Clinical Evidence Guidelines
Beyond The CSR - Demystifying Clinical Evidence Requirements For Medical Devices

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Agenda

• Introduction
• Essential Principles
• Clinical Investigation Data
• Literature Review
• Post market Data
• Substantial Equivalence
• The Clinical Evaluation Report
• The Clinical Expert
• Errors / Shortcomings
Clinical Evidence Guidelines for Medical Devices

• Version 1.0 published on 24th February 2017
• Aligned with:
  – Legislation (Therapeutic Goods Act 1989)
  – Regulations (Therapeutic Goods (Medical Devices) Regulations 2002)
  – Guidance from Global Harmonization Task Force (GHTF) and European Medical Device Regulations (EU MEDDEVs)
• Intent is to support manufacturers of medical devices by defining what constitutes clinical evidence, and how relevant data are generated and evaluated
  – Critical review of available data with a discussion which weighs risks and benefits of a different device
  – Details will vary by device type, class and intended purpose
  – Provide clinical assessor with a balanced view of the relevant treatment modality and the particular device evaluated
Clinical Evidence Guidelines - Scope

• Applies throughout life cycle of medical device on ARTG
  – Data requires periodic re-evaluation post-market
  – May be requested at any stage by the TGA
• Specific Information for device types:
  – Joint Prostheses
  – Cardiovascular devices to promote patency or flow
  – Implantable pulse generators
  – Heart valve prostheses
  – Supportive devices, e.g. meshes, patches, etc.
  – Implantable devices in MRI
• Not Exhaustive
Essential Principle 14: Clinical Evidence

“Every medical device requires clinical evidence, appropriate for the use and classification of the device, demonstrating that the device complies with the applicable provisions of the Essential Principles.”

• Schedule 3 part 8 of the Medical Device Regulations

• Types of Clinical Data:
  – Clinical Investigation Data
  – Literature Review

• Critical Evaluation by an “expert in the relevant field”
## Essential Principles

### Essential Principles (EPs)

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Essential Principle 1

- Use of medical devices not to compromise health and safety
- Consider intended use, patient population, context of use.
- Consider adverse events from clinical investigations, literature reviews, and post-market data.
Essential Principle 3

- *Medical devices to be suitable for intended purpose*
- What is the evidence for performance?
- Each claim or intended use must be substantiated in some way.
- Those substantiating data must meet certain requirements, e.g. how literature review was carried out.
Essential Principle 6

- **Benefits of medical devices to outweigh any undesirable effects**
- Product development and clinical data should have identified risks associated with device use.
- Risk analysis should be performed and a risk management plan created.
- All risk items should be mitigated to the fullest extent, e.g. by warnings in IFU.
- Residual risk must be determined to be acceptable.
- A positive benefit-risk ratio must be demonstrated.
Essential Principle 13.4: Instructions for Use

• Legislation provides a list of 29 items to be included in the IFU.
  – Item 4: Information about the intended performance of the device and any undesirable side effects caused by use of the device
  – Item 5: Any contra-indications, warnings, restrictions, or precautions that may apply in relation to use of the device
  – Item 19: For an implantable medical device – information about any risks associated with its implantation
Clinical Investigation Data

• For the device itself – Direct clinical evidence:
  – Gives highest level of confidence in the device
  – Interventional studies, e.g. RCT
  – Observational studies
  – Single arm study
  – Subject device of the investigation?

• Indirect clinical evidence:
  – Predicate/ similar… substantial equivalence?
  – May provide benchmark for acceptable risk

• Expectations vary with novelty of device, risks and intended use
  – Gap analysis to indicate the need for investigations – e.g. new claims, new features/ materials, new user, duration of use, etc.
Literature Review

- Direct v indirect
  - Use of comparators – acceptable risk
- Search protocol and selection criteria
  - Databases searched
  - Reasons for excluding publications
  - Is it reproducible?
- Aids:
  - Flow charts
  - Tabulating results
- Critical appraisal
Post Market Data

