REGULATORY REQUIREMENTS AND MEDICAL DEVICE STUDIES

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Overview

REGULATORY REQUIREMENTS

• Medical Device Directive
  CE Marking
  Essential requirements
  Harmonised standards

• EUDAMED – database storing clinical investigation information

CONDUCTING MEDICAL DEVICE STUDIES

• ISO 14155 “Clinical investigation of medical devices for human subjects – Good Clinical Practice”

• Clinical investigations

• Post market surveillance studies
Regulatory Requirements

- 3 European Directives covering Medical Devices
  - Active implantable, In-vitro Diagnostic, Medical Device Directive
- “New approach” Directives, all medical devices must be CE marked
- Many other new approach Directives, eg Toy Directive, CE marked
- Entirely different to the Pharmaceutical Regulations
- Regulated by the Medicines and Healthcare products Regulatory Agency (MHRA)
Notified Bodies

- Medical device manufacture in the UK is regulated by the UK Competent Authority, the Medicines and Healthcare products Regulatory Agency, MHRA
- Notified Bodies, are independent organisations who audit manufacturers to check compliance with the Medical Device Directives
- UK Notified Bodies include, BSi, SGS, LRQA, AMTAC
CE marking

- Device is fit for its INTENDED use
- That it is SAFE for its intended use
- CE marking needed PRIOR to placing product on the European market

- Requirements documented in the Medical Device Directive, 93/42/EEC
- IT’S THE LAW
CE Marking

- Once have obtained a CE mark, product can be sold on the market in all 27 European countries
- Different Regulations exist for other markets of the world, all need separate registrations:
  Canada, US, Australia, Japan, India, South Korea, Brazil, Latin America, Singapore, New Zealand, China, South Africa........
Classification

- World of medical devices very diverse
- Sticking plasters, wheelchair, pacemaker, hip replacement, MRI scanners, bandages, contact lens
- Medical Device Directives need to capture all the issues concerning all devices
- Risk based classification system
- Class I, IIa, IIb, III
- Necessary to compile a Design Dossier for Class III products and a Technical File for all other classes of product
Essential requirements

- Applicable to all devices – ESSENTIAL
- Clinical data
- Design history
- Manufacture
- Biocompatibility
- Labelling & packaging, instructions for use
- Risk Management, benefit must always out weigh the risk
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**2007/47/EC**

- 93/42/EEC has been amended, 2007/47/EC
- Came into force on 21\(^{st}\) March 2010
  - numerous changes wrt Clinical Investigations; a focus on clinical evidence
- European database had to be established by the European Commission
  - EUDAMED
  - went live on 5\(^{th}\) May 2011
  - numerous items to be entered
  - for Competent Authority use only
EUDAMED

- Details of Manufacturers & their products to be stored on the database, including data relating to Clinical Investigations
  - Data relating to registration of Manufacturers & Authorised Reps
  - Data relating to certificates issued, modified, supplemented, suspended, withdrawn or refused
  - Data obtained in accordance with the Vigilance procedure
  - Data relating to clinical investigations
WHAT IS ISO 14155?

🔗 An International Standard intended to be used worldwide for medical device clinical investigations

🔗 Recently updated current version - Clinical Investigation of medical devices for human subjects- Good Clinical Practice-dated 1 February 2011

🔗 In Europe supports the Medical Device Directive and the Active Implantable Medical Device Directive
WHAT IS ISO 14155?

Contains 9 Sections:

1-Scope
2-Normative references
3-Terms & definitions
4-Ethical Considerations
5-Clinical investigation planning
6-Clinical investigation conduct
7-Suspension, termination and close out of the clinical investigation
8-Responsibilities of sponsor
9-Responsibilities of the PI
WHAT IS ISO 14155?

Contains 6 Annexes:
- A-Clinical investigation plan
- B-Investigators brochure
- C-Case report
- D-Clinical investigation report
- E-Essential clinical investigation documents
- F-Adverse event categorization
Medical Device Studies

Two types of medical device study

- Clinical Investigations
- PMS studies
What is a clinical investigation?

