Clinical evaluation –
Latest development in expectations EU and USA

Medical Devices: staying ahead of regulatory developments
Gert Bos – BSI Israel – 22 April - Herzliya
EU Regulatory Requirements for Clinical Evaluation

MDD, AIMDD and IVDD
Piece of Legislation - Definition

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  • published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated;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

• Mandatory clinical evaluation
• ER 5a/6a. Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.
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.
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.
USA Regulatory Requirements for Clinical Evaluation
What is Good Clinical Practice (GCP)?

- GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials or studies

- Additional terms defined:
  - Clinical Investigation
  - Clinical Investigator
  - Human Subject
  - Institutional Review Board (IRB)

Why is GCP Important?

- GCP compliance provides public assurance that the rights, safety and well-being of human subjects involved in research are protected

Abstracts from www.fda.org
What are The Goals of GCP?

• To protect the rights, safety and welfare of humans participating in research
• To assure the quality, reliability and integrity of data collected
• To provide standards and guidelines for the conduct of clinical research
• Good Clinical Practice = Ethics + Quality Data
The Historic Perspective – Towards ICH-GCP

Helsinki
• Well-being of subject takes precedence
• Respect for persons
• Protection of subjects health and rights
• Special protection for vulnerable populations

Belmont
• Respect for Persons
  • Informed consent
  • Protection of vulnerable populations
• Beneficence
  • Non-malfeasance
• Justice
  • Fairness

• GCP is an international quality standard that is provided by the International Conference on Harmonisation (ICH)
• Goals: Harmonize technical procedures and standards; improve quality; speed time to market
• In 1997, the FDA endorsed the GCP Guidelines developed by ICH
• ICH guidelines have been adopted into law in several countries, but used as guidance for the FDA in the form of GCP
13 Principles of ICH-GCP

• Ethics:
  • 1. Ethical conduct of clinical trials
  • 2. Benefits justify risks
  • 3. Rights, safety, and well-being of subjects prevail

• Protocol and science:
  • 4. Nonclinical and clinical information supports the trial
  • 5. Compliance with a scientifically sound, detailed protocol

• Responsibilities:
  • 6. IRB/IEC approval prior to initiation
  • 7. Medical care/decisions by qualified physician
  • 8. Each individual is qualified (education, training, experience) to perform his/her tasks

• Informed Consent:
  • 9. Freely given from every subject prior to participation

• Data quality and integrity:
  • 10. Accurate reporting, interpretation, and verification
  • 11. Protects confidentiality of records

• Investigational Products:
  • 12. Conform to GMP’s and used per protocol

• Quality Control/Quality Assurance:
  • 13. Systems with procedures to ensure quality of every aspect of the trial
How does FDA Implement GCP?

- 21 CFR 11 – Electronic Records & Signatures
- 21 CFR 50 – Protection of Human Subjects
- 21 CFR 54 – Financial Disclosure
- 21 CFR 56 – Institutional Review Boards
- 21 CFR 812 – Investigational Device Exemptions
- 21 CFR 814 – Premarket Approval of Medical Devices

Further Guidance and Instructions

- Compliance Program Guidance Manual 7348.809 Institutional Review Boards (CPGM 7348.809)
- Compliance Program Guidance Manual 7348.810 Sponsor Inspections (CPGM 7348.810)
- Compliance Program Guidance Manual 7348.811 Investigator Inspections (CPGM 7348.811)
- 42 USC section 1320a-7b. The Anti-kickback Statute
- And other related guidance and documents
Typical Questions to Ask Yourself

- Is a 510(k) justifiable?
- Is a feasibility study necessary?
- Should you pursue a PDP or letter of determination?
- What written guidance and precedents are applicable?
- Can foreign data be utilized to support registration?
- What experimental design and control group are most appropriate?
- What primary study endpoints lead to the smallest sample sizes?
- What effectiveness and safety endpoints are relevant?
- When is MedDRA appropriate vs. a pre-specified adverse event list?
- Will the FDA accept a composite endpoint?
- How do 21 CFR 812 and 21 CFR Part 11 apply?
- Can adaptive designs Bayesian modeling be beneficial?
US FDA Pre-Sub (Pre-IDE) Consulting

- FDA offers Pre-Submission Consulting (Pre-Sub consulting, ex. Pre-IDE consulting) for medical device manufacturers before they begin their regulatory application or clinical and non-clinical testing.

- FDA Pre-Sub consulting is available for sponsors and manufacturers to obtain regulatory feedback on various medical device-related applications, including Investigational Device Exemptions (IDE) necessary for high risk medical device clinical investigations, premarket notification (510(k)) submissions, and clinical or non-clinical study protocols.

- The FDA Pre-Sub program can prove especially valuable for devices utilizing novel technologies, or those with indications qualify them as “first of a kind” devices.

- not mandatory, but highly encouraged
- before initiating your 510(k) or premarket application (PMA) review process

- Pre-Sub submission should include a cover letter explaining the reason for your submission, a description of your medical device along with its proposed intended use, and specific questions related to your planned IDE or marketing application.
In the US, the need to collect postmarket clinical data is determined by FDA, although manufacturers may voluntarily collect these data. It is an established process and defined in US regulations. In Europe, a guideline, which is not legally binding, describes European expectations for these types of data.

- **21 CFR 822, Postmarket Surveillance (class II and III only)**

This provides manufacturers with more flexibility in determining the need for postmarket clinical data and the type of data to be collected. At the same time, there will be more uncertainty regarding the correctness of these decisions and the adequacy of the postmarket clinical data that are collected until more experience is gained.
The END ....
For further information

Name:  Gert Bos

Title:  Head of Regulatory and Clinical Affairs (NB0086 & NB0535)
       Head of Notified Body (NB0535)

Address:  BSI
       Kitemark Court, Davy Avenue, Knowlhill, Milton Keynes, MK5 8PP, UK

Mobile:  +31 (0)6 50459651
Home-office:  +31 (0)8500 21471
Email:  Gert.Bos@bsigroup.com
Links:  www.bsigroup.com/healthcare
       www.linkedin.com/in/gertbos
          @bsihc
          @gertwbos