- Device marketed overseas prior to Australia
- Larger / longer term data
  - Evaluation of less frequent risks
- Predicate device – may even have local data
- Various sources:
  - National and/or regional registries e.g. AOANJRR
  - Manufacturer’s own
  - Complaints
  - Reportable events
  - Recalls
Substantial Equivalence
Substantial Equivalence

- Recognition of incremental development of devices
  - Allows recognition of evidence/experience obtained with the predicate or similar devices
  - Practicalities of conducting studies or gathering other data in small $n$
- Demonstrate that changes will not adversely impact safety and performance
  - Tabulation of differences
  - Discussion of individual differences and their impact on safety and performance
- Should be based on a single device
  - Most appropriate?
  - NB small change in design ≠ small change in performance
- Intended purpose
- Not always appropriate e.g. high risk, highly novel technologies
Substantial Equivalence

Predicate vs Similar Device

- Predicate Device
  - Previous iteration of the device under consideration
  - Same intended purpose
  - Same manufacturer/ lineage (this varies from FDA)

- Similar Marketed Device
  - Currently marketed device
  - Similar structure and design
  - Same intended purpose
  - Not from the same manufacturer

- Where either is cited, they should have clinical evidence available to support performance/ safety
Substantial Equivalence

GHTF Statement

• “The devices should have the same intended use and will need to be compared with respect to their technical and biological characteristics. These characteristics should be similar to such an extent that there would be no clinically significant difference in the performance and safety of the device.”
Demonstration of substantial equivalence

1. Identification of appropriate predicate of similar device
   - Have any safety concerns been raised?
   - Has the device been removed from any jurisdictions?

2. Review intended purpose of the two devices – condition treated, stage/ severity of disease, patient population, site of use
   - If not the same, requires justification – data for population of the subject application present

3. Compare technical (design, specifications, physicochemical properties, energy intensity, deployment method, principles of operation) and biological (biocompatibility of materials in contact with the body) characteristics
   - Information showing similarities and differences should be tabulated, with differences clearly and explicitly stated
   - If not substantially similar, additional evidence needs to be provided demonstrating that differences will not adversely impact safety and performance

4. Final assessment with critical appraisal
The Clinical Evaluation Report
The Clinical Evaluation Report

• Not a simple summary of available data followed by a statement that the data demonstrates safety and performance – expectation is of Critical Evaluation, with a well-reasoned analysis of the risks and benefits of the device, considering:
  – The strengths and limitations of available data
  – The significance of the benefits for the intended purpose
  – A prediction about the proportion of “responders”
  – Safety issues / hazards associated with use for the intended purpose and “misuse” of the device
  – Probability of harm and severity / duration of the effect
  – Risk mitigation strategies
  – Uncertainty about the device or data presented
The Clinical Evaluation Report

• Device description – lineage and version. Includes description of materials used, sizes, models, components, mechanical and functional characteristics
  – Diagrammatic representation helpful
• Intended purpose / indication and product claims
  – Includes single/ multiple use, MRI status for implantables, duration of use
  – Supported by evidence provided
• Regulatory status in other countries
  – Approvals AND recalls, suspensions, withdrawal, cancellation
  – Exact wording of Intended purpose
  – Trade names
• Relevant pre-clinical data summary
The Clinical Evaluation Report

- Direct vs Indirect Data
  - Demonstration of substantial equivalence
  - Evaluation of data needs to consider the whether there is the potential for harm based on differences between the device and the substantial equivalent
  - Needs to specify which device the data relates to
- Summary of clinical data and appraisal
  - By a competent clinical expert
- Risk Benefit analysis
The Competent Clinical Expert

• An expert in the relevant field:
  – Typically medically qualified and a practitioner in the specialty which will use the device
  – Experience of use of the device or device type in a clinical setting
  – Recent clinical experience preferably within 5 years
  – Suitability may depend on novelty of device and recent developments within the field
  – Demonstrated by CV
  – Additional justification may be needed - >5yrs out of clinical practice

• More than just an endorsement
Errors in the CER

• Question the validity of the conclusions
• Requests for more information / clarification
  – Lengthen application process
• Rejection of application
  – Could have been addressed by the information provided from the outset
High Risk Devices

