Specific Types of Studies and Practical Hurdles from a Legal Perspective

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Overview

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I. Introduction
Clinical evaluation

- Clinical evaluation = assessment and analysis of clinical data pertaining to a medical device in order to verify

Clinical safety

Performance
Clinical evaluation is

- an ongoing process conducted **throughout the life cycle of a medical device**
- performed during the conformity assessment process leading to the marketing of a medical device
- 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
Clinical evaluation

- Clinical evaluation and life cycle of a medical device
II. Study Types
Clinical investigation

Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety or performance of a medical device.
Clinical investigation

- Clinical investigation – general objectives
  - to verify that, under normal conditions of use, the performance of the devices conform to the Essential Requirements, and
  - to determine any undesirable side-effects, under normal conditions of use, and
  - to assess whether undesirable side-effects constitute risks when weighed against the intended performance of the device
Non-interventional studies

- Art. 15 of MDD 93/42/EEC and Annex X do not provide for any demarcation aspects
- Art. 15 (8) of MDD 93/42/EEC

“The provisions of paragraphs 1 and 2 do not apply where the clinical investigations are conducted using devices which are authorized in accordance with Article 11 to bear the CE marking unless the aim of these investigations is to use the devices for a purpose other than that referred to in the relevant conformity assessment procedure. The relevant provisions of Annex X remain applicable.”
Non-interventional studies

- Intervention or non-intervention as demarcation aspect?
- Subject to national laws (e.g., § 23b German Medical Devices Act)
Non-interventional studies

- Additional invasive investigations?
  - Blood samples (non routine)
  - Tissue samples (non routine)
  - Biopsy (non routine)
  - Other surgical measures (non routine)

- **Caution:** classification into routine or non routine measures is difficult in medical practice
Non-interventional studies

➢ Other burdensome investigations?
  ❖ MRT investigation
  ❖ X-ray examination
  ❖ Electrocardiogram
  ❖ Randomisation into investigation groups
  ❖ Additional measuring activities which might prolong medical treatment

➢ **Caution:** the classification as „burdensome“ is subjective and depends on the concrete clinical investigation
Registries/Data collection

- Registries
  - Important PMCFU tool (e.g., regarding implants)
  - Device registries defined by MEDDEV 2.12/2 rev2, January 2012, as
    “An organised system that uses observational study methods to collect defined clinical data under normal conditions of use relating to one or more devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical or policy purpose(s).”
  - A non-interventional PMCFU study type
Registries/Data collection

- Data collection
  - Observational and non-interventional study type
  - Follow-up of medical practice and routine without any control methods (e.g., randomisation)
  - Therapeutical decision of the responsible physician is not affected by the implementation of the study
  - Sound scientific background and surveillance plan
  - “Look over the physician’s shoulder”
PMCFU studies

Interventional studies

PMCFU studies

Non-interventional studies
PMCFU studies

Types and design of PMCFU studies?

<table>
<thead>
<tr>
<th>Clinical investigation (e.g., randomized controlled trials, cohort studies, case-control studies, case series)</th>
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<td>Medical device registry</td>
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<td>Prospective data collection</td>
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<td>Retrospective data collection</td>
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<td>Clinical follow-up of patients (enrolled in clinical investigations without CE-marking)</td>
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<td>Investigator initiated trial (IIT)/data collection?</td>
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</table>
PMCFU studies

- **MEDDEV 2.12/2 rev2, Jan 2012**
  - are carried out following the CE-marking and
  - with medical devices used in accordance with its approved labelling
  - are intended to answer specific questions relating to clinical safety or performance = residual risks
  - are not intended to replace the pre-market data necessary to demonstrate conformity with the provisions of the legislation
  - are critical in order to update the clinical evaluation
  - shall ensure long term safety and performance
PMCFU studies

Potential impact

- Additional clinical evidence for the ongoing clinical evaluation process
- Re-assessment of compliance with the Essential Requirements
- Implementation of corrective or preventive actions, such as
  - changes to the labeling/instructions for use
  - changes to manufacturing processes
  - changes to the device design
  - public health notifications
PMCFU studies

- Interim measures of the European Commission as of 24 September 2013
  - EC adopted two measures to improve the safety of medical devices fulfilling its commitment to restore patient confidence in the medical devices sector following, amongst others, the Poly Implant Prothèse (PIP) breast implants scandal
  - One Commission Implementation Regulation clarifying the criteria to be met by notified bodies, which are responsible for inspecting manufacturers of medical devices
  - One Recommendation clarifying the tasks these bodies have to undertake when they perform audits and assessments
PMCFU studies

Interim measures of the European Commission as of 24 September 2013

Recommendation Annex II (18) – Quality System Assessment

“At each annual surveillance audit, the notified bodies should verify that the manufacturer correctly applies the approved quality management system and the post-market surveillance plan.“

Measures will also increase pressure on manufacturers
PMCFU studies

When is a PMCFU study necessary?

