED**
Annex X, Clinical Evaluation, Section 2.3.5

- All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.

- Clinical module in EUDAMED active and being used by CA; much more follow up actions

- MORE COEN REQUEST TO GET NB INVESTIGATIONS
Annex X, Clinical Evaluation, Section 2.3.7

- The written report, signed by the medical practitioner or other authorized person responsible, must contain a critical evaluation of all the data collected during the clinical investigation.

- Differences between MDD Annex X and AIMDD Annex 7?
  - AIMDD has essentially the same requirements as MDD, but language is more straightforward
  - AIMDD makes explicit statements regarding the conduct of the clinical trial, information to be recorded, confidentiality, etc (Annex 7, Section 2.3)
  - AIMDD makes explicit the requirement for compliance with harmonised standards (Annex 7, Section 1.1)
  - AIMDD does not make explicit reference to requirements for post-market surveillance (referenced in other annexes)
The Clinical Evaluation Process

1. **Set objectives**: Identify the relevant Essential Requirements that require clinical data (safety and performance criteria)

2. **Identify available clinical data** relevant to the device and its intended use

3. **Evaluate data** in terms of its suitability for establishing the safety and performance of the device

4. **Generate** any clinical data needed to address outstanding issues

5. **Prepare clinical evaluation report**: Use available clinical data to **conclude** safety and performance criteria are met
Process Step 1: Identify Objectives

ER#1 = Safe
ER#3 = Perform
ER#6 = Benefits > Risks
Any Other ERs
ER#2 = State of the Art
ER #4, #7, #9, #13
Marketing Claims
Other Regulatory Requirements
MEDLINE, EMBASE, Cochrane, Health Technology Assessments, Agency for Healthcare & Research & Quality, Safety & Efficacy Registry...

Search Terms

Unpublished data

Inclusion & Exclusion Criteria

Process Step 2: Identify Relevant Clinical Data
Process Step 3:

- **Evaluate** data in terms of its suitability for establishing the safety and performance of the device
  - Quality of the individual publication, study design, patient numbers, similarity of device under evaluation, etc
  - Overall volume of data available (from sum of literature available)
  - All requirements addressed (patient populations, indications for use, specific claims or identified risks, etc)
  - Adequate mitigation of identified risks?

- **Evaluate overall** data for adequacy:
  - Sufficient patient numbers / number of publications / volume of data to draw statistically robust conclusions?
  - All indications covered?
  - All risks identified and addressed?
  - All product variants covered?
  - Length of follow up consistent with intended product lifetime?
  - Risk benefit conclusion supported?
Process Steps 4 and 5:

- **Generate** any clinical data needed to address outstanding issues
  - Define objectives
  - Develop CIP or other mechanism to generate relevant data
  - Execute plan
  - Analyse data and incorporate into Clinical Evaluate Report

- Bring all the clinical data together to reach **conclusions** about the clinical safety and performance of the device
  - Is data adequate to demonstrate safety and performance of the device over its intended lifetime?
  - Is risk-benefit conclusion adequately demonstrated?
  - Are there any outstanding issues requiring PMCF?
  - Define PMS / PMCF Plan
Two Key Questions:

- Is a *premarket* clinical trial necessary?
- Is a *postmarket* clinical trial necessary?
Is a Premarket Clinical Trial Necessary?

- Are devices which are genuinely similar to your device available on the market?

- Is clinical data available in the public domain for these devices?

- Is the volume, quantity and relevance of this data adequate to reach conclusions regarding the safety and performance of your own device?

- Are the conclusions reached adequate to demonstrate compliance to the relevant Essential Requirements without a pre-market trial?
Is a Postmarket Clinical Trial Necessary?

- What are the residual clinical risks?
- Are clinical safety and performance data available for the devices themselves?
- Is this data adequate?

CAs expect manufacturers to have mechanisms in place to collect safety and performance data on the devices themselves. Whether or not PMCF is required will depend on the outputs of the pre-market clinical evaluation residual risks.
If you do a trial: current Standards


ISO 14155 : 2011

- EN ISO 14971:2007 ~ Risk Management to Medical Devices
So what has changed in ISO 14155?

- Merger of parts 1 (general) and 2 (CIP)
- 32+20 => 68 pages
- Logic structure and hands-on instructions: general requirements, planning, conducting, closing of study, responsibilities of sponsor and PI
- Annexes: clinical investigation plan, investigator’s brochure, CRFs, clinical investigation report, essential documents, adverse event flow chart
- Electronic clinical data systems
- Now harmonized in EU
Ethical considerations – more NB emphasis

- Ethical considerations from 1 => 7 pages
- Compensation / additional health care
- Details on communication with ethical committee
- Vulnerable populations
- Details on obtaining informed consent
  - Legal authorized representatives
  - Subjects unable to read/write
  - Emergency treatments
  - Information to patients & updates thereof
Further guidance

BSI Clinical Strategy Review
For CE marking
Helps You To

Attain a High Level of Confidence your Clinical Evaluation Plan will be acceptable and sufficient to meet CE Marking Requirements needed by the Notified Body
Customer Benefits

• Gain a clear Understanding of what the Notified Body expects Early in CE Marking Process

• Work with Experienced and Knowledgeable Product Experts

• Modular Approach helps to Streamline final submission review
Customer Benefits

• Benefits Multinational Corporations to Start-ups

• Meet timelines by Minimizing Risks of unexpected questions or requirements just prior to Launch

• Receive a BSI Report providing Feedback on your Clinical Strategy Plan
First Steps to the BSI Clinical Strategy Review

1. Manufacturer evaluates all relevant available Literature
2. Manufacturer determines if sufficient clinical evidence already exists to support CE Marking or if a Clinical Investigation is required
3. Manufacturer submits Clinical Evaluation Plan to BSI
BSI conducts Clinical Review based on Plan

LITERATURE REVIEW
BSI provides feedback on the manufacturer's conclusion on their clinical data

CLINICAL INVESTIGATION
BSI provides feedback on proposed Clinical Investigation Plan

Manufacturer attains a High Level of Confidence

Manufacturer Receives Feedback from BSI
Manufacturer completes the final Clinical Evaluation Report based on analysis of all relevant data including from Literature, Investigation and Experience.

Manufacturer submits full Clinical Evaluation Report to BSI as part of their normal Technical/Dossier Review.

BSI conducts a full Technical/Dossier Review to determine compliance to the Directive. If consistent with above expectations, process would be streamlined. If certified by BSI, the manufacturer can then affix CE Marking.
BSI Clinical Strategy Review
Helps Ensure Your Clinical Evaluations
“Are Right from the Start”
The END ....
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