Clinical trial data requirements: Based on medical requirements

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Disclosure

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I have the following potential conflicts of interest to report:

☒ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

☐ I do not have any potential conflict of interest
Introduction

- The medical device manufacturing industry is becoming a major player in health-care delivery.
- In 2008 the FDA received more reports of adverse events from these devices than from pharmaceuticals.
- Medical device manufacturers can conduct clinical trials more easily in Europe, where currently regulatory barriers to clinical testing have less constraints.
- The regulatory barrier to starting a device clinical trial in India, China, or Korea is almost nonexistent.

http://www.slideshare.net/emergogroup/conducting-medical-device-clinical-studies-in-europe-10997146
Introduction

• Data may be considered questionable given different requirements in reporting.
• ISO 14155 defines procedures for conducting clinical investigations of medical devices.
• An ISO 14155 trial will reveal adverse events under normal use and allow researchers to assess acceptable risks while considering the device's intended performance.
• Proportion of small and medium enterprises >90%.
• Lifecycle of medical devices as short as two years.

http://www.slideshare.net/emergogroup/conducting-medical-device-clinical-studies-in-europe-10997146
Study design

Pilot study necessary prior to studies covering large populations?

• Situation is simple for most pharmaceuticals: Yes
• Situation for medical devices:
  – It depends.....

Science in studies.
  – Pharmaceutical studies: Double blind randomised controlled
  – Medical device studies: It depends.....
Science in studies

• Control arm necessary?
  – Device factors, user skills, patient factors all having influence on results that is impossible to sort out.
  – Hypotheses or pass/fail criteria based on historic controls not comparable to the study population or study situation.

• Validity of trial results can be rejected later on by regulators and inspectors.

• Biased clinical trials are unethical and illegal.

• For all studies professional statistical planning is necessary!
Study CRF

- A thorough check of the CRF regarding congruency with the protocol is necessary, especially for
  - Inclusion and exclusion criteria
  - Study procedures at each visit
  - Patient questionnaires in local language(s)
  - AE-, SAE-, and MAE-forms with correct definitions and reporting procedures
  - Anonymization (no patient names, no combination of initials and date of birth).
Validity of data – Endpoints

• Endpoints are: relevant to disease process, easy to interpret
  – Free from measurement or assessment error
  – Sensitive to treatment differences
  – Measurable within a reasonable period of time

• The primary and secondary endpoints are best selected when they are based on previously published clinical or relevant preclinical data.

• The study sample size should be designed to prove the primary safety and effectiveness of the endpoints.

• The endpoints used in a clinical trial must correspond to the scientific objectives of the study and the methods of outcome assessment should be accurate (free of bias).
Selection of Hard & Soft EPs

• Hard endpoints:
  – Quantitative measurement of hard endpoints
  – Well-defined in study protocol
  – Definitive with respect to disease process
  – Not subjective
  – Examples: Death, time to disease progression/relaps

• Soft endpoints are those that do not relate strongly to the disease process or require subjective assessments by investigators and/or patients.

• Some endpoints fall between these two classifications.
  – E.g.: the grading of x-rays and the grading of cell and tissue lesions/tumors. There is some degree of subjectivity, but they are valid and reliable endpoints in most settings.
Endpoints

- End point definitions are necessary in clinical trials so that events are clearly characterized by objective criteria and reported uniformly.

- **Primary effectiveness endpoints**
  - Demonstrate the clinical outcome
  - Demonstrate reduction of mortality and reduction or improvement of clinical symptoms

- **Primary safety endpoint:**
  - determines the rates of MAEs

- **Secondary endpoints:**
  - Evaluation of the rate of AEs,
  - capture procedure complications, rates of device failures, technical success, device performance parameters
Definition of complications

- Complications should be reported according to the general clinical research guidelines and the applicable (local) laws.

- Guidance documents on definitions for complications:
  - International Society for Standardization (ISO) 14155
  - the International Conference on Harmonization-Good Clinical Practice (ICH- GCP) guidelines
  - Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) chapter x812.3.

Definition of complications

- Any untoward occurrence in a subject should be differentiated as follows:
  - Adverse events (AE)
  - Serious adverse events (SAE)
  - Adverse device effect
    - (Serious) Adverse device effect (SADE)
    - Unanticipated adverse device effect (UADE)
  - Major adverse event (MAE)

### Definition of complications

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Non-device related</th>
<th>Device- or procedure related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-serious</td>
<td>Adverse Event (AE)</td>
<td>Adverse Device Effect (ADE)</td>
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<tr>
<td>Serious</td>
<td>Serious adverse event (SAE)</td>
<td>Serious Adverse Device Effect (SADE)</td>
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<td>Anticipated</td>
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<td></td>
<td></td>
<td>Anticipated Serious Adverse Device Effect (ASADE)</td>
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</tbody>
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Definition of AEs

• Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
  – Includes events related to the investigational device or the comparator.
  – Includes events related to the procedures involved (any procedure in the clinical investigation plan).
  – For users or other persons this is restricted to events related to the investigational medical device.

• All AEs, whether serious or not, must be rated “related or unrelated” to the investigational product.
Definition of SAEs

A SAE is an AE that

- led to a death
- led to a serious deterioration in the health of the subject that resulted in
  - a life-threatening illness or injury
  - permanent impairment of a body structure or a body function
  - inpatient hospitalization or prolongation of existing hospitalization (except: planned hospitalization due to pre-existing condition)
  - medical or surgical intervention to prevent permanent impairment to body structure or a body function
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Definition of MAEs

- The MAE definition is different for each protocol and must be defined in the protocol.
  - The CEC/DSMB adjudicates all SAEs and determines if an event is a MAE or not.

Reporting of AEs / SAEs

• Following AEs must be adjudicated and reported:
  – procedural-related serious adverse events
  – investigational product related serious adverse events
  – device failure or malfunction.

• Next to the MAE, the reported AE/SAE should be classified and reported according to the following four complication categories:
  – access site complications,
  – vessel specific complications (treatment site including proximal and distal to the site),
  – organ-specific complications,
  – systemic complications.

Summary

- The medical device manufacturing industry is becoming a major player in health-care delivery.
- For all studies professional planning is necessary!
  - Study design, control arm, science, endpoints, MAEs
- Complications should be reported according to the general clinical research guidelines.
- The MAE definition is different for each protocol and must be defined in the protocol.
- CEC/DSMB is essential for the adjudication of AEs, SAEs, and MAEs.
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