Joint Prostheses

• Difficulties with substantial equivalence
  – Small differences in geometry
• Specific requirements from clinical trials
  – 2 year follow up
  – Surrogate marker to indicate longer term risk of revision e.g. radiological
• Risk analysis
  – Post market data
  – Joint registries
• Components of a system
High Risk Devices

Cardiovascular devices to promote patency of functional flow

- Arterial stents (coronary, carotid, peripheral), AAA stents, implants for PDA repair, IVC filters
- Patient selection – details of population studied
- Timeline studied needs to be aligned with intended use of the device
- Appropriateness of outcome measures:
  - Mortality
  - CVA/ MI
  - PE
- Surrogate markers to predict long term failure
- Post market data and risk analysis
High Risk Devices

Implantable pulse generator systems

- Pacemakers, cardiac resynchronisation therapy ± defibrillation, implantable electric nerve stimulators
- Follow-up data – peri-operative, acute, chronic (>3 months), long enough to indicate performance over the intended life of the device, allow identification of late adverse events
- Benchmarking against devices of same class, reported in registries
- End points suitable to the device type – death, pain scores
- Testing of individual component combinations, consistent with IFU
  - Is the clinical investigation data indicative of systems that will be used?
- Safety endpoints
High Risk Devices

Heart valve prostheses

- Surgical or percutaneous
- Mechanical or biological
- ISO 5840 – requirement for 400 valve years follow up for each valve type
  - Adjustment may be acceptable if the subject valve is a modification of a previously included device, but this needs to be rationalised
- Early (<30 days), mid (>30 days) and long term (1/2 yrs) reporting of Objective Performance Criteria
- Pre-clinical data – support intended use and anticipated in-vivo lifespan
- Anticoagulation
High Risk Devices

Supportive Devices – meshes, patches and tissue adhesives

• Apply to various indications and of varying origin, biological and non, permanent and absorbable
• Need to demonstrate mechanical, biocompatibility and physical characteristics support the intended purpose and anticipated lifespan *in-vivo*
• Minimum follow up – 24 months suggested
• Consideration of long-term complications – pain? Erosion?
• Benchmarking for revision data – registry if available
High Risk Devices

Implantable devices in the magnetic resonance environment

• AIMDs – dependent on an energy source
• PIMDs – include orthopaedic implants. Stents, valves, clips/ coils
• Need to consider all components of a system, where relevant
• MR safe vs MR Conditional vs MR unsafe
• When MR conditional, conditions need to be articulated in the submission, the IFU and supported by data
• For PIMDs, non-clinical data alone suffices e.g. displacement forces, torque, heating, artefacts
• For AIMDs:
  – Safety – hazards need to be assessed – force/ torque, vibration, device interaction, heating, cardiac stimulation
Errors / Shortcomings

- Absence of required components of the CER or referenced attachments/appendices
- Inconsistency between documents provided
  - IFU vs CER
    - Intended purpose
    - Risks
    - Adverse events
- Lack of support for the intended purpose in the data provided
- Unclear intended purpose
- Lack of information regarding regulatory history in other countries
- Where substantial equivalence is claimed:
  - Inappropriate selection
  - Inadequate discussion
Errors / Shortcomings

- >1 substantial equivalent claimed
  - Cherry picking?
- Insufficient data presented
  - Clinical Investigation/ literature/ post market
  - For device or Substantial equivalent
- Inadequate Literature Review
  - Methodology – documented?
  - Poor quality search protocol
  - Too many publications with some of dubious relevance
  - Identification of the device(s) referenced by each publication
  - Summary of each article
  - Cherry picking
Errors / Shortcomings

- Critical evaluation of clinical evidence lacking (literature review, clinical evaluations and post-market)
  - Relative strengths of data
  - Data for other device not demonstrated substantial equivalent
  - Outcome measures
  - Endorsement of clinical expert, pertaining to the differences
- Poor post-market data
- CER out of date, not signed, etc
- Unsuitable clinical expert or lack of information about the clinical expert