- Innovative medical device
- Post-market study
- High device related risks
- CE-marking was based on equivalence
- Unanswered questions of long term safety and performance
- High risk target populations or anatomical locations
- Risks identified from literature or other data sources
PMCFU studies

- Decision to conduct post-market studies must be based on

- Identification of possible residual risks

- and/or

- Unclarity on long term clinical performance

- Impact on benefit/risk ratio
PMCFU studies

- May not be required
  - When the medium/long-term safety and clinical performance are already known from previous use of the device or
  - Where other appropriate post-market surveillance activities would provide sufficient data to address the risks
II. Financial Support
Financial support

Commercial Studies
Non-commercial Studies
Medical Device Manufacturer
CROs
University Hospitals, Academic Institutions
Financial Support

- Demarcation of responsibilities
  - Who is the **sponsor** of the study?
  - Who owns the data and study results?
  - Protection of IP rights
  - Will the data/results be included in the technical documentation of the respective device?
  - Purchase of raw data/study results – possible?
  - Data protection and quality assurance/monitoring/audits
III. Contract Management
Legal aspects to be considered

- The applicable regulatory framework has to be defined (clinical investigation, data collection, registry, etc.)
- Precise allocation of responsibilities between the contracting parties (e.g., sponsor, CRO, study site, investigator, consultant, etc.)
- Adequate compensation (fair market value)
- Provision of medical devices and other equipment (e.g., control instruments, laptops, etc.)
- Publications rights and publicity
Legal aspects to be considered

- Data protection (!) and secrecy
  - Use of personal data and re-identification
  - Use of pseudonymised data
  - Transfer and storage of data
- Storage of blood samples and tissue
- IP-rights and ownership of data
- Monitoring and audits
- Term and termination of the contract
- Responsible contact
- Exhibits: study plan, case report forms, patient informed consent form
Legal aspects to be considered

- **Business Compliance/Anti-Bribery**
  - Adequate compensation of performances (e.g., Gebührenordnung für Ärzte)
  - Fair market value?
  - Transparency (Sunshine Act): disclosure of compensation
  - Appropriate documentation and follow-up
IV. Disclosure and access to clinical data
Disclosure and access to clinical data

- Current situation
  - Clinical data are part of the technical file
  - Owner: manufacturer/company
  - EUDAMED is the European database for medical devices
  - established under the MDD and is a secure web-based portal acting as a central repository for information exchange between national competent Authorities and the Commission
  - EUDAMED contains data on: registration of manufacturers, authorised representatives and devices, data relating to certificates, data obtained in accordance with the vigilance procedure and data on clinical investigations
  - Access is restricted to the Medical Devices National Competent Authorities
Disclosure and access to clinical data

- Current development
  - Example for voluntary disclosure: Johnson & Johnson announced in January 2014 that its subsidiary, Janssen Research and Development, LLC, has entered into a novel agreement with Yale School of Medicine’s Open Data Access (YODA) Project that will extend its commitment to sharing clinical trials data to enhance public health and advance science and medicine
Disclosure and access to clinical data

- **Future development**
  - Obligation for manufacturers of high-risk devices to make **publicly available** a summary of safety and performance with **key elements of the supporting clinical data**
  - EUDAMED will contain integrated electronic systems on a European UDI, on registration of devices, relevant economic operators and certificates issued by notified bodies, **on clinical investigations**, on vigilance and on market surveillance
  - **A large part of the information in EUDAMED will become publicly available** in accordance with the provisions regarding each electronic system

- **Protection of business secrets?**
Thank you for your kind attention!

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Dr. Heike Wachenhausen

» Heike provides advice across the full range of regulatory matters relating to medicinal products and medical devices on German and European level with particular focus on development, marketing authorization/CE-marking and product safety (vigilance).

» Heike has been working as a regulatory lawyer for 14 years. She started her career in the practice group “Healthcare, Life Sciences and Chemicals” in the Düsseldorf office of Clifford Chance and for six years she worked with law firm Sträter in Bonn before she became Head Legal Regulatory & Development in the legal department of Novartis AG based in Basel, Switzerland. Following her involvement as a partner in a regional law partnership based in Lübeck, she has further intensified her Lübeck-based activities since June 2013 as founder of the law firm Wachenhausen Rechtsanwälte. Heike holds a PhD in law. Her doctoral thesis deals with clinical trials with persons incapable of giving informed consent.

» Heike is co-editor of the German Medical Device Journal and Chair of the Forum for Medical Technology e.V. She has widely published on matters relating to development and authorisation of medicinal products and medical devices. Heike regularly holds seminars and presents papers at symposia.

» Languages: German, English