Australian Regulatory Landscape with the Therapeutic Goods Administration (TGA)

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Devices Clinical Evaluation Section

Objectives:

- Clinical evidence requirements for Orthopaedic medical devices -
  - Clinical evidence basics
  - Substantial equivalence
  - Types of clinical data and appraisal expectations
  - Key outcomes and demonstrating compliance with the Essential Principles

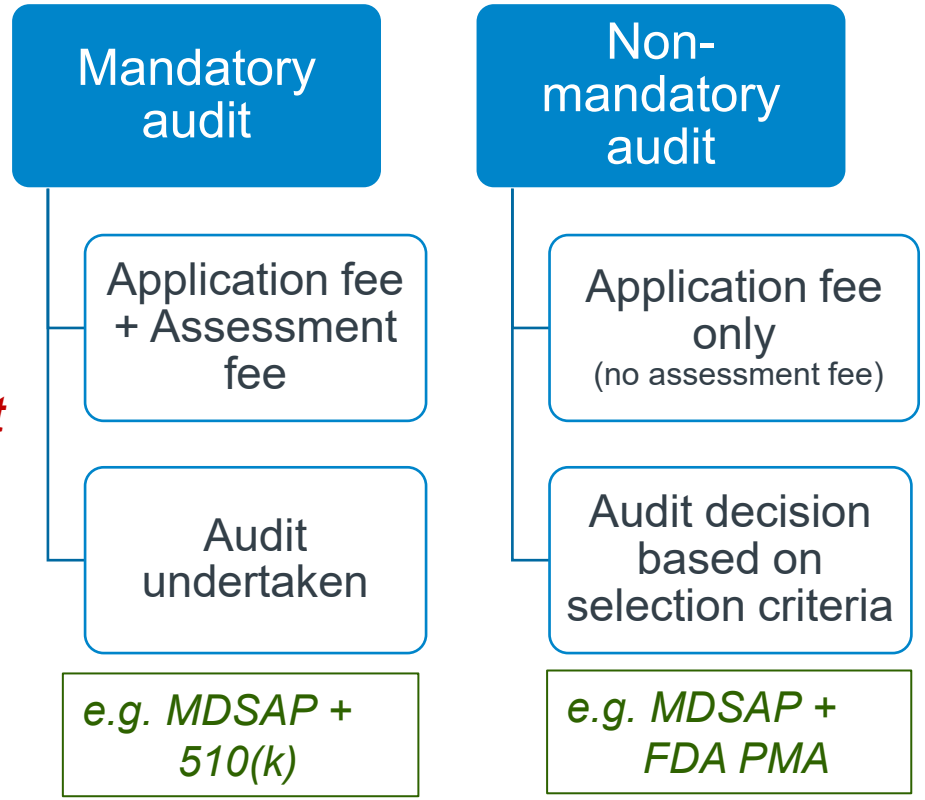
New application audit framework and guidance

Case management and **selection for non-mandatory audit**

- New guidance documents are currently open for comment **(until 17 February 2025)**

- Discuss proposed changes to **case management procedures**
  - ➢ *Procedures apply to both mandatory and non-mandatory audit*