Any systematic investigation or study in or on one or more human subjects undertaken to assess the safety and or performance of a medical device.
Clinical Investigations (CI)

- New device proposed for market (does not have a CE mark)
- Existing device modified/new features
- Established device proposed for new purpose/indication
- Incorporates materials in contact with human body – no prior clinical experience
- Class IIa or IIb implantable long term
- Class III

- Unless safety and performance can be adequately demonstrated in other ways, a clinical investigation will be required
Clinical Investigation Planning

- Design of the CI should be based on the evaluation of pre-clinical data and the results of a “clinical evaluation.
- The clinical evaluation is a scientific activity that should be done with rigour and objectivity according to scientific standards using the principles of GHTF clinical evaluation.
- Results of the clinical evaluation are used to determine and justify the optimal design of the clinical investigation and to identify relevant endpoints and confounding factors to be taken into consideration and to serve to justify any comparator(s).
- The CI should be designed to evaluate whether the device is suitable for the purpose(s) and the population(s) for which it is intended.
- The CI should be designed in a way that ensures that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives.
At a minimum the following documents should be maintained in the investigator &/or sponsor files-see Annex E- Tables E1,E2,E3

- Clinical Investigator Brochure (CIB)
- Clinical Investigation Plan (CIP)
- Investigator CVs (current & signed/dated)
- Name of Hospitals where CI is being conducted
- Documented REC approval & correspondence
  - Correspondence with CAs
- Agreement between Investigators & sponsor
  - Insurance
  - Patient Information & Consent
  - Case Report Forms (CRFs)
  - AE Reporting Forms
- Name/contact details of monitor(s)
Clinical Investigation Conduct

PRIOR TO THE START OF THE CI

- The CI shall be conducted in accordance with the CIP
- The CI shall not commence until receipt of written approval from the EC/CA/R&D (where applicable)
- The sponsor shall conduct & document an initiation visit at each participating site or alternatively an investigator meeting. Appropriate logs shall be completed identifying names, initials, signatures & delegated functions of all staff.

DURING THE CI

- The CI shall be monitored in accordance with the monitoring plan, visits are generally on-site but may also in exceptional circumstances be conducted remotely but must be documented accordingly and justified.
- All AEs shall be documented & reported in a timely manner throughout the CI & in the interim & final report.
- All device deficiencies shall be documented, reported (if applicable) & appropriately managed by the sponsor
Adverse Event Categorisation - F

1. Adverse Event
   - Does it meet Seriousness Criteria?
     - If No: AE
     - If Yes: SAE
       - Is it Device-Product related?
         - If No: SADE
         - If Yes: ADE
           - Is it Anticipated?
             - If No: Unanticipated SADE
             - If Yes: Anticipated SADE
Clinical Investigation Report

• Annex D specifies the contents of the Clinical Investigation report and describes the design, execution, statistical analysis and results of a Clinical Investigation.

• There is an example format report form within Annex D which can be used for Interim, Progress, Annual and Final Reports if required,
Approvals

Clinical Investigations
- MHRA or Competent Authority from each member state
- Ethics Committee
- R&D approval in the UK, Hospital approval in Europe

PMS
- Ethics Committee (if applicable)
- R&D approval in the UK, Hospital approval in Europe
What is Post Market Surveillance (PMS)

- PMS is the follow-up of device(s) post CE marking
- PMS is a “safety net” to ensure continued safety and effectiveness of marketed products
- PMS is following new devices into the “real world”
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POST MARKET PHASE

- CE Marked Device
  - Implant registry
  - Post market clinical studies
  - Adverse Incident Reporting
  - Analyse post market data
What can PMS achieve?

- Detection of manufacturing problems
- Product quality improvement
- Confirmation (or otherwise) of risk analysis
- Knowledge of long-term performance/reliability and/chronic complications
- Knowledge of changing performance trends
- Knowledge of performance in different user populations
- Identification of vigilance reports
- Knowledge of ways in which the device is misused
Post CE mark clinical studies – why?

• Manufacturers must have an appropriate system for gaining and reviewing use of a product once CE marked
• MDD Conformity Assessment procedures
• Notified bodies have to audit verify an effective system is in place
• Clinical Investigations provide limited information
• Early warning system
• More emphasis on PMS
How To Obtain Clinical Data

PMS acts as a “safety net” to ensure continued safety and effectiveness of marketed products

- Implant Registries
- Prospective Studies
- Phase IV Studies
- Vigilance systems
Tips for PMS Studies

**Pre-study**
- Good Protocol & Study Design
- Good Planning & Realistic Timelines
- Select appropriate sites
- Monitoring plan

**During-study**
- Monitor Recruitment carefully & communicate regularly with site
- Complete vigilance reporting for any device related incidents

**Post-study**
- Lessons Learnt – formal close out, ensure don’t make same mistakes again