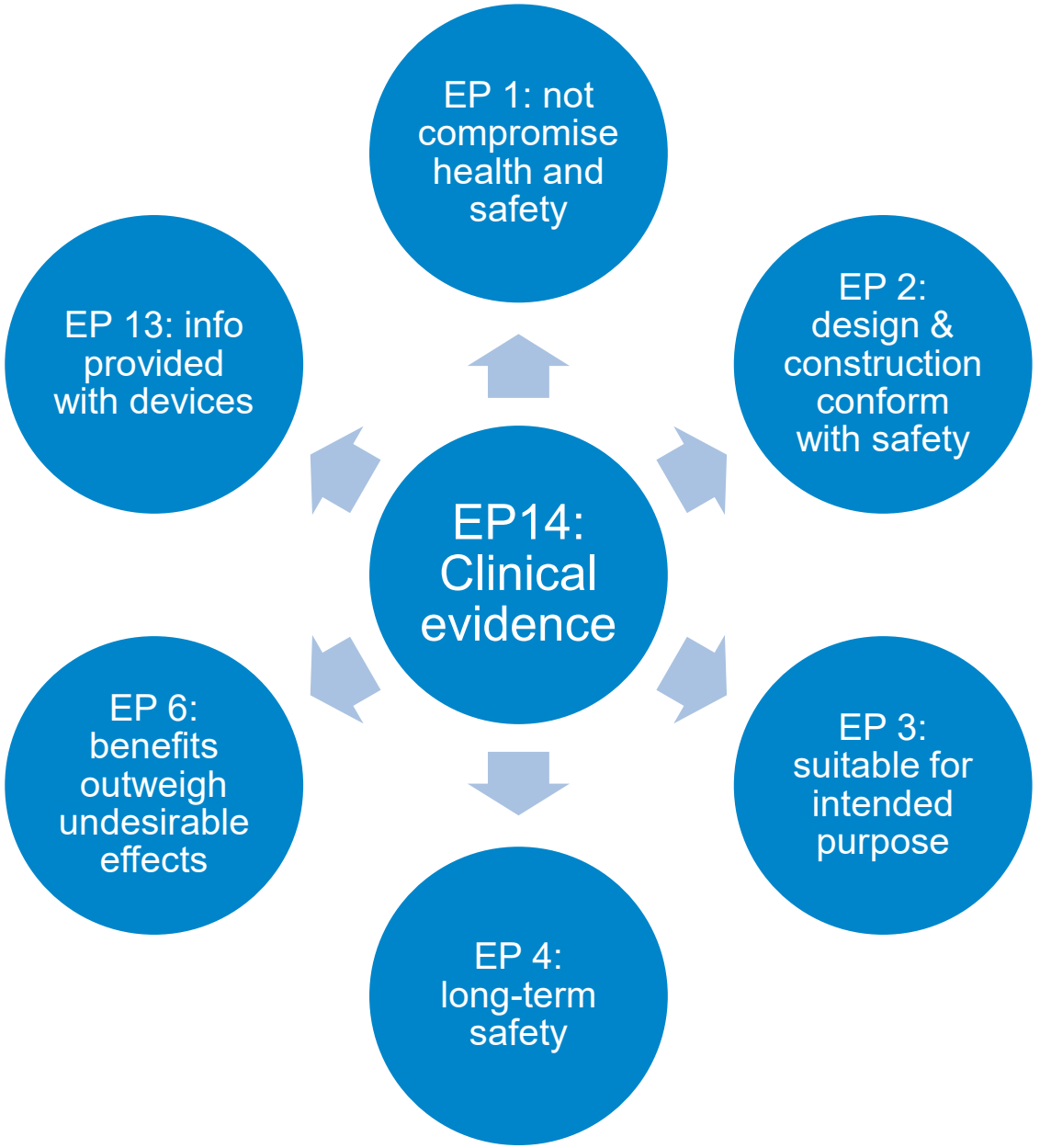
- Discuss proposed **selection criteria** for ***non-mandatory audit***
  - Criterion 1 – Aspects related to the application and the device
  - Criterion 2 – Regulatory reforms
  - Criterion 3 – Post market signals
  - Criterion 4 – Factors related to the sponsor or manufacturer



Clinical evidence requirements

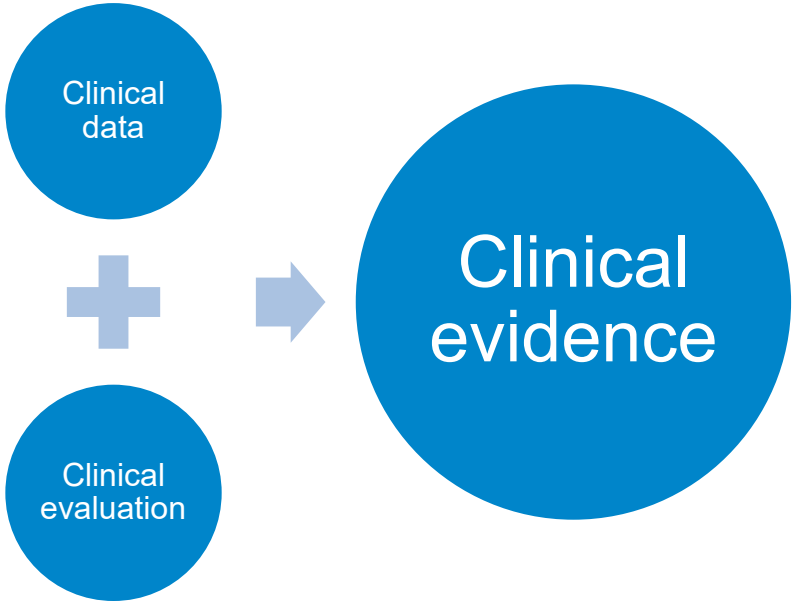
Essential Principle 14

"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".



Clinical evidence

- clinical data: safety/performance information generated from the use of a medical device in human subject(s)
- clinical evaluation: activities that use scientifically-sound methods for the assessment and analysis of the clinical data to verify safety and performance of a medical device when used as intended by the manufacturer



- Direct clinical evidence: from the device itself
- Indirect clinical evidence: generally, from a substantially equivalent device

Substantial equivalence

- Most similar to the device under evaluation, to such an extent that there would be no clinically significant difference in safety and performance.
- Claims of equivalence should include detailed (tabulated) comparison between:
  - Clinical characteristics
  - Technical characteristics (including pictures/diagrams from different angles, where possible)
  - Biological characteristics

  - All differences should be discussion from a clinical expert with a reasoning why each difference is not expected to adversely affect the safety and performance of the medical device.

- Comparable, but **not substantially equivalent technology**, may be used to help inform about the current state of the art and risk management, but is not generally sufficient to establish safety and performance of a higher-class medical device.

a) **Clinical** characteristics to consider for Orthopaedic implants

Including but not limited to:

- Intended purpose
- Indications for use
- Intended patient population
- Anatomic location (e.g. hip vs knee prostheses)
- Intended user (i.e. Orthopaedic surgeon)
- User environment (i.e. hospital)
- Expected implant lifetime

Acceptable justification for differences not adversely affecting safety/performance:

- intended purpose is **narrower** in the subject device
  e.g. subject device is only intended for primary hip arthroplasty,
  whereas the claimed substantially equivalent device is intended for primary and revision hip arthroplasty.

Difference that may be expected to adversely affect safety/performance

- Use in different anatomic location *e.g. hip vs knee prosthesis*

b) **Technical** characteristics to consider for Orthopaedic implants

Including but not limited to:

- **Design and geometry**
  – helpful to provide side-to-side pictures/diagrams from multiple angles to appreciate the differences
  (including orthopaedic implants as a system, and how the components are used together)
- Method of fixation (and how the device interact with the other system components)
- Dimensions (size variants)
- Materials and specifications (e.g. coating, coating thickness, porosity, rigidity, fatiguability, torsional strength, tensile strength and degradation characteristics)
- Surgical implantation including operating principles

Acceptable justification for differences not adversely affecting safety/performance:

- Size range is **narrower** in the subject device

Differences that may generally be expected to adversely affect safety/performance

- *Large differences (e.g. CR Vs PS knee; cemented Vs cementless fixation; modular Vs monoblock designs) or multiple additive differences*

For Orthopaedic implant systems, it is recommended that substantial equivalence of all characteristics be presented for **each component individually,** but discuss how they interact as a system

c) **Biological** characteristics to consider for Orthopaedic implants

Including but not limited to:

- Biocompatibility of materials in contact with body fluid/tissue
- Degradation profile
- Biological response (inflammatory, immune, tissue integration)

Types of clinical data

- **Manufacturer conducted clinical investigation(s)**
- **Literature review**
- **Post-market experience**
- **Real-world evidence**

Each source of clinical data should be critically appraised individually, and the clinical expert should draw reasonable conclusions on this basis.

Considerations should include but not be limited to:

- **Study design** and **level of clinical evidence**
- **Relevance** to the subject device for its intended purpose and target population
- **Sample size** – statistically powered to demonstrate non-inferiority to the current standard of care?
- **Comparator arm** – comparison of data obtained through different methods should be avoided
- **Follow-up** – can it demonstrate long-term safety?
- **Clinically relevant patient-centred outcome measures** or surrogate outcome measures?

Real World Evidence

Registry data: common clinical evidence strategy

- Useful source of data for medical devices that have been marketed

- Evaluation should consider:
  - Completeness of the specific registry and other limitations
  - ‘in-built’ contemporary comparator arm
    (e.g. similar technology for the same intended purpose/patient population)
  - Statistical analysis of outcomes
  - Follow-up

Key outcome measures:

- **Revision data** (time component and confidence in the outcome is considered important):
  - *E.g. cumulative percent revision (CPR) at x years (95%CI)*
    Kaplan-Meier survivorship estimate at x years (95%CI)

- **Standardised functional scores** including **Patient Reported Outcome Measures** (PROMs)
  - *E.g. Harris Hip Score (HHS)*
    Western Ontario and McMaster Osteoarthritis Index (WOMAC)
    Oxford Shoulder Score (OSS)
  - Should consider the Minimum Clinically Important Difference (MCID) for the chosen score.

Has the clinical evidence demonstrated that the device is suitable for the intended purpose?

EP 3 – Medical device to be suitable for the intended purpose

- Does the clinical evidence (e.g. Clinical trials, Scientific Literature, Post market experience) support use across the full range of the claimed intended purpose?

  E.g. primary and revision procedures, all intended patient populations.

Safety

EP 1 - Use of medical devices not to compromise health and safety

EP 4 – Long-term safety

- Require short- and long-term clinical evidence (minimum 2-years for pre-market approval) to demonstrate compliance with EPs 1 and 4, respectively.

- Generally, **revision rates** and **adverse events** from clinical evidence inform about safety. This requires critical appraisal from a clinical expert.

Have risks been adequately mitigated?

EP 2 – Design and construction of medical devices to conform with safety principles

- Expect manufacturers to hold detailed risk management reports (e.g. Failure Modes Effects Analysis; FMEA) that document:
  - Identification of hazards and associated risks for intended purpose and foreseeable misuse
  - Eliminate risks as far as possible
  - Place adequate protection measures, as appropriate
  - Inform users of residual risks

- This is a continual process throughout the lifecycle of the device.

Benefit-risk balance

EP 6 – Benefits of medical devices to outweigh any undesirable effects

- Benefit-risk balance should consider the current standard of care; at least non-inferiority should generally be established.
  - Incorporates both **performance** and **safety** outcomes

- Importance of robust, **comparative** clinical investigations with an appropriate control for class III devices (such as joint replacement medical devices).

Information For Use (IFU)

EP 13 – Information to be provided with medical devices

- Specific information must be included
  [as per EP13A.3(3) Therapeutic Goods (Medical Devices) Regulations 2002]

- For example:
  'Information about any risk arising because of other equipment likely to be present when the device is being used for its intended purpose (for example, electrical interference from electro-surgical devices or **magnetic field interference from magnetic resonance imaging devices**)'

  a similar item is required in the patient information leaflet [item 6, EP 13A.3(3)]

Patient Information Leaflet (PIL)

EP 13 A – Patient information about implantable medical devices or active implantable medical devices to be made available

- PILs should assist patients in:
  - Understanding the medical device being implanted, both prior to and following surgery;
  - Have informed conversations with their health professional; and
  - Report any adverse events associated with their implantable device.
- It should **not** be intended for advertorial or promotional purposes

- Contents must:
  - include specific items *[list in EP 13A.3(3) Therapeutic Goods (Medical Devices) Regulations 2002]*
  - be written in a way that is readily understood by patients
    [EP 13A.3(4) Therapeutic Goods (Medical Devices) Regulations 2002]

- Some Orthopaedic devices are exempt from PIL requirements
  (e.g. screw, wedge, plate, wire, pin, connector); but providing a PIL is still **encouraged**

Key points:

1. Clinical evidence is a key part of demonstrating compliance with many of the Essential Principles.

2. Acceptable substantial equivalence claims does not itself provide clinical evidence, but allows use of indirect clinical evidence.

3. Benefit-risk balance should consider the current standard of care.

4. Patient information leaflets (PILs) should assist patients to understand the medical device and not be promotional.

If you have any concerns about a specific device and TGA regulatory processes, please reach out us early to arrange a pre-submission meeting:
https://www.tga.gov.au/resources/resource/reference-material/pre-submission-meetings-tga-0

Useful resources:

- Clinical evidence guidelines for medical devices: https://www.tga.gov.au/resources/guidance/clinical-evidence-guidelines-medical-devices

- 2024 Medical device regulation changes: https://www.tga.gov.au/news/news/medical-device-regulation-changes

- Consultation on the audit framework for medical devices: https://consultations.tga.gov.au/medical-devices-and-product-quality-division/review-of-draft-guidance-documents-audit-framework/

- Providing patient information leaflets and implant cards for medical devices: https://www.tga.gov.au/resources/guidance/providing-patient-information-leaflets-and-implant-cards-medical-devices

Questions?

www.tga.gov.au

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration