Australian Government

Department of Health

Therapeutic Goods Administration

Clinical evidence guidelines for medical devices

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TGA Health Safety Regulation

Contents

About these guidelines

These guidelines provide details and guidance on the clinical evidence requirements for medical devices, including in vitro diagnostic medical devices (IVDs), under Australian legislation. For IVDs, there is also a supplementary document titled 'Clinical evidence guidelines supplement: In vitro diagnostic (IVD) medical devices', which should be reviewed in conjunction with these guidelines. The guidelines are intended to be a common reference point for both **industry** and **the regulator** – assisting sponsors and manufacturers to collect, compile and present clinical evidence in a manner that meets regulatory requirements, while reflecting the TGA's approach to how it assesses clinical evidence.

Although it is recognised that other approving regulatory bodies might be comparable, the evaluation strategies of manufacturers intending to market a medical device in Australia should be consistent with these guidelines.

These guidelines provide information on:

Legislative framework

This is the relevant Australian legislation for the regulation of medical devices particularly as it relates to the Essential Principles (EPs) and clinical evidence requirements to demonstrate compliance with the EPs.

The Essential Principles

The Essential Principles (EPs) are divided into 'General EPs' (EPs 1 through 6) and 'Specific EPs' (EPS 1 through 15). The Specific EPs include EP 14 which covers the requirement for clinical evidence, and the impact of clinical evidence on compliance with EPs.

Clinical evidence requirements

This section addresses key concepts and approaches for different device classifications and types, including different evidence strategies that can be used to demonstrate compliance with the EPs. Although manufacturers may make assertions about sufficiency of clinical evidence, the decision regarding sufficiency is taken by the TGA.

Sources of clinical data

Sources of clinical evidence, include clinical investigation studies (and a discussion of multiple study designs), literature reviews and clinical experience data (including post-market data). The TGA recognises a hierarchy of clinical evidence and will consider whether the level of the clinical evidence is commensurate with the risks and benefits posed by the device.

Clinical evaluation and the Clinical Evaluation Report (CER)

This section provides an explanation of the content and format requirements of the CER and supporting documents, including the role of critical analysis and expert opinion and a useful checklist.

Comparable devices including substantially equivalent devices

This section gives an explanation of the steps involved in demonstrating substantial equivalence and information on the applicability of clinical evidence from comparable devices.

Requirements for specific device types

This section provides information on the specific requirements for certain types of devices.

International activities and alignment

Australian regulatory processes are increasingly aligned with other international frameworks, subject to Australian legislative requirements and other limitations relevant to the Australian setting. For example, Australia takes part in the International Medical Device Regulators Forum

(IMDRF) which is a voluntary group of medical device regulators from around the world working towards international medical device regulatory harmonisation.

Consequently, some approaches taken by consensus groups such as the IMDRF and by regulators in other jurisdictions have been incorporated into these guidelines, particularly insofar as they relate to clinical evidence, with modifications as needed for the Australian setting. This process is ongoing. Where documentation or guidance from international settings is inconsistent with Australian legislative requirements, it is the Australian legislative requirements with which manufacturers and sponsors must comply. Approval by other regulators does not guarantee approval by the TGA. On subjective matters, the TGA may adopt a different view from other regulators.

Part 1 – General requirements

Legislative framework

The relevant Australian legislation for the regulation of medical devices is:

- *Therapeutic Goods Act 1989* (the Act), particularly Chapter 4
- *Therapeutic Goods (Medical Devices) Regulations 2002* (the MD Regulations).

Therapeutic Goods Act

The Act requires **ongoing compliance with the EPs** (which are detailed in the MD Regulations) **throughout the lifecycle of a medical device**. In brief, the Act:

- requires that medical devices comply with EPs about safety and performance characteristics (Part 4-1)
- provides for compliance with medical device standards to be one way to establish compliance with EPs, though it is not the only way (Part 4-2)
- requires that conformity assessment procedures (or requirements comparable to conformity assessment procedures) are applied to medical devices, and empowers the Secretary to issue TGA conformity assessment certificates (as a means of demonstrating the application of such procedures) having regard to compliance with the EPs, as relevant (Parts 4-2, 4-3 and 4-4)
- provides for TGA conformity assessment certificates to be subject to the condition that the manufacturer cooperate in any review to determine whether conformity assessment procedures having been applied, including those relating to the certification of compliance with EPs (section 41EJ(2)(b))
- provides for the Secretary to include kinds of medical devices in the Australian Register of Therapeutic Goods (ARTG), having regard to compliance with the EPs, as relevant (Part 4-5)
- provides that the inclusion of a kind of medical device in the ARTG, is subject to conditions that relate to ongoing compliance with the EPs. For example, at all times while a kind of device is included in the ARTG, the sponsor must have available sufficient information to substantiate compliance with the EPs or have procedures in place with the manufacturer to ensure that such information can be obtained from the manufacturer. The sponsor must give this information to the TGA if asked to do so (section 41FN(3)(a) and (c))
- empowers the Secretary, in a broad range of contexts, to seek information relating to compliance with the EPs (Part 4-8, section 41JA)

- Includes offence and civil penalty provisions regarding non-compliance with the EPs - importing, supplying, or exporting a medical device that does not comply with EPs without the consent of the Secretary (Part 4-11).

Note: While some medical devices are exempt (under the MD Regulations) from the requirement to be included in the ARTG, this does not mean that the device is exempt from the requirement to comply with the EPs (and to apply relevant conformity assessment procedures, or have comparable procedures applied, to the device: though see further below regarding regulation 3.11 which contains some limited exceptions in relation to the application of clinical evaluation procedures).

Medical Device Regulations

The Medical Device (MD) Regulations detail the EPs (and the conformity assessment procedures), and require clinical evidence and the application of clinical evaluation procedures:

- **Schedule 1** sets out the EPs. **EP 14** provides that every medical device **requires clinical evidence** demonstrating that the device complies with the applicable provisions of the EPs.
- **Schedule 3** sets out the conformity assessment procedures. In particular, **Part 8** of the Schedule sets out **clinical evaluation procedures** for manufacturers to obtain and evaluate clinical data (see further below regarding the clinical evaluation procedures).
- **Regulation 3.11** (subject to limited exceptions) provides that the clinical evaluation procedures, i.e., as set out in Part 8 of Schedule 3, **must also be applied to a device for the purpose of demonstrating that the device complies with the applicable EPs**, and in particular, EPs 1, 3 and 6.
- The limited exceptions, where the clinical evaluation procedures themselves are **not** required to be applied, relate to some devices exempt from inclusion in the ARTG (though not to custom-made medical devices) , and to devices subject to an approval for special or experimental uses or an authority under the authorised prescriber scheme (under sections 41 HB or 41HC, respectively). However, every medical device still requires clinical evidence demonstrating compliance with applicable Eps, even where there is no requirement to apply the clinical evaluation procedures.

Clinical evaluation procedures

The clinical evaluation procedures in Part 8 of Schedule 3 of the MD Regulations provide that the manufacturer **must obtain and evaluate clinical data** in relation to the device in the form of *clinical investigation data* or a *literature review*, or both (clause 8.3). See below for requirements relating to clinical investigation data and literature reviews.

The manufacturer must ensure that:

- the clinical data (whether it is clinical investigation data or a literature review) is **evaluated by competent clinical experts** (clause 8.6); and
- clinical evidence demonstrating that the device complies with the applicable provisions of the EPs is **documented in writing** (clause 8.6).

Clinical investigation data (clause 8.4) includes:

a) documentation in relation to the design, approval, conduct and results of each investigation carried out by the manufacturer in relation to the use of the device in or on a human body;

b) a record of qualitative or quantitative information obtained through observation, measurement, tests, or any other means used to assess the operation of the device; and

c) a written report by an expert in the relevant field, being a report that contains a critical evaluation of all the clinical investigation data held in relation to the device.

If clinical investigation data is collected in Australia, the investigation must have been conducted in accordance with the ethical standards set out in the relevant 'National Statement' relating to ethical conduct in human research published by the National Health and Medical Research Council (NHMRC), as in force from time to time (clause 8.4(4)).

If clinical investigation data is collected outside Australia, the investigation must have been conducted in accordance with the principles of the Declaration of Helsinki, as in force at the time and place where the investigation was conducted (clause 8.4(5)).

See Compliance with standards for further information regarding the relevant NHMRC ethical standards and the principles of the Declaration of Helsinki.

A **literature review** (clause 8.5) includes:

a) a compilation, prepared using a documented methodology, of published literature and unpublished scientific literature, both favourable and unfavourable, relating to medical devices of that kind, including the following:

   i. expert opinion;

   ii. information about the hazards and associated risks arising from the use of the device for its intended purpose, and the foreseeable misuse of the device;

   iii. information about the performance of devices of that kind, including a description of the techniques used to examine whether devices of that kind achieve their intended purpose; and

b) a written report by an expert in the relevant field, being a report that contains a critical evaluation of the compilation of literature mentioned in paragraph (a).

The Essential Principles

A medical device must comply with the Essential Principles (EPs) in the MD Regulations, which set out requirements relating to device safety and performance.

Summary of the Essential Principles

There are 6 general and 10 specific EPs.

General:

- Principle 1: Use not to compromise health and safety
- Principle 2: Design and construction to conform with safety principles
- Principle 3: Must perform the way the manufacturer intended
- Principle 4: Must be designed and manufactured for long-term safety
- Principle 5: Must not be adversely affected by transport or storage
- Principle 6: Benefits must outweigh any undesirable effects

Specific:

- Principle 7: Chemical, physical and biological properties
- Principle 8: Infection and microbial contamination
- Principle 9: Construction and environmental properties
- Principle 10: Principles for medical devices with a measuring function
- Principle 11: Protection against radiation
- Principle 12: Medical devices connected to or equipped with an energy source
- Principle 13: Information to be provided with a medical device
- Principle 13A: Patient implant cards and patient information leaflets
- Principle 14: Clinical evidence
- Principle 15: Principles applying to IVDs only

Demonstrating compliance with the Essential Principles

Compliance with the applicable EPs is required for all devices (whether included in the ARTG or exempt under the Regulations from inclusion). The intended purpose, risk profile, classification, and other specific features of a device will be relevant to the type of evidence required to substantiate compliance with the EPs.

EPs 1, 2, 3, 4, 6, 13, 13A and 14 are particularly relevant to meeting clinical evidence requirements. Essential Principle 14 is the overarching principle, and is addressed immediately below, followed by principles 1 through 4, 6, 13, and 13A.

Principle 14: Clinical evidence

EP 14 states that 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 EPs. In addition to other procedures, manufacturers must apply clinical evaluation procedures to the medical devices they supply (regulation 3.11 of the MD Regulations).

The way in which EP 14 is applied must take into consideration the recognised hierarchy of clinical evidence. Where evidence is not of the highest order, particularly for high-risk devices, robust justification should be provided.

These clinical evaluation procedures must be implemented in accordance with the requirements specified in Part 8 of Schedule 3 of the MD Regulations. Part 8 requires the manufacturer to:

- obtain clinical data, in the form of 'clinical investigation data' (clause 8.4) and/or 'literature review' (clause 8.5)
- ensure that the clinical data held in relation to the device is critically evaluated by competent clinical experts in the relevant field, and that the clinical evidence demonstrating that the device complies with the applicable provisions of the EPs is documented in writing (clause 8.6).

Regulation 3.11 of the MD Regulations, when addressing that clinical evaluation procedures must be applied (for the purpose of demonstrating compliance with the applicable EPs) focuses on demonstrating compliance, in particular, with EP 1, 3 and 6. In addition, all other EPs should also be considered because of their interaction with EP 14.

Thus, while it is expected that clinical evidence will primarily demonstrate that the device complies, in particular, with EPs 1, 3 and 6, manufacturers and sponsors should also consider other EPs as necessary. EPs 1, 2, 3, 4, 6 and 13 and 13A are addressed further in the guidelines below.

Evidence must be a true and complete account of available scientific knowledge and the sponsor and manufacturer must apply due diligence.

Principle 1: Use not to compromise health and safety

A medical device must be designed and produced in a way that does not compromise the clinical condition or safety of patients, the safety and health of users or, where applicable, other persons. Risks associated with the use of the device must be acceptable when weighed against the intended benefit to the patient, and compatible with a high level of protection of health and safety. Clinical evidence must be available to support this.

Key considerations from a clinical perspective include:

- The context of how the device is to be used. For example, whether it is to be used by specialist medical practitioners only, or by the general public. This is relevant to the safety assessment for many devices.
- How the device is used. For example, the type of treatment administered, or procedure or testing undertaken, and any inherent dangers that have implications for the safety of the device.
- Any inherent dangers in the proposed treatment setting should also be taken into account. The patient, user and any other person in the vicinity of the device may need to be considered.
- The number of patients exposed to the device and whether this sample is large enough to ensure that all health and safety issues have been described and quantified accurately.

Principle 2: Design and construction to conform with safety principles

The design and construction of a medical device must conform with safety principles, having regard to the generally acknowledged state of the art. This requires that any risks associated with the use of the device are identified and minimised.

Manufacturers are required to mitigate risk to the lowest possible level. Manufacturers must establish, implement, document and maintain a quality management system (QMS) to ensure the ongoing safety of a medical device. Risk management is a continuous process throughout the lifecycle of a medical device that requires regular updating.

Manufacturers should:

- establish and document a risk management plan for the device
- identify and analyse hazards and risks arising from the use or foreseeable misuse of the device – this includes ensuring that the clinical evidence is sufficient to reliably inform the nature and frequency of such hazards;
- ensure confidence in the quantification of hazards posing the highest level of risk through measurement in a sufficient sample size
- eliminate, reduce or control the identified risks - for example, by design considerations
- inform users of residual risks - for example, by warnings in the Instructions for Use (IFU)

- evaluate the impact of new information generated over the lifecycle of the device (for example, previously unrecognised hazards or changes to the state of the art) on risk acceptability and (if necessary) amend control measures accordingly
- document the risk management process - for example, by a risk management report and failure mode & effects analysis (FMEA).

The TGA will examine risk management documents and have regard to the current state of the art to determine whether:

- all risks and hazards have been identified in accordance with current knowledge
- the risks are eliminated or reduced as far as possible by the design and construction of the device
- any residual risks have been mitigated to the lowest possible level through the information provided with the device (labels, IFU, patient information leaflet, patient implant card) and other risk mitigation strategies.

Principle 3: Must perform the way the manufacturer intended

Medical devices must achieve the performance intended by their manufacturer and be designed and manufactured in such a way that, during intended conditions of use, they are suitable for their intended purpose. The intended purpose(s) is determined from:

- labelling
- instructions for use
- any advertising material relating to the device and/or technical documentation describing the mechanism of action of the device.

The TGA will examine and judge whether there is sufficient clinical evidence to demonstrate that the device performs as intended on a case-by-case basis. Whilst a manufacturer may make assertions about sufficiency, the TGA is the arbiter in determining sufficiency. Performance should be measured using validated mortality and morbidity measures.

Where multiple intended uses are claimed, each use should be separately substantiated by clinical evidence relevant to that use.

If the range of indications is broad and diverse, it may be reasonable to provide evidence of safety and performance for the higher risk and most common indications, with a justification as to why these were selected as ‘worst case scenarios’ and/or common indications and how these results can be extrapolated to other indications.

Principle 4: Must be designed and manufactured for long-term safety

A medical device must be designed and manufactured in a way that ensures its characteristics and performances (as mentioned in EP 1, 2 and 3) are not adversely affected if the device is used within the period in which it can be safely used (as indicated by the manufacturer), is not subjected to stresses outside of normal conditions of use, and is regularly maintained and calibrated (in accordance with the manufacturer’s instructions).

The characteristics in EP 1 and 2 relate to health and safety. In considering EP 4 in relation to health and safety, the design and production of the device must ensure these characteristics are not affected to such a degree that the health or safety of the patient, user or other persons are compromised (during the expected life of the device, when it is subjected to the stresses which can occur during normal conditions of use).

EP 3 focuses on the medical device performing as intended. In considering EP 4 in relation to performance, the TGA will have regard to the intended purpose of the device. The clinical evidence must demonstrate that the device, as designed and produced, performs as intended for the length of time appropriate to the intended purpose.

For some devices, it may be difficult to demonstrate performance and safety through clinical investigations for the intended permanent duration. In such cases, the duration of follow-up in clinical investigations should be a reasonable surrogate of the device's intended permanent duration. In many circumstances, this will require follow up data collection from an adequate number of patients to prove a suitable end point. Post-market data for the device may be used to *supplement* the clinical evidence on long term safety and performance, noting the well documented issues in post-market data such as under-reporting of adverse events.

The broad framework in the Act (see above) relating to compliance with the EPs provides for compliance to be a requirement that must be met throughout the lifecycle of devices. The importance of continuing to obtain clinical evidence, including in the post-market environment, is emphasised.

Principle 6: Benefits must outweigh any undesirable effects

The benefits to be gained from the use of a medical device for the performance intended by the manufacturer must outweigh any undesirable effects arising from its use. As noted above, under the Australian regulatory framework, medical devices must have clinical evidence that provides assurance of safety and performance.

Typically, where a state of the art (for established device types) or the current standard of care (for novel devices) exists, a randomised controlled trial will be expected to provide assurance of safety and performance. In practical terms, the level of assurance required will vary according to the risk of the device. Essentially, the greater the risk for the subject device relative to the state of the art/standard of care, the greater the benefit that needs to be demonstrated to ultimately demonstrate that the benefits outweigh any undesirable effects.

Where use of the device augments an existing treatment pathway, the additive risks should be considered and informed by an adequately powered study. The treatment pathways will vary in different geographies; the risks and benefits posed by the device should reflect the standard of care in Australia's health system.

It should be clearly stated if the proposed use of the device is in addition to or instead of the current standard of care when demonstrating that the benefits outweigh the risks of use, In doing so, consideration should be given to the type of trial that is required. Typically, where the device is proposed for use in addition to the standard of care, a superiority trial is necessary to demonstrate that any additive risks, however small, are balanced by a measurable benefit.

> **Example:** A device is proposed for treatment of non-healing wounds to improve oxygenation at the wound base. The device is applied to the wound via a spray and is intended to be used in conjunction with the existing standard of care such as dressings. It is claimed that, when used in conjunction with the existing standard of care, the device is superior to the standard of care only. There are some minor risks associated with the use of the device, as well as some risks that are difficult to quantify. The submitted clinical evidence did not demonstrate a statistically significant improvement in mean time to complete wound healing. As the device introduces some risks without clear benefits, the claim of superiority was not substantiated. The requirements of EP 6 were not satisfied.

For more general information on balancing considerations of benefit and risk refer to FDA, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications, 2016. Note that in the Australian context, the relevant assessment is made against the wording of EP 6.

In developing the device (and consistent with EP 2), all possible methods to minimise hazards identified in the risk assessment should have been incorporated into the device design and risk mitigation strategies. Users are to be informed of residual risks. Such risks will also be considered in the context the benefits of using the device. Manufacturers should be able to demonstrate that any residual risks are acceptable.

Clinical investigations should be appropriately designed to provide an assessment of the benefit-risk profile for the medical device when it is used for its intended purpose(s). A safety profile can be established via clinical investigations, literature reviews and clinical experience (from post-market data, adverse event data and special access use). It may also be appropriate, on occasion, to rely on data from comparable devices to support the safety of a device.

The ISO 14971:2019 standard is recommended as a guide when making benefit-risk determinations.

Principle 13 and 13A: Information to be provided with a medical device/Patient implant cards and patient information leaflets

Certain information must be provided with a medical device (or certain medical devices). This includes information about:

- the intended purpose of the device
- risks or undesirable side effects
- contraindications, warnings, restrictions or precautions
- installation, calibration and maintenance during its intended life
- instructions for use and other instructions.

The type of information required by EP 13 and 13A is critical to understanding and complying with EPs 1, 2, 3, 4 and 6.

A clear intended purpose is required. The TGA will determine the intended purpose of the device from documentation provided with or in relation to the device. Any claims/statements in relation to the performance and safety of the device provided on the labelling and/or packaging, instructions for use, patient or clinician cards, leaflets, manuals, brochures etc., must be consistent with each other and supported by the clinical evidence available for the device.

The patient groups for whom the device has a positive benefit-risk balance need to be well defined. This information should explain how to insert, implant or use the device safely. It must highlight any potential hazards, with appropriate contraindications, warnings or precautions. Requirements for handling or storage, and any risks associated with the disposal of the device should also be outlined. Other information provided with the device must also be consistent and supported by the evidence. This should be reflected in the wording of the information provided.

EP 13A provides for a patient implant card and patient information leaflet to be provided with certain medical devices. Patient information leaflets include very specific information about how to use the device safely, side effects and risks, and the expected device lifetime (along with information on intended purpose and performance).

The information provided with a medical device has an impact on the risks and therefore the safety of the device. Unclear or ambiguous terms or statements, poor grammar and spelling, foreign words or poor diagrams can all negatively impact on the ability of a patient or person to safely use the device as intended and therefore negatively affect the benefit-risk profile of the device.

Compliance with standards

Compliance with recognised standards published by an Australian or International Standards Agency may be used to support compliance with the relevant EPs, especially for devices based on technologies with well-established safety and performance characteristics. Compliance with such standards is not a legislative requirement, but it is a typical part of an evidence strategy (this can be contrasted with requirements to meet ethical standards or principles, which are requirements in the MD Regulations, see below). Where relevant standards are not met, explanation should be provided for why this has not occurred.

If a manufacturer chooses to use other standards or solutions (for example, an internal safety test), this must be consistent with the state of the art, and they must demonstrate the relevance and adequacy of this approach for supporting performance and safety requirements.

Compliance with one or more relevant standards does not equate to ongoing compliance with safety and performance requirements contained in the EPs. A broader process for continuous compliance is required that incorporates clinical evidence, a robust quality management system and appropriate risk management processes.

There are three main International Standards Organization (ISO) documents relevant to general clinical evidence requirements and ongoing compliance for medical devices:

- ISO 13485:2016 - Quality Management Systems (QMS)
- ISO 14971:2019 - Application of risk management to medical devices
- ISO 14155:2020 - Good Clinical Practice

ISO 13485:2016 Quality Management Systems

The primary objective of this standard is to facilitate harmonised medical device regulatory requirements for quality management systems (QMS), with an emphasis on meeting national regulatory requirements. The standard is based on the ISO 9000 family of standards that define, establish and maintain a quality assurance system for manufacturing and service industries.

Manufacturers are expected to continue to monitor the performance and safety of devices, including IVDs, via a surveillance program as part of their QMS once the device is marketed. These programs should be appropriate to the use and risks of the device. Data from safety and adverse event reports and complaints, newly identified risks, literature, any updated or new clinical investigations, significant regulatory actions and formal surveillance activities such as registries should be used to review the performance, safety and benefit-risk assessment of the device. This data should be evaluated and the CER updated in line with this new information.

The CER should be updated every 1-5 years depending on the novelty of the device and risk (as per MEDDEV 2.7/1 revision 4). As this information is incorporated into the ongoing risk analysis, it may result in changes to the IFU and other information supplied with the device.

Compliance with ISO 13485:2016 is not mandatory in Australia. However, under the Conformity Assessment Standards Order (Standard for Quality Management Systems and Quality Assurance Techniques) 2019, compliance with ISO 13485:2016 is considered to satisfy the QMS requirements specified in the legislation.

ISO 14155:2020 Good clinical practice

ISO 14155:2020 provides guidance on the design and conduct of clinical investigations involving medical devices. It can also be used by regulatory bodies and ethics committees when reviewing clinical investigational plans. Thirteen principles are included, such as adherence to ethical principles (as per the Declaration of Helsinki), subjects' rights, a determination that benefits outweigh risks and oversight by an independent ethics committee.

Clinical investigation data collected in Australia is subject to the ethical standards set out in the National Health and Medical Research Council's (NHMRC) National Statement of Ethical Conduct in Human Research (clause 8.4(4) of Part 8 of Schedule 3 of the MD Regulations). The investigation must have been conducted in accordance with these ethical standards, including that research needs to meet the requirements of ISO 14155:2020. For clinical investigation data collected outside of Australia, clause 8.4(5) states that:

> *If clinical investigation data is collected outside Australia, the investigation must have been conducted in accordance with the principles of the Declaration of Helsinki, as in force at the time and place where the investigation was conducted.*

The clinical evaluation procedures also refer to the obtaining of clinical data. The manufacturer must ensure that the clinical data obtained takes account of any standards that may apply to the device (clause 8.3(2) of Part 8 of Schedule 3 of the MD Regulations).

ISO 14971:2019 Application of risk management to medical devices

ISO 14971:2019 Application or risk management to medical devices specifies a process for a manufacturer to identify the hazards associated with medical devices, including IVDs, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls. It addresses assessing benefit, and benefit-risk determinations. The requirements of ISO 14971:2019 are applicable to all stages of the lifecycle of a medical device.

Standards applicable to specific medical devices

Examples of device types that have specific ISO standards outlining requirements for demonstrating clinical evidence are the current editions of the series of standards:

- ISO 11979-7:2018 - Ophthalmic implants - intraocular lenses
- ISO 5840-1:2021, ISO 5840-2:2021 and ISO 5840-3:2021 - Cardiovascular implants- cardiac valve prostheses
- ISO 14708:2020 - Implants for surgery - Active implantable medical devices
- ISO 14117:2019 - Electromagnetic compatibility test protocols for active implantable medical devices.

There is also a technical specification ISO/TS 10974:2018 titled 'Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device', which refers to non-clinical testing of AIMDs in an MR environment.

Clinical evidence requirements

Clinical evidence comprises clinical data and its evaluation pertaining to a medical device. It should provide the TGA with a current and accurate picture of both the state of scientific knowledge in relation to the treatment modality to which a device relates, and in relation to the subject device specifically. From this information, an acceptable benefit-risk profile may be demonstrated for a medical device, by showing that it performs as intended and that all identified undesirable effects and hazards, having been minimised during the design and development process, are outweighed by the benefits.

This section outlines the critical role of clinical evidence in establishing the safety and performance of a medical device, requirements regarding the submission of clinical evidence, and the expectations regarding the detail and extent of evidence required for different medical devices.

Key definitions and concepts

For the purpose of these guidelines, the terms below have the following meanings. In so far as is possible (and subject to the Australian regulatory framework) these terms align with the IMDRF document Clinical Evidence - Key Definitions and Concepts (IMDRF MDCE WG/N55 FINAL:2019).

Clinical investigation: Systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.

Note: 'Clinical trial' or 'clinical study' is synonymous with 'clinical investigation' and these terms are used interchangeably in this document.

Clinical data: Safety and/or performance information that is generated from the clinical use of a device.

Note: Under the clinical evaluation procedures in Part 8 of Schedule 3 of the MD Regulations, the manufacturer must obtain clinical data in relation to the device in the form of clinical investigation data, or a literature review, or both.

Clinical evaluation: A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety and/or performance of a medical device when used as intended by the manufacturer.

Note: The clinical evaluation procedures (in the MD Regulations) set out requirements in relation to the obtaining and evaluation of clinical data.

Clinical evidence: The clinical data and the clinical evaluation pertaining to a medical device.

Note: EP 14 provides that every medical device requires clinical evidence demonstrating that the device complies with applicable EPs.

Definitions of additional terms used throughout these guidelines are as follows:

Adverse event: Any untoward medical occurrence in patients/subjects, users or other persons. In the context of clinical investigation, for patients/subjects, this would include all untoward medical occurrences, whether or not related to the device that is the subject of the investigation that occurred in the course of the investigation. In the context of clinical experience, this would only include untoward medical occurrences that may be related to the medical device.

Clinical use: Use of a medical device in or on living human subjects.

Note: This includes use of a medical device that does not have direct patient contact.

Clinical Investigation Plan: Document that states the rationale, objectives, design and pre-specified analyses, methodology, monitoring, conduct and record-keeping of the clinical investigation.

Competent clinical expert: Generally expected to be someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting.

Note: The clinical evaluation procedures (in the MD Regulations) require the manufacturer to ensure that the clinical data is evaluated by competent clinical experts.

Critical analysis: The process of the careful and systematic examination, appraisal and evaluation of both favourable and unfavourable data.

Predicate: A previous iteration of the device, within the same lineage of devices, with the same intended purpose and from the same manufacturer, in relation to which a manufacturer may seek to demonstrate substantial equivalence.

Comparable device: A medical device with related function chosen by the manufacturer to inform the clinical evaluation of the device in question.

Note: A 'comparable device' is distinct from a 'comparator', which is the state of the art/standard of care against which a medical device may be compared (for example, in a clinical study).

Serious Adverse Event: An adverse event that led to a death or led to a serious deterioration in health (one that results in a life-threatening illness or injury; results in a permanent impairment of a body structure or body function; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; led to foetal distress, foetal death or a congenital abnormality/ birth defect).

Substantial equivalence: A finding that comparable devices are similar to such an extent that there would be no clinically significant difference in safety and performance, taking into account the intended purpose and clinical, technical and biological characteristics of the devices.

Why clinical evidence is required

All medical devices supplied in Australia must have clinical evidence sufficient to demonstrate an appropriate level of safety and performance when used for their intended purpose(s). This is to maintain the quality of the Australian healthcare system, and to help ensure the health of the Australian population. Clinical evidence is an important component of the technical documentation of a medical device which, along with other documentation (such as the device description, labelling, risk analysis and manufacturing information), is necessary for a manufacturer to demonstrate that the device complies with the EPs, including EP 14.

Who is responsible for providing clinical evidence

The manufacturer and sponsor must provide, or have available, clinical evidence to demonstrate compliance of the devices with the EPs, if requested. The obligation to collect and compile clinical evidence (typically in the form of a CER) lies with the manufacturer, who provides this to the sponsor. The sponsor must be able to provide information to the TGA to demonstrate such compliance. This applies to all medical devices regardless of classification.

For devices that are included in the ARTG, the legislation requires, pursuant to conditions specified in section 41FN of the Act, that:

- the sponsor must have available sufficient information to substantiate compliance with the EPs

  OR

- have procedures in place with the manufacturer that will allow them to obtain such information from the manufacturer.

Further, devices included in the ARTG are subject to the condition that the sponsor will, if asked by the Secretary (or Delegate), give such information to the TGA.

For a medical device to be supplied in Australia, it must be able to be demonstrated that the applicable EPs (as set out in Schedule 1 of the MD Regulations) be met to ensure the device is safe and performs as intended. The Act (under Part 4-11) provides for offence and civil penalty provisions for importing, supplying or exporting a medical device that does not comply with applicable EPs.

When to submit clinical evidence

Clinical evidence is required to be available throughout the lifecycle of a device, though is typically submitted to the TGA at the time of application for a conformity assessment certificate or application for inclusion in the ARTG, and as part of post-market surveillance or reviews. It should be evaluated and updated periodically as new information on safety and performance is obtained from clinical studies, literature or clinical experience in relation to the subject device and/or comparable devices.

The TGA may request and review this clinical evidence at any time. The clinical evidence requirements described in these guidelines apply in each of these circumstances.

Requirements for different device classifications

Medical devices are classified according to their level of risk:

- Medical devices are classified under Schedule 2 of the MD Regulations from lowest to highest risk into Classes I (which includes Im, being devices with a measuring function, and

Is, being devices supplied in a sterile state), IIa, IIb, III and Active Implantable Medical Devices (AIMDs). Refer to Medical devices overview for more information.

- IVDs are classified under Schedule 2A of the MD Regulations from lowest to highest risk Classes 1 to 4. Refer to Classification of IVD medical devices for more information.

Some EPs do not apply to certain classes of devices in certain circumstances (for example, EP 13.4(2) in relation to when instructions for use need to be provided). Further, the EPs may impose requirements subject to whether or not the device has a measuring function or whether the device is intended to be supplied in a sterile state, a non-sterile state, or both. Clinical evidence requirements must be met for applicable provisions of the EPs (noting many aspects of the EPs are applicable to all medical devices).

Greater scrutiny will be given by the TGA to higher classification devices as part of ensuring safety and performance. Further, the classification, design and use of the device are relevant factors when considering the nature, type and range of evidence appropriate to being able to demonstrate compliance with applicable provisions of the EPs. EP 14 itself notes that 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 EPs.

Direct and indirect evidence

The TGA recognises the following types of clinical evidence for the purpose of substantiating compliance with the EPs:

- **Direct clinical evidence** - this is derived from an evaluation of clinical data pertaining to the subject device.
- **Indirect clinical evidence** - this is derived from an evaluation of clinical data pertaining to a comparable device with which **substantial equivalence** has been demonstrated.

Evidence from comparable devices that are not substantially equivalent may support or supplement direct or indirect clinical evidence. However, it will not generally constitute sufficient clinical evidence for substantiating compliance with the EPs (except for certain low risk, well established technologies).

When there is no or limited clinical data

In some instances, it may be difficult to collect direct clinical data for a device due to very small numbers of eligible patients, high risk procedures limiting use, or practical or ethical considerations that limit the feasibility of conducting a high quality clinical investigation. If there is no (or limited) clinical data for the specific device, depending upon the nature of the device, you may be able to provide a clinical justification for why clinical evidence is either not required or only partially required.

Evidence strategies for different device types

Evidence strategies refer to the mix of clinical evidence sources (see below regarding Sources of clinical data) that are used, together with critical analysis and expert opinion, to demonstrate compliance with the EPs. The following points should be noted:

- Evidence strategies will be scrutinised more for higher risk devices and for those with greater novelty, with greater expectations around direct evidence and/or high-quality clinical investigation data.
- The clinical evidence must distinguish the safety and efficacy of the device from that of the procedure itself. The clinical merits of established procedures are not under assessment by the TGA.

- Where a novel device necessitates the introduction of an invasive procedure and/or modification of an established treatment algorithm, the clinical evidence must consider the safety of the procedure or the modification in the overall risk/benefit balance.
- New components within established device systems should consider the safety and performance of the device system. However, new clinical investigation data involving the use of the new component may not be required. Instead, conformance with the relevant standards, together with a reasoned clinical argument regarding why this new component would not adversely affect safety and performance, may be sufficient.

As stated by IMDRF, a number of factors are relevant when considering the type of evidence required to substantiate compliance with regulatory requirements:

> *Clinical evaluation of medical devices that are based on existing, established technologies and intended for an established use of the technology is most likely to rely on compliance with recognised standards and/or literature review and/or clinical experience of comparable devices.* ***High risk devices, those based on technologies where there is little or no experience, and those that extend the intended purpose of an existing technology (i.e. a new clinical use) are most likely to require clinical investigation data.*** *The manufacturer will need to give consideration to the advantages and limitations of each data type.*

Possible sources of clinical data that form the basis of the clinical evidence pertaining to device safety and performance are discussed below.

Sources of clinical data

Clinical data (meaning safety and performance information that is generated from the clinical use of a medical device) may be generated for either the subject device or a comparable device (including substantially equivalent devices). It includes:

- data from clinical investigations (synonymous with trials and/or studies)
- literature reviews
- post-market data
- other clinical experience data (also known as Real World Data).

The manufacturer is responsible for identifying relevant data and determining the extent of data needed for a complete clinical evaluation (as per IMDRF MDCE WG/N56FINAL:2019 Clinical Evaluation section 6).

The following section provides further guidance on the sources of clinical data and how they may be used to demonstrate compliance with the EPs to establish the safety and performance of the medical device for its intended purpose(s). As appropriate, the guidance is aligned with the publicly available IMDRF and related MEDDEV documents (in particular, MEDDEV 2.7/1 Revision 4).

Clinical investigations

A clinical investigation is any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance and/or effectiveness of a medical device. Clinical investigation data is further explained in clause 8.4 of Part 8 of Schedule 3 of the MD Regulations. Clinical investigations are further discussed in the IMDRF MDCE WG/N57FINAL:2019 Clinical Investigation document.

Clinical investigations include feasibility studies, studies conducted for the purpose of gaining market approval, and those conducted following market approval (see IMDRF MDCE

WG/N55FINAL:2019 Clinical Evidence – Key Definitions and Concepts). Clinical investigation data sourced directly from the device produces a higher level of confidence in its relevance and capacity to inform the safety and performance characteristics of the device and is the preferred option for fulfilling clinical evidence requirements.

It should be clearly indicated if the subject device has been modified since the clinical data were gathered, to clarify the device version and the nature of the changes.

In some circumstances direct clinical investigation data are not available for the subject device or are insufficient in quantity or quality. In this situation clinical investigation data from a comparable device may be used to support the safety and performance of the device under assessment (the subject device). The approach taken to determine if a comparable device is substantially equivalent, and hence can be used as a source of indirect evidence, is described in Comparable devices including substantially equivalent devices.

As per MEDDEV 2.7/1 revision 4, June 2016 p35-35, the manufacturer should perform a detailed gap analysis to decide if additional clinical investigations need to be carried out:

The gap analysis should determine whether the existing data are sufficient to verify that the device is in conformity with all the Essential Requirements (equivalent, but not identical to, the EPs) *pertaining to clinical performance and clinical safety.*

Special attention should be given to aspects such as:

- *new design features, including new materials*
- *new intended purposes, including new medical indications, new target populations (age, gender, etc.)*
- *new claims the manufacturer intends to use*
- *new types of users (e.g. lay persons)*
- *seriousness of direct and/or indirect risks*
- *contact with mucosal membranes or invasiveness*
- *increasing duration of use or numbers of re-applications*
- *incorporation of medicinal substances*
- *use of animal tissues (other than in contact with intact skin)*
- *issues raised when medical alternatives with lower risks or more extensive benefits to patients are available or have become newly available*
- *issues raised when new risks are recognised (including due to progress in medicine, science and technology)*
- *whether the data of concern are amenable to evaluation through a clinical investigation.*

Data on the safety and performance of other devices and alternative therapies, including benchmark devices and equivalent devices, should be used to define the state of the art or identify hazards due to substances and technologies. This will allow the clinical data requirements to be established more precisely in relation to the intended purpose of a device. Precision in this analysis and the choice of selected medical indications and target populations may reduce the amount of clinical data needed from additional clinical investigations.

Note: the EU term 'equivalence' is very similar to the Australian term 'substantial equivalence' (in the case of high risk devices, the EU term is considered stricter) and is discussed in the EU

document MDCG 2020-5 Clinical Evaluation – Equivalence. See also these guidelines' chapter on Comparable devices including substantially equivalent devices.

Conducting clinical investigations

A properly conducted clinical investigation will comply with both the clinical investigation plan and the laws and requirements in the location it is conducted in, along with any additional requirements imposed by Australian legislation, to ensure the protection of human subjects and the integrity of the data. Clinical investigations may be undertaken in Australia or outside of Australia:

- When clinical investigation data is collected in Australia, the investigation must comply with the NHMRC National Statement of Ethical Conduct in Human Research (clause 8.4(4) of Part 8 of Schedule 3 of the MD Regulations). The NHMRC National Statement refers to further requirements that research needs to meet. As updated, these include the requirements of the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice and ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good clinical practice. Trials should comply with the requirements in both of these documents.
- When clinical investigation data is collected outside Australia, the investigation must comply with the principles of the Declaration of Helsinki (clause 8.4(5) of Part 8 of Schedule 3 of the MD Regulations). The Declaration refers to the need to take into account applicable international laws and standards. Trials should also comply with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice and ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good clinical practice.

The clinical investigation report should note if the clinical investigation was carried out in accordance with the relevant standards or principles (and name the regulatory authority or ethics committee(s) giving approval). Clinical investigations not conducted in accordance with the applicable ethical standards or principles (as required by clauses 8.5(4) and (5)) should not be relied upon by the manufacturer or sponsor and the reasons for this noted in the Clinical Evaluation Report (CER).

Clinical trials should be registered in line with Declaration of Helsinki and World Health Organisation recommendations. Since 1 July 2005, the International Committee of Medical Journal Editors (ICMJE) has required (and recommended that all medical journal editors require) registration of clinical trials in a public trials registry at or before the time of first patient enrolment as a condition of consideration for publication. For more information refer to ICMJE clinical trial registration requirements.

Registries include clinicaltrials.gov or any registry participating in the WHO International Clinical Trials Registry Platform, such as the Australian New Zealand Clinical Trials Registry (ANZCTR).

Clinical trials can be conducted within Australia under either the Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) schemes for devices not currently included in the ARTG, or to extend the intended purpose of a medical device beyond the current market approval.

Reporting standards for clinical investigations

International guidance on reporting standards for clinical trials can be found in ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice. Annex D of this ISO provides useful information on what should go into a clinical trial report.

In addition to high-level guidance on how to structure a full clinical trial report, the reporting requirements for specific trial designs are also included, as outlined below.

The following checklists are intended to inform reporting standards for peer-reviewed publications and should be viewed as **minimum requirements only** for full clinical trial reports.

Reporting standards for randomised controlled trials

The Consolidated Standards of Reporting Trials (CONSORT) statement provides an evidence-based set of minimum guidelines for reporting parallel group randomised-controlled trials. The statement provides a 25-item checklist and flow diagram displaying the progress of all participants through randomised clinical trials. The focus is on transparent reporting of how the trial was designed, analysed and interpreted.

Reporting standards for observational studies

The Strengthening the Reporting of Observational studies in epidemiology (STROBE) statement is used for reporting observational studies, including case series and surveys. The statement provides a 22-item checklist for reporting criteria, and the use of a flow diagram is suggested but no official format is given. The STROBE statement provides guidance on how to report observational research well and is endorsed by leading journals.

Reporting standards for diagnostic accuracy studies

The Standards for the Reporting of Diagnostic accuracy studies (STARD) statement is used for the reporting of *in vivo* diagnostic accuracy studies. The statement provides a 25-item checklist and flow diagram describing the design of the study and the flow of patients through the study. The focus of the statement is on identifying the quality of reporting.

Reporting standards for systematic literature reviews

Guidelines for reporting systematic literature reviews are outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. It is recommended that the PRISMA be followed closely when compiling a literature review as part of a submission for pre- and post-market reviews. The statement includes a 27-item checklist and flow diagram describing the study selection process in systematic literature reviews. Guidelines for Meta-analysis of Observational studies in Epidemiology (MOOSE) may also be used for meta-analyses of observational studies.

Literature review

Conducting a literature review is useful for identifying clinical data that is not in in the possession of the manufacturer. A literature review may be presented in addition to clinical investigation data described above, or on its own. Studies identified in a literature review that do not pertain directly to the subject device or a substantially equivalent device may be used to present the state of the art and inform risk management. If such studies are being relied on to help meet clinical evidence requirements, a reasoned justification is necessary as to why any data obtained for another device may be used to support the safety and performance of the subject device (see chapter on Comparable devices including substantially equivalent devices).

A literature review in relation to a medical device includes a compilation, prepared using a documented methodology, of published and unpublished scientific literature, both favourable and unfavourable, relating to the medical device (Part 8 of Schedule 3 of the MD Regulations (clause 8.5)). This includes expert opinion, information about the hazards and associated risks arising from the use of the device for its intended purpose and the foreseeable misuse of the device, and information about the performance of the device, including a description of the techniques used to examine whether the device achieves its intended purpose. A written report

must be prepared by an expert in the relevant field containing a critical evaluation of the compilation of literature.

The manufacturer of the medical device must ensure that the clinical data is evaluated by a competent clinical expert and that clinical evidence demonstrating that the device complies with the applicable provisions of the EPs is documented in writing (clause 8.6).

In brief, therefore, a literature review involves the systematic identification, synthesis and analysis of the literature on the device or device type (culminating in a written report by an expert). The highest standard of literature review is a systematic review with meta-analysis. In all cases, it is critical that the methods used to conduct the literature review are transparent and reproducible in order for the clinical assessor to evaluate objectivity (lack of bias) and quality.

A literature review should consist of the following components.

Search protocol

Prior to conducting a literature review, a protocol should be developed to identify, select and collate relevant literature. The protocol should include the search aim(s) and outline the population, intervention, comparator(s) and outcome(s) (PICO) criteria for the review. A record must be kept of databases searched with justification, search terms used (including key words and MeSH headings), date searched, period covered by the search, search limits applied (including language, study design, etc.) and inclusion and exclusion criteria. This must contain enough detail for a clinical assessor to reproduce the search. The search protocol should describe the method used to extract data from included studies and any processes for confirming data extracted by investigators.

Selection strategy

The selection criteria applied to the resulting list of studies should be defined in enough detail to enable the clinical assessor to understand how the list of studies included in the review was compiled. When selecting papers, the study design, quality of the data reported, quality of analysis and the clinical significance of the results should be considered. Any weighting criteria applied to the included studies should be detailed. Variables for data extraction should be listed and defined.

A flow diagram should detail each step in the screening process, including total numbers of studies screened, assessed for eligibility and included in the review. Objective, non-biased, systematic search and review methods should be used such as PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) or Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines in accordance with the section Reporting standards for clinical trials. The report should also summarise how each citation did or did not fit the selection criteria for inclusion in the review. This may be presented as an appendix of excluded studies with justification for the decision.

Review and critical analysis

It is preferred that the study characteristics and results of individual studies are summarised in tabular format. This should include, for all outcomes considered (including safety and performance measures), an effect size estimate and confidence interval for each study. Where relevant, the range found across all studies for outcomes (e.g. adverse event rates for different types of adverse events) should be presented. Then critical analysis of the literature should be undertaken. This is not a simple summary of the individual study results, but a critique and discussion of the study method, results and outcomes and how these apply to the device when used for its intended purpose.

Literature report

A report must be provided, analysed and endorsed (evidenced by signature and date) by a competent clinical expert, containing a critical appraisal of this compilation, as per the legislative requirements. Reviews should be prepared by researchers skilled in systematic review methods in conjunction with a clinical expert. Where the review relies in part or wholly on literature for a substantially equivalent or comparable device, the report should also clearly justify how the device described in the compiled literature is relevant to the safety and performance of the subject device. It is important that the published literature be able to establish the clinical performance and safety of the device and demonstrate a favourable risk profile.

For further guidance on performing a literature review see MEDDEV 2.7/1 revision 4 (section 9 and appendices 5 and 6).

Post-Market Data

Post-market data should be provided for pre-market and post-market TGA assessments and reviews. Post-market data may be collected by manufacturers, sponsors, regulatory agencies or others. All post-market data available to the sponsor should be reported. Examples include:

- The number of units sold (or unit demand) worldwide since launch stratified by year and by country (particularly if numbers are small) or geographic region. Note: this may not always be appropriate for high use devices, those with several components or those on the market for many years.
- The number and types of complaints to the manufacturer regarding the device, both as reported and as confirmed on analysis and, in the case of new devices, stratified by year of occurrence of complaint.
- The total number of adverse events (including serious adverse events) and vigilance data reported to regulatory agencies, both as reported and as confirmed on analysis and categorised by type (e.g. device malfunction, use error, inadequate design or manufacture) and clinical outcome (e.g. death, amputation, surgical procedure required, no harm to patient). These should be stratified by year of supply and/or year of occurrence of event.
- Any regulatory actions such as voluntary or mandatory recalls, including recalls for product correction, removals, suspensions, withdrawals or other corrective actions occurring in the market for IFU changes or other reasons and cancellations of the device anywhere in the world, or any other corrective and preventive actions (CAPAs).
- Any data from Post-Market Clinical Follow-up (PMCF) studies, including interim and final reports, and where relevant, interim datasets.

The manufacturers should clearly indicate whether the data reported is for the device or a comparable device. The data should be compiled into a complaints, adverse events, and vigilance report(s) that will allow the clinical assessor to better evaluate the benefit-risk profile of the device. The CER should include an analysis and commentary on the profile, severity and frequency (rate) of events reported. Adverse event and complaint data and rates should be discussed and critiqued to enable an understanding of the safety profile of the device in a 'real-world' setting. As the time since first approval worldwide lengthens, the relevance of post-market data for comparable device(s) diminishes and should be replaced by data for the device itself.

Post-market data can support the substantiation of the safety and performance claims of the device, and guide risk identification, assessment and mitigation. It is useful for identifying less common but serious device-related adverse events and it provides valuable long-term information about the safety and performance of a device. Post-market data is particularly important where there may be a paucity of clinical data from other sources, or when data from

other sources is not sufficiently robust to establish a favourable benefit-risk profile for the device.

When updated post-market data is provided to the TGA for any regulatory purpose, any new regulatory actions and any new serious adverse events should be identified and described.

Adverse events and complaints

Adverse events are required to be reported to the governing bodies of the countries in which the device is used when the event leads to or may lead to death or serious injury. Adverse events and complaints data are available in the manufacturer's own internal complaint handling log and in publicly available databases such as the FDA's Manufacturer and User Facility Device Experience (MAUDE) database or TGA Incident Reporting and Investigation Scheme (IRIS).

One of the serious limitations of post-market adverse event and complaint reports is under-reporting by end-users. This limitation should be considered in any post-market analysis. More information on reporting adverse events (and complaints) can be found on the Database of Adverse Event Notifications - medical devices page on the TGA website. Serious adverse events should be subject to particular scrutiny as part of post-market surveillance and reporting.

Post-market regulatory actions

Information about recall actions and suspension or cancellation of marketing approval (in any jurisdiction) is also valuable. Recall actions generally take place to resolve a problem with a device for which there are deficiencies or other issues concerning safety, quality or performance. There are generally two key types of recall action (a) correction, which may involve temporary removal from use for example, for changes to the IFU, and (b) permanent removal of deficient, defective or unsafe medical devices from use. In the case of implanted devices, hazard alerts may apply. The full range of recall actions are described in the TGA's Uniform recall procedure for therapeutic goods (URPTG). More information about recall actions can be found on the System for Australian Recall Actions (SARA) page on the TGA website.

The occurrence of and reasons for suspensions, removals, withdrawals, cancellations or other corrective actions in any jurisdiction, should be reported.

Post-Market Clinical Follow-up (PMCF) studies

A PMCF study is a study carried out following marketing authorisation intended to answer specific questions (uncertainties) relating to safety, clinical performance and/or effectiveness of a device when used in accordance with its labelling. Data obtained from PMCF studies are a subset of post-market data. PMCF studies can be used to collect additional clinical data to address the remaining uncertainties about the potential benefits and residual risks of the device.

Further guidance on PMCF studies can be obtained from the IMDRF document titled Post-Market Clinical Follow-Up Studies, which examines:

- circumstances where a PMCF study may be indicated
- elements of a PMCF study including objectives, design and implementation
- use of information from PMCF studies.

When PMCF studies are planned as part of a risk management strategy, including as part of pre-market applications, then a Clinical Investigation Plan should be provided. PMCF studies conducted post approval in other jurisdictions may also be used as clinical investigation studies for pre-market applications in Australia.

Other clinical experience data

Clinical experience data encompasses data generated through any clinical use of the device that is not related to clinical investigation. This may include post-market surveillance reports, sales and complaints data, vigilance reports and clinically relevant field corrective safety actions (all part of post-market data, above), and other sources of clinical experience data.

Other sources of clinical experience data are often referred to as Real World Data (RWD) and may come from the following sources:

- Electronic Health Records (EHRs)
- claims and billing activities
- product and disease registries
- patient-generated data including in home-use settings
- data gathered from other sources that can inform on health status, such as mobile devices.

Real-world evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

The FDA document titled Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices provides further guidance. In some situations, RWD may be of sufficient quality to help inform the benefit-risk profile of devices at various points in their lifecycle and hence inform regulatory decisions.

Clinical experience data may be relevant and useful regardless of whether it is used as direct or indirect clinical evidence to demonstrate compliance with the EPs. However, as the time since first approval worldwide lengthens, the importance of direct device data increases.

Device registries

Device registries are systematic collections of data of medical outcomes following use of medical devices. They play a unique and important role in medical device surveillance. These can provide additional detailed information about patients, procedures, and devices not routinely collected by other means. Registries can provide valuable information on device performance in terms of functional outcomes and quality of life of patients. Registries using multiple device types may provide a suitable in-built comparator, such as the average of a particular performance and/or safety marker across the device category (for example, joint registries may provide average revision rates across different types of joint prosthesis). In other instances (for example, single device registries), comparators derived from the literature will be required. Use of registries should take appropriate account of data limitations, variation across registries with respect to data structure and analysis and populations covered. Examples of Australian device registries include the Australian Breast Device Registry, the Australian National Orthopaedic Association National Joint Replacement Registry (AOANJRR) and the Victorian Cardiac Outcomes Registry.

Regulatory approval in other jurisdictions

If the device is approved for use in another jurisdiction the manufacturer should provide regulatory status, including the certificate number, date of issue and name under which the device is marketed. The exact wording of the intended purpose and any specific conditions in other jurisdictions should be provided. For example, if magnetic resonance imaging (MRI) designation in other jurisdictions is provided, this will improve the efficiency of the assessment. The sponsor should specify whether the approval process included a clinical assessment, and may wish to provide copies of clinical assessments and other relevant documents.

Clinical evaluation

The IMDRF document IMDRF MDCE WG/N56FINAL:2019 *Clinical Evaluation* is an international consensus document on clinical evaluation. Clinical evaluation is a set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety and clinical performance of the device when used as intended by the manufacturer. The clinical evaluation should enable conclusions to be drawn on the balance of risks and benefits of the device.

The three steps in clinical evaluation are (i) data identification, (ii) appraisal, and (iii) analysis. The first step - identification of relevant clinical data – is described in the previous section. The next step is appraisal of each data set to determine the limitations and merits of the clinical data in terms of relevance, clinical significance and quality. The final step is to analyse the data to draw a conclusion on the balance of benefits and risks. This section covers steps (ii) and (iii).

- Clinical evaluation is an ongoing process conducted throughout the lifecycle of a medical device. Manufacturers must periodically review the performance, safety and benefit-risk profile of the device and update the clinical evidence accordingly.
- Over the lifecycle of the device the clinical evaluation will change. For instance, when the device has been on the market for a number of years, the relevance of comparable device data is less significant, and direct clinical experience data is likely to be of greater relevance.

Appraisal of the clinical data

The clinical data should be appraised to elucidate its merits and limitations. Appraisal involves:

- assessing each piece of data to determine its quality, its relevance to the subject device or comparable device and its clinical significance, considering the target population and intended purpose
- determining the contribution of each dataset to the overall performance and safety profile of the subject device, considering the data generation/collection methods and potential sources of confounding or bias that may influence results.

Assessment of evidence quality should consider study type, size and design, and also comparability (to standard of care or alternative treatments). The quality and relevance of clinical evidence provided is a significant consideration in determining whether the requirements of the EPs have been met. The following should be noted:

- Although there is no rule regarding study size, those involving a sample size that is not statistically-powered will generally be considered poor quality evidence.
- Where possible, studies should be statistically-powered to demonstrate non-inferiority against the established standard of care.
- Single arm studies (and other study designs) with no comparator arm are generally considered inadequate evidence.
- Comparisons of datasets obtained through different methodologies (for example, a case series using the subject device with standard of care outcomes established from a literature search) are generally considered poor quality evidence and may be subject to greater scrutiny, as necessary, when assessing whether that data supports compliance with the EPs.

- Clinical safety and performance should generally be expressed in terms of person-centred outcomes, such as mortality, morbidity, adverse events, and patient reported outcome measures (PROMs).
- Where study findings are expressed in terms of markers or intermediate measures of safety and performance, a clinically reasoned argument should be provided linking the study findings with patient centred outcomes.

Refer also to the matters raised below in relation to MEDDEV 2.7/1 Rev 4 appendix 6, Appraisal of clinical data.

Studies conducted by manufacturers or sponsors, or those who have received funding or support from manufacturers or sponsors, will be considered on their merits. Peer reviewed articles should clearly identify any conflicts of interest (actual or perceived). It is accepted that certain studies require support from manufacturers (such as large-scale pre-market approval studies) or will be conducted by manufacturers (such as PMCF studies). A discussion of the extent of involvement of manufacturers or sponsors should form part of the study report and the critical analysis contained in the CER.

An important part of the clinical evaluation is determining the overall strength of the evidence presented. A widely accepted tool for ranking different types of study design is the National Health and Medical Research Council's (NHMRC) levels of evidence. The levels of evidence rank different study designs into a hierarchy according to their potential to adequately answer a particular research question (e.g. diagnostic, intervention, screening etc.). The hierarchy is based on the level of bias inherent in the study design. Using this hierarchy, systematic reviews of randomised controlled trials represent the strongest level of evidence, followed by individual randomised controlled trials, pseudo randomised controlled trials, non-randomised comparative trials, and case series. The level (or sufficiency) of evidence ultimately affects the confidence that can be placed in the study results. Manufacturers should source the highest level of evidence available that demonstrates the safety and performance of the device for the intended purpose(s).

Several appraisal tools are available for assessing the quality, suitability and contribution of the clinical data, noting that it is preferable to use tools that have been validated. The evaluator should choose tools that are appropriate for the data set in question, and indicate which ones were used, along with checklists and other relevant information in appendices.

The following table includes commonly used quality appraisal tools.

Table 1: Commonly used quality appraisal tools

Tool	Applicable study designs	Source
Jadad Score	Randomised studies	https://www.ncbi.nlm.nih.gov/pubmed/8721797
Downs & Black	Randomised & non-randomised studies	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/
QUADAS	Studies of diagnostic accuracy	http://www.bristol.ac.uk/population-health-sciences/projects/quadas/
AMSTAR	Systematic reviews	http://amstar.ca/

Additional guidance on quality appraisal tools is provided by the Scottish Intercollegiate Guidelines Network (SIGN), the Centre for Evidence-Based Medicine (CEBM), and the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions.

With regards to appraisal tools to determine the suitability and weighting contribution of each dataset, IMDRF provides examples of possible appraisal criteria in their Clinical Evaluation document, as follows:

Table F1: IMDRF Sample Appraisal Criteria for Suitability

Suitability Criteria	Description	Grading System
Appropriate device	Were the data generated from the device in question?	D1 Actual device D2 Comparable device D3 Other medical device
Appropriate device application	Was the device used for the same intended use (e.g. methods of deployment, application, etc.)?	A1 Same use A2 Minor deviation A3 Major deviation
Appropriate patient group	Were the data generated from a patient group that is representative of the intended treatment population (e.g. age, sex, etc.) and clinical conditions (i.e. disease, including state and severity)?	P1 Applicable P2 Limited P3 Different population
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	P1 High quality P2 Minor deficiencies P3 Insufficient information

Table F2: IMDRF Sample Appraisal Criteria for Data Contribution

Data Contribution Criteria	Description	Grading System
Data source type	Was the design of the study appropriate?	T1 Yes T2 No
Outcome measures	Do the outcome measures reported reflect the intended performance of the medical device?	O1 Yes O2 No
Follow up	Is the duration of follow-up long enough to assess treatment effects and identify complications?	F1 Yes F2 No

Data Contribution Criteria	Description	Grading System
Statistical significance	Has a statistical analysis of the data been provided and is it appropriate?	S1 Yes S2 No
Clinical significance	Was the magnitude of the treatment effect observed clinically significant?	C1 Yes C2 No

The appraisal process should be described in sufficient detail to allow the clinical assessor to undertake a rational and objective assessment of the information provided. This may take the form of a table, in which each study is assessed in terms of its quality, suitability and weighting contribution, though the layout and presentation of this information may vary depending on the tools used for evaluation. The manufacturer should present data on the risk of bias in each study and outcome level assessments. The results of any assessment of risk of bias across studies (such as publication bias and selective reporting within studies) should also be presented where such information is available. Funding sources should be included if it is one of the variables for data extraction.

Manufacturers and sponsors are also referred to MEDDEV 2.7/1 Rev 4 appendix 6, Appraisal of clinical data for examples of studies that may lack scientific validity for demonstration of adequate clinical performance and/or clinical safety.

a. Lack of information on elementary aspects

This includes reports and publications that omit disclosure of

- *the methods used*
- *the identity of products used*
- *numbers of patients exposed*
- *what the clinical outcomes were*
- *all the results the clinical study or investigation planned to investigate*
- *undesirable side-effects that have been observed*
- *confidence intervals/ calculation of statistical significance*
- *if there are intent-to-treat and per protocol populations, definitions and results for the two populations.*

b. Numbers too small for statistical significance

Includes publications and reports with inconclusive preliminary data, inconclusive data from feasibility studies, anecdotal experience, hypothesis papers and unsubstantiated opinions.

c. Improper statistical methods

This includes

- *results obtained after multiple subgroup testing, when no corrections have been applied for multiple comparisons*
- *calculations and tests based on a certain type of distribution of data (e.g. Gaussian distribution with its calculations of mean values, standard deviations, confidence intervals, t-tests, other*

tests), while the type of distribution is not tested, the type of distribution is not plausible, or the data have not been transformed. Data such as survival curves, e.g. implant survival, patient survival, symptom-free survival, are generally unlikely to follow a Gaussian distribution.

d. Lack of adequate controls

In the following situations, bias or confounding are probable in single arm-studies and in other studies that do not include appropriate controls.

- *when results are based on subjective endpoint assessments (e.g. pain assessment)*
- *when the endpoints or symptoms assessed are subject to natural fluctuations (e.g. regression to the mean when observing patients with chronic diseases and fluctuating symptoms, when natural improvement occurs, when the natural course of the disease in a patient is not clearly predictable)*
- *when effectiveness studies are conducted with subjects that are likely to take or are foreseen to receive effective co-interventions (including over-the-counter medication and other therapies)*
- *when there may be other influencing factors (e.g. outcomes that are affected by variability of the patient population, of the disease, of user skills, of infrastructure available for planning/ intervention/ aftercare, use of prophylactic medication, other factors)*
- *when there are significant differences between the results of existing publications, pointing to variable and ill-controlled influencing factors.*

In the situations described above, it is generally not adequate to draw conclusions based on direct comparisons with external or historic data (such as drawing conclusions by comparing data from a clinical investigation with device registry data or with data from published literature).

Different study designs may allow direct comparisons and conclusions to be drawn in these situations, such as randomised controlled design, cross-over design, or split-body design.

e. Improper collection of mortality and serious adverse events data

Demonstration of adequate benefits and safety is sometimes based on mortality data or occurrence of other serious outcomes that limit a subject's ability to live in his home and be available for follow-up contacts. In this type of study,

- *consent of the subjects for contacting reference persons/ institutions for retrieval of medical information should be obtained during recruitment; when subjects can no longer be found, outcomes should be investigated with the reference persons/ institutions*
- *the consequences of missing data on the results should be analysed (e.g. with a sensitivity analysis); alternatively, when patients can no longer be found and their outcomes cannot be identified, they should be considered to meet the SAE endpoint under investigation (e.g. the mortality endpoint of a study).*

In mortality studies (and other studies addressing serious outcomes) procedures for investigating serious patient outcomes, numbers of subjects lost to follow-up, reasons why subjects leave the study, and the results of sensitivity analysis should be fully disclosed in reports and publications.

f. Misinterpretation by the authors

Includes conclusions that are not in line with the results section of the report or publication, such as

- *reports and publications not correctly addressing lack of statistical significance/confidence intervals that encompass the null hypothesis*
- *effects too small for clinical relevance.*

g. Illegal activities

Includes clinical investigations not conducted in compliance with local regulations. Clinical investigations are generally expected to be designed, conducted and reported in accordance with EN ISO 14155 or to a comparable standard, and in compliance with local regulations and the Declaration of Helsinki.

Analysis of the clinical data

The objective of analysis is to make a benefit-risk determination regarding whether the appraised data sets available for a medical device collectively demonstrate the safety, clinical performance and/or effectiveness of the device in relation to its intended use.

Following the appraisal of all the clinical data, the manufacturer should provide a well-reasoned and documented analysis of the foreseeable risks that could occur with the use or misuse of the device, and compare these with an analysis of the expected benefits that may be provided to the end user. The nature, extent, probability and duration of benefits should be considered. This analysis should be clearly supported by evidence, including appropriate references. In demonstrating whether the expected benefits of the device outweigh the undesirable effects, the analysis may consider (but should not be limited to) the following criteria:

- the strengths and limitations of the clinical data presented in support of the safety and performance of the device for the intended purpose(s) e.g. level and nature of evidence, bias, confounders, length of follow-up
- the clinical significance of the benefits of the device for the intended purpose(s) as demonstrated by the clinical data
- based on the clinical data provided and on a sound statistical approach, a reasonable prediction of the proportion of 'responders' out of the target group or subgroups should be made
- the safety issues identified in the clinical investigation data and/or literature review and post-market data (clinical experience) for the intended purpose(s), as well as reasonably foreseeable hazards associated with the clinical use of the device that the data may not have captured e.g. misinterpretation or misuse of the device
- the probability of patients experiencing a harmful event, that is, the proportion of the intended population that would be expected to experience a harmful event and whether an event occurs once or repeatedly may be factored into the measurement of probability
- the duration and severity of adverse events caused by the device or the procedure
- whether there are mitigation strategies that have been implemented to address real or theoretical safety issues i.e. risk management documentation and IFU/labelling
- any issues of uncertainty surrounding the application of the device for its intended purpose, e.g. limitations in the statistical analysis, generalisability of results to an Australian population.

The clinical expert should comment on the risk analysis and risk management approach by the manufacturer and make a determination of the benefit-risk profile of the use of the device in the intended target groups for the indications sought. The Clinical Evaluation Report (CER) should clearly demonstrate a favourable profile based on current knowledge and the state of the art in the relevant medical fields, considering the totality of the clinical data on the device.

The Clinical Evaluation Report (CER)

After the completion of the clinical evaluation process, a CER should be compiled that includes:

- scope and context of the evaluation
- clinical data
- data appraisal and analysis
- conclusions reached about performance, safety and presentation (including labelling, patient information and IFU) of the medical device when used for the intended purpose(s)
- a benefit-risk determination.

The clinical evaluation report should contain sufficient information to be read as a standalone document by an independent party (including a regulatory authority) for the purposes of assessing legislative compliance regarding clinical evidence requirements.

The following section provides an overview of the recommended content and format of the clinical evaluation report (CER), which is a standard component of pre-market applications and may also be required to be provided to the TGA in relation to post-market matters. The CER should be updated periodically through the lifecycle of the device to incorporate new evidence including clinical experience data and updated benefit-risk analyses. A record of reviews and amendments should be kept (along with a copy of each historical version and the most recent version).

Critical analysis and expert opinion

All clinical data in the CER must be critically evaluated by a competent clinical expert, who arrives at a reasoned conclusion on the benefit-risk profile of the subject device and provides their written endorsement and/or signature. Critical analysis requires consideration of all relevant clinical evidence regarding the device, including evidence that is less favourable to the device. The manufacturer must show due diligence in ensuring all relevant clinical evidence is identified and discussed.

Competent clinical expert

A competent clinical expert is generally someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting. For a novel, high risk device, the clinical expert is expected to have current or recent clinical experience with the device type (preferably within the past two years).

The selection of a clinical expert will therefore depend on the device type and its intended purpose(s). For example, for a coronary stent submission the clinical expert should be a cardiologist or equivalent. For a lower risk device that is not typically used by a medical practitioner, another health practitioner who uses the device or similar devices in a clinical setting may be considered an appropriate clinical expert. In order for the clinical assessor to determine whether an appropriate clinical expert has been chosen, the full curriculum vitae of the clinical expert should be included with any convergence of interests or potential for conflict with the manufacturer or sponsor noted.

CER content

The content and format of the CER should be as follows, to facilitate timely review by the TGA. Manufacturers may also refer to the IMDRF document Clinical Evaluation (Appendix G) and MEDDEV 2.7/1 revision 4.

The content of the CER should include all of the following.

a) General details

b) Description of the medical device and its intended application

c) Intended therapeutic and/or diagnostic indications and claims

d) Context of the evaluation and choice of clinical data types

e) Summary of relevant pre-clinical data

f) Discussion regarding comparable devices including substantially equivalent devices

g) Summary of the clinical data and appraisal

h) Data analysis

i) Conclusions

j) Name, signature and curriculum vitae of the clinical expert and date of report

General details

The subject device should be identified by its proprietary name (and any code names assigned during its development), and its manufacturer.

Description of the medical device and its intended purpose

A description of the subject device should be provided, including the following information, cross-referenced to relevant sections of the manufacturer's technical information where applicable:

- models and sizes
- the device group to which the device belongs (e.g. biological artificial aortic valve)
- materials used, including whether it incorporates a medicine (new or existing), biological tissues and/or blood products
- the device components (including software and accessories)
- mechanical characteristics
- how the device functions
- any other relevant information relating to the device such as sterility and radioactivity.

Diagrams or photographs of the device including steps for assembly and use are helpful. The description should be detailed enough to allow for a valid evaluation of compliance with EPs, retrieval of meaningful literature and, if applicable, assessment of equivalence to other devices described in the literature, or alternatively, assessment of the novelty of the design, features or mechanism of the device. If the application is for a multi-component procedure pack, each component in the system must be adequately described.

Intended therapeutic and/or diagnostic indications and claims

It is important to describe the indications for use, including the clinical condition being managed (with reference to the severity and stage of disease), the intended patient population, and the intended application of the device (whether single use/reusable; invasive/non-invasive, implantable, duration of use or contact with the body, and the organs, tissues or body fluids contacted by the subject device).

The magnetic resonance (MR) status of the device (MR unsafe, MR conditional, MR safe or 'safety in magnetic resonance environment not evaluated') should be provided for all implantable devices (and components of these devices that may be taken into the MR scanner room). Additionally, any contraindications, clinical performance/safety claims and warnings should also be documented. Particular attention should be paid to whether the indications and claims are supported by the clinical data.

Context of the evaluation and choice of clinical data types

Outline the developmental context for the medical device. The information should include whether the medical device is based on a new technology, a new clinical application of an existing technology, or the result of incremental change of an existing technology. The amount of information will differ according to the history of the technology.

Where a completely new technology has been developed, this section will need to give an overview of the developmental process and the points in the development cycle at which clinical data have been generated. For long standing technology, a shorter description of the history of the technology (with appropriate references) could be used. Clearly state if the clinical data used in the evaluation are for a comparable device. Identify the comparable device(s) and provide a justification of the comparability, cross-referenced to the relevant nonclinical documentation that supports the claim.

State the EPs relevant to the device in question, in particular, any special design features that pose special performance or safety concerns (e.g. presence of medicinal, human or animal components) that were identified in the device risk management documentation and that required assessment from a clinical perspective. Outline how these considerations were used to choose the types of clinical data used for the evaluation. Where published scientific literature has been used, provide a brief outline of the search and retrieval process, cross-referenced to the literature search protocol and reports.

The CER should describe the developmental and regulatory context for the subject device. The developmental context (often referred to as the 'state of the art') includes whether the device is based on a new technology, a new clinical application of an existing technology, or the result of incremental change of an existing technology. If the device has evolved from predicate(s) over time, the number and dates of certificates for these may be useful in exploring the history of the device.

The regulatory context includes a list of the countries in which the subject device has been marketed and the dates of introduction into each country. The exact wording of the intended purpose in other jurisdictions should also be provided. It is preferable that certificates of conformity in other regulatory jurisdictions (e.g. CE marking, FDA, Health Canada) be provided including the number and date of issue of international certificates, as these allow verification of post-market data (e.g. through searches of FDA's Manufacturer and User Facility Device Experience (MAUDE)), and may increase confidence in performance and safety claims.

The trade name(s) of the device in other regulatory jurisdictions should also be clearly stated, if different from the name used in Australia. A description of the notification or approval process undertaken by the overseas regulator is also helpful (specifically, if this involved clinical assessment). Information on concurrent applications for registration in the other jurisdictions, particularly Europe, the USA, Japan and Canada, is helpful, if available.

Summary of relevant pre-clinical data

Pre-clinical data may be provided where it adds to the clinical evaluation or risk management strategy. It should be provided where pre-clinical testing (e.g. bench testing including verification and validation, animal testing) is being relied upon as evidence of device safety and/or performance, including to verify claims made in the device labelling not adequately substantiated by the clinical data.

Discussion regarding comparable devices including substantially equivalent devices

In some circumstances, the safety and performance of the subject device may be substantiated by presenting evidence from a substantially equivalent device (indirect clinical evidence) or supported by evidence from a comparable device. Information to help manufacturers determine the extent to which clinical evidence from comparable devices (including substantially equivalent devices) can be relied on to meet the requirements of the EPs can be found in the section Comparable devices including substantially equivalent devices. Where indirect evidence is presented, the CER should summarise the clinical, technical and biological differences between the subject and comparable devices and provide a critical analysis regarding the impact of these differences on clinical outcomes (see Comparing device characteristics).

Note: If the evidence strategy relies on clinical evidence for a comparable or substantially equivalent device, this evidence must be provided as part of the submission. Under the Australian legislative framework, it is not sufficient to demonstrate substantial equivalence to an ARTG-included device – the clinical evidence for the substantially equivalent device needs to be evaluated in order to demonstrate compliance of the subject device with the EPs.

Summary of the clinical data and appraisal

What constitutes appropriate clinical data will vary depending on the type of device under assessment and its state of development, but may include clinical investigation data, literature review data and/or clinical experience data pertaining to the subject device, substantially equivalent device and/or comparable device. The CER should include a summary of all clinical data used in the evaluation accompanied by a critical analysis outlining how this data supports device safety and performance.

For key clinical investigations, either the full clinical investigation report and/or copies of full text journal articles should be provided in the CER, or as supporting documents. Brief summaries of studies with insufficient detail to enable a thorough assessment of the study methodology are not acceptable. Details of literature searches should be included in the CER or provided in the supporting documents. An outline of the data appraisal methods used in the evaluation (such as quality, suitability and weighting assessments) and a summary of the key results should be provided. For further information refer to Appraisal of clinical data and MEDDEV 2.7/1 Rev 4 appendix 6, Appraisal of clinical data.

Data analysis

A competent clinical expert should evaluate all the clinical data and provide a well-reasoned argument as to how the clinical data demonstrate the performance and safety of the subject device when used for the intended purpose(s), and hence a positive benefit-risk profile. It typically involves a discussion of the following performance, safety and labelling aspects:

- Performance: key data sets that contribute to the demonstration of the performance of the subject device and (where useful) particular performance characteristics; the consistency of the results; statistical and clinical significance of effects.

- Safety: safety issues identified in the clinical investigation data, literature review and/or clinical experience data; the total experience with the subject device to date; a summary of device-related adverse events (with a focus on serious adverse events).
- Product labelling: the consistency of the product labelling with the clinical data and whether residual risks associated with the use of the device are adequately conveyed in the IFU.

Emphasis should be placed on explaining the links between the clinical evidence and the intended purpose, indications, contraindications, warnings and precautions, and actual and potential adverse effects of the device on health.

- It is critical that a CER (which serves to detail the clinical evidence as required by the legislation) is not simply a summary of the data, followed by a statement that the data demonstrate safety and performance. This approach does not represent an adequate clinical evaluation.
- It must be explicitly clear to the clinical assessor whether direct clinical evidence (pertaining to the device) or indirect clinical evidence (pertaining to a substantially equivalent device) are provided.
- It is important to identify any changes made to the device since the clinical data were gathered and if so to document the changes and to clarify the exact version of the device.

The CER should include an evaluation of the post-market data presented in the submission and any other data from clinical experience (special access schemes etc.) and comment on its clinical significance. The detailed datasets can be provided in the supporting documents. In assessing the post-market data, the clinical expert should comment on adverse events, vigilance reports and complaint rates and any recalls, withdrawals, removals, suspensions and cancellations for any reason in any jurisdiction and discuss the implications for the safety of the device. The evaluation of the post-market data should clearly indicate whether the data reported is for the subject device or a comparable device.

Conclusions

The conclusion of the CER should clearly outline key findings from the evaluation regarding the performance and safety of the subject device, with respect to its intended purpose. Statements that address the following should be included. Whether the:

- clinical evidence demonstrates compliance with EP 14 and the other EPs
- clinical evidence on the device and/or substantially equivalent device is supportive of the safety and performance of the subject device
- residual risks have been adequately mitigated with appropriate justification, for example, inclusion of relevant statements in the IFU and risk management documentation, and through post-market clinical follow up studies
- risks associated with the use of the subject device are acceptable when weighed against the benefits to the patient.

Name, signature and curriculum vitae of clinical expert and date of report

As stated in clause 8.6 of Part 8 of Schedule 3 of the MD Regulations:

> The manufacturer of a kind of medical device must ensure that the clinical data is evaluated by competent clinical experts.

The manufacturer must ensure that clinical evidence demonstrating that the device complies with the applicable provisions of the EPs is documented in writing.

For further information refer to Critical analysis and expert opinion.

Overview for constructing a CER

The following diagram outlines the components that comprise clinical evidence for a medical device and the process to compile a CER.

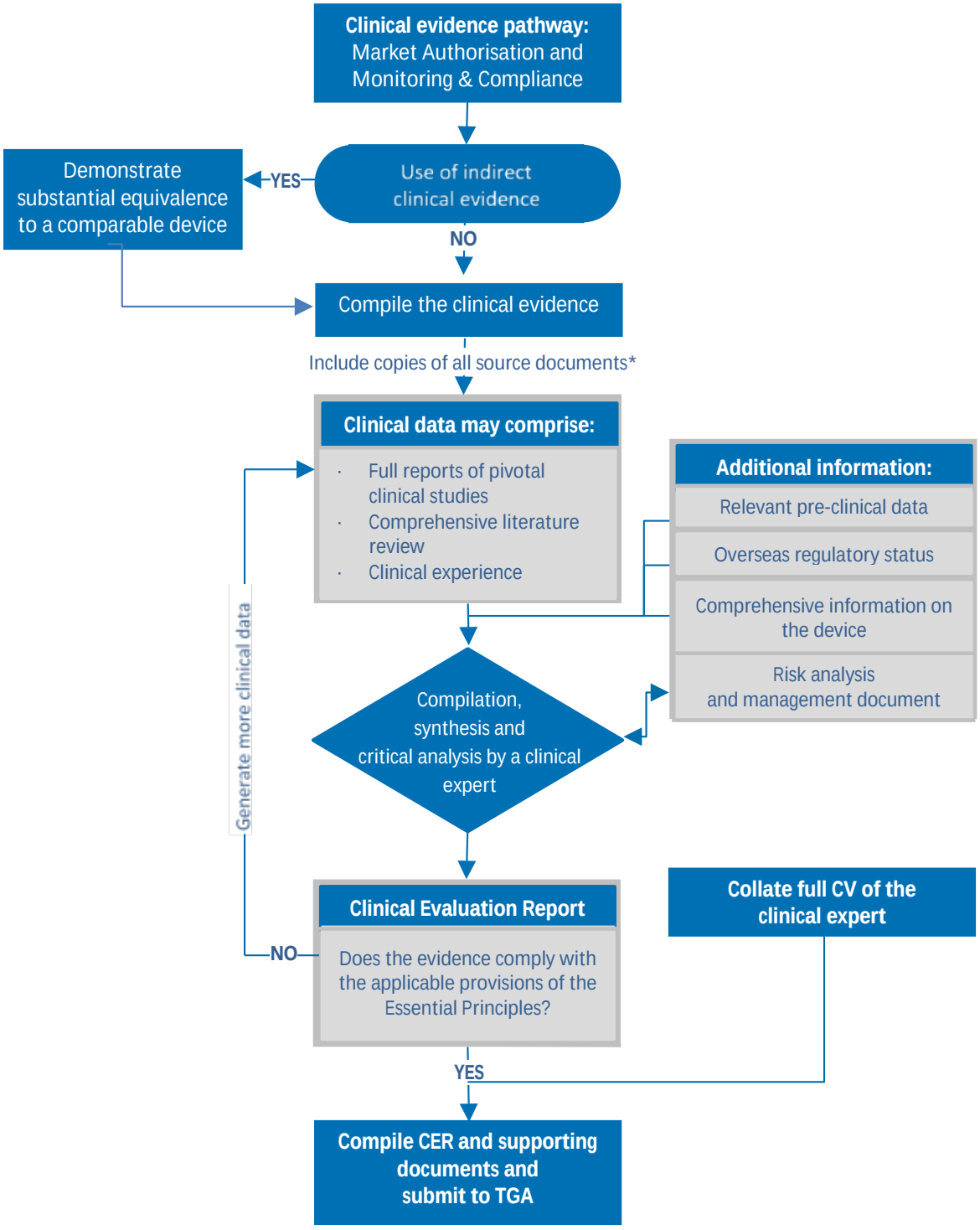

Figure 1. Overview of the process of constructing a CER

* Source documents for clinical data may not initially be required for a clinical assessment requested as part of an audit of an application for inclusion based on EU certification, provided that the CER contains sufficient detail for the TGA assessor to appreciate how the clinical expert was able to demonstrate compliance with the EPs.

Common errors in the CER

There are a number of common errors or deficiencies in CER submissions that can be avoided, including:

- absence of the required components of the CER and/or referenced attachments and appendices missing
- intended purpose(s), indication and claims inconsistent between documents - for example, the application, IFU and CER list different intended purpose(s)
- intended purpose(s), indication and claims not supported by clinical data
- lack of information about the regulatory history of the device in other countries, for example recalls, withdrawals, removals from market, suspensions and cancellations and the reasons for these in any jurisdiction
- information on comparable devices not included and/or substantial equivalence not demonstrated (if relevant)
- insufficient or incomplete clinical investigation(s) data, literature and post-market data with the device or comparable device (if relevant)
- in submissions where a literature review is provided:
  - no documented method and/or no demonstrated comprehensive literature review
  - insufficient information and/or poor-quality search protocol that result in inability to reproduce or understand the literature review strategy
  - provision of a multitude of publications with little or no explanation as to why they are of relevance
  - no identification of device used or indication for use in articles reviewed
  - no summary of study characteristics and findings for each included article
- little or no synthesis and critical evaluation of the clinical investigation data, results of the literature review and post-market data:
  - no discussion of relative strengths of the data, for example randomised controlled trials, case control studies, case series
  - substantial equivalence covering technical characteristics, biological characteristics and clinical use not established to validate the data for a different device (i.e. comparable device) to the device under review
  - lack of discussion of the validity or otherwise of outcome measures used
  - no endorsement by the clinical expert that the differences will not adversely affect the safety or performance of the device
- inadequate critique and summary of the totality of evidence provided for the device
- no post-market data including adverse events, vigilance reports, complaints, failures in cases where this information is available
- CER not endorsed/signed by clinical expert and/or CER not dated or out-dated
- inappropriate selection of clinical expert/s
- CV of clinical expert/s not provided.

It must be explicitly clear to the clinical assessor whether direct clinical evidence (pertaining to the subject device) or indirect clinical evidence (pertaining to a comparable device that has been demonstrated to be substantially equivalent) are provided for assessment. Further, it is important to clarify if any changes have been made to the device since the clinical data were gathered.

The CER must be in English and in an easily readable form. Avoid unclear or ambiguous terms, poor grammar and spelling, and poorly organised information.

Avoiding these common errors will help to ensure that submissions for pre-and post-market clinical assessments are processed efficiently, thereby reducing the time required to report back to the applicant.

Supporting documents

The following supporting documents add to the evidence provided in the CER (they may be provided separately or as part of the CER):

- risk assessment and risk management documents
- Instructions for Use (IFU), labelling, product manual and all other documents supplied with the device
- additional information on the device
- pre-clinical data (if relevant)
- clinical investigation reports (full study reports or peer reviewed journal articles)
- literature search and selection strategy
- pivotal articles from the literature review
- post-market surveillance reports.

Further guidance is set out below.

Risk assessment and risk management documents

A well-reasoned and comprehensively documented risk analysis outlining the potential hazards related to the device is necessary in order to demonstrate compliance with the EPs. The manufacturer should ensure that all risks identified in the clinical data are included in the risk assessment; that is, risks relating to patient treatment, method of operation of the device including potential device failures, and risks relating to usability i.e. harm to the patient that results from use of the device but is not caused by the device itself.

Device-related hazards include, but are not limited to, chemical, mechanical, thermal, electrical, radiation, and biological hazards. Use-related hazards[1] refer to hazards associated with user interactions with the device and include, but are not limited to, hazards that occur when the device is used as intended by appropriately trained clinicians but there are inherent risks associated with the procedure or use of the device, when the device is not used as intended, users are not suitably trained or equipped to use the device, users are not capable of using the device, or when the user's expectations about the device are not consistent with the intended use of the device.

All ongoing safety concerns (risks) should be specified as to the potential causes, nature, probability, extent, duration, frequency and severity of occurrence. This type of analysis should

[1] FDA guidance: Applying Human Factors and Usability Engineering to Medical Devices (Feb 2016), page 5

commence before beginning product development as it generates the safety requirements for the design specification. Once all potential hazards arising from the use of the device for its intended purpose(s) in the target population have been identified, the manufacturer is expected to implement a Quality Management System (QMS) to mitigate and monitor these undesirable effects and hazards. Expected rate of occurrence/frequency of hazards is especially useful in post-market when attempting to determine whether a particular adverse event is occurring more than it ought to.

Strategies to mitigate and minimise these risks such as contraindications or warnings in the IFU, check lists, educational initiatives, patient cards and any others documents supplied with the device should be discussed, including the expected impact of these risk mitigation and minimisation strategies. Residual risks that remain after the implementation of risk mitigation strategies should be identified – where required these should be addressed through post-market surveillance, including post-market clinical follow-up (PMCF) studies. Documentation of the risk management and QMS is necessary to allow the clinical expert to comment on whether these have been mitigated adequately and to draw conclusions on the overall benefit-risk profile of the device. ISO 14971:2019 can provide further guidance on this.

The risk management documentation should be reviewed and updated throughout the lifecycle of the device. When new risks or issues arise post-market, these should be incorporated into risk management documents.

Instructions for use (IFU), labelling and other documents supplied with the device

The IFU, product manuals, patient cards, labelling and promotional materials, surgical technique/instructions and other documents should be provided. These must highlight the risks and ensure that they are appropriately communicated to user. They should be commented on in the CER, as they relate to identification of relevant issues regarding safety and performance, and in some instances it may be useful to include particular documents in the CER itself (i.e., as appendices). The IFU should take into account who may use the device. For example, self-use devices may require an IFU that is aimed at a different audience compared with devices intended to be used by a medically qualified person.

The clinical evaluation should discuss the supporting documents, including whether these are consistent with the clinical evidence, with particular attention paid to indications for use, target population, contraindications and adverse events. The IFU should include all identified hazards and other clinically relevant information that may impact on the use of the device and sufficient warnings to mitigate risks where possible. Foreseeable safety or performance concerns that may arise from the hazards identified in the IFU, labelling and other documents should have been identified and incorporated into the overall benefit-risk analysis.

> When available, the clinical assessment report from a European Union notified body may aid timely clinical review of the submission.

Additional information on the device

Further description of the device may be required. As a guide, sufficient detail would generally be provided through satisfying the requirements of Appendix 3 of MEDDEV 2.7.1 Rev 4 on Device description – typical contents.

Pre-clinical data (if relevant)

Medical devices may contain elements that cannot be assessed solely through clinical testing, but which are critical to the safety or performance of the device. In such cases, a concise summary of

the pre-clinical data may be required to establish the safety and performance profile for the device. In some cases, it may be relevant to include a summary of the following in the supporting documents when recommended for the device type by relevant ISO technical specifications, standards or by other international regulatory agencies such as the US FDA:

- physical and chemical analyses
- engineering assessment
- sterilisation and stability
- microbiology
- in vivo and in vitro testing
- engineering studies under simulated conditions of use
- modelling data
- Good Laboratory Practices (GLP) testing

For applications for inclusion based on EU certification which are selected for clinical audit only, pre-clinical data should be presented in a manner relevant to the TGA clinical assessment.

Clinical investigation reports

This may be provided in the form of full study reports or peer reviewed publications. Full study reports should include significantly more detail than peer-reviewed publications and may be the most appropriate evidence form in some circumstances. Clinical investigation reports should include the design, subject selection and inclusion/exclusion criteria, population demographics, duration, safety and performance data, adverse events and complications, patient discontinuation, device failures and replacements, tabulations of data from all individual subject reporting forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and other information, as appropriate.

Literature search and selection strategy

It is recommended that the full electronic search strategy for at least one database searched, and the strategy for selecting studies which were included in the review, are covered in this part of the supporting documents as a way to demonstrate the rigour of the search and selection strategy. The search strategy should include a summary justification as to how each citation did or did not fit the selection criteria for inclusion.

Pivotal articles from the literature review

The full text of pivotal articles in the literature review contributing to the clinical evidence base used to demonstrate compliance with the EPs should be provided.

Post-market surveillance reports

Post-market surveillance (PMS) reports (or equivalent) are one way to present the post-market data relevant to a device. Where reports cover a range of devices, it may be necessary to stratify data by device type to provide satisfactory clinical evidence for the subject device/s. Similarly, data stratification by year, geographical region, or clinical indication may also be required to

meet regulatory requirements. Where a PMS report does not contain all the post-market data required, then additional datasets and critical analysis may be required.

Clinical evidence checklist

The following checklist sets out the recommended heading structure for the CER.

Indicate that each of the relevant recommended sections has been included, who authored each section, and on which page(s) they can be located within the CER.

Section	Included	Author(s)	Page(s)
1. General details and device description -including GMDN, UDI, lineage and version *(if applicable)*	☐ Yes ☐ No ☐ N/A		
2. Intended purpose, indications and claims	☐ Yes ☐ No ☐ N/A		
3. Developmental context and state of the art	☐ Yes ☐ No ☐ N/A		
4. Regulatory status in other countries (including evidence and supporting documents)	☐ Yes ☐ No ☐ N/A		
5. Summary of relevant pre-clinical data *(if applicable)*	☐ Yes ☐ No ☐ N/A		
6. Demonstration of substantial equivalence or comparability *(if applicable)*	☐ Yes ☐ No ☐ N/A		
7. Summary and appraisal of clinical data	☐ Yes ☐ No ☐ N/A		
8. Data analysis and benefit-risk analysis	☐ Yes ☐ No ☐ N/A		
9. Conclusions	☐ Yes ☐ No ☐ N/A		
10. Name, signature and curriculum vitae of clinical expert and date of report	☐ Yes ☐ No ☐ N/A		
11. Risk assessment and management documents	☐ Yes ☐ No ☐ N/A		
12. IFU, labelling and other documents supplied with the device	☐ Yes ☐ No ☐ N/A		

Section	Included	Author(s)	Page(s)
13. Full clinical investigation reports	☐ Yes ☐ No ☐ N/A		
14. Literature search and selection strategy	☐ Yes ☐ No ☐ N/A		
15. Full text of pivotal articles from the literature review	☐ Yes ☐ No ☐ N/A		
16. Post-market surveillance reports	☐ Yes ☐ No ☐ N/A		
17. Additional relevant information on the device *(if applicable)*	☐ Yes ☐ No ☐ N/A		

Part 2 – Special topics

Comparable devices including substantially equivalent devices

The International Medical Device Regulators Forum (IMDRF) defines a comparable device as: 'A medical device with **related function** chosen by the manufacturer to inform the clinical evaluation of the device in question'.

The first step in the comparability process is for the manufacturer to select an appropriate comparable device. The comparable device should have (or include) the same intended purpose.

Substantially equivalent devices are a subset of comparable devices where the devices are similar to such an extent that there would be no clinically significant difference in safety and performance.

Note: it is not a requirement that a comparable or substantially equivalent device be included in the ARTG. However, regulatory approval in Australia and/or other jurisdiction(s) will be taken into account by the TGA alongside the quality and applicability of the evidence.

Comparable devices

The extent to which clinical evidence for a **comparable device** can be used to support safety and performance of the subject device will depend on how similar the devices are. Comparable devices should be considered with respect to clinical, technical and biological characteristics.

For more information refer to Comparing characteristics.

To inform the clinical evaluation, these characteristics should be broadly similar, but consideration should be given to how differences may affect the clinical safety and performance of the device.

Comparable devices should also belong to the same generic family in terms of their intended use and commonality of technology.

Clinical evidence for comparable devices may provide important background information on the course of a disease, current state of the art and treatment options and the evolution of device technologies. The risks identified for comparable devices may help inform the risk management of the subject device. Scientific literature on comparable devices may assist in establishing performance and safety measures and benchmarks, including rates of adverse events.

Clinical evidence for comparable devices that are not substantially equivalent may form part of clinical evaluation and may support or supplement direct clinical data. It will not typically, in itself, constitute sufficient clinical evidence for the purpose of demonstrating compliance with the EPs - except for certain categories of lower risk devices, whose clinical effects are well understood and characterised.

Substantially equivalent devices

Substantially equivalent devices are those that are the most similar to the subject device, to such an extent that there would be no clinically significant difference in safety and performance. Clinical data for substantially equivalent devices can be used as indirect evidence for the subject device – it may constitute the sole or major clinical data source for demonstrating compliance with the EPs.

The TGA approach to substantial equivalence differs slightly from other jurisdictions, partly due to differences in legislation.

For example, European guidance requires that equivalence claims for implantable devices and class III devices not from the same manufacturer 'must have a contract in place that allows full access to the technical documentation on an ongoing basis'.[2]

The FDA (via the 510(k) pathway) requires that the new device is as safe and effective as the predicate[3] though the FDA and TGA have different definitions of the term 'predicate'.

Our position for determining substantial equivalence is that:

- all relevant clinical, technical and biological characteristics of the devices should be compared (preferably with the aid of tables) and discussed
- a sufficiently detailed critical analysis should demonstrate that the devices are similar to such an extent that there would be no clinically significant difference in safety and performance
- a suitable clinical expert must endorse the above.

Where the manufacturer's technical data is not available for a comparable device, a robust method of analysis that quantifies this may be provided as an alternative. Reference to an applicable ISO standard may be of assistance. If a comparable regulator has previously determined the devices to be substantially equivalent, we will consider this factor in our assessment.

In general, if substantial equivalence between two devices cannot be demonstrated then direct clinical evidence for the subject device will be required to demonstrate compliance with the EPs.

Predicates

Predicates are comparable devices that represent a logical starting point for gathering clinical evidence. They can often be demonstrated to be substantially equivalent.

A predicate:

- is a previous iteration of the subject device
- has the same intended purpose as the subject device
- is within the same lineage of devices as the subject device
- is from the same manufacturer as the subject device.

Where there are multiple devices in a lineage, you may demonstrate substantial equivalence between the subject device and any device whose clinical investigation data is being used as indirect evidence in the clinical evaluation, even if that device was several iterations earlier in the lineage.

However, be cautious when claiming substantial equivalence to a predicate very early in the device lineage. You should consider the relevance of the comparison and the potential impact of multiple incremental changes on safety and performance; such devices may be more

[2] EU MDCG 2020-5 *Clinical Evaluation – Equivalence. A guide for manufacturers and notified bodies.* April 2020

[3] US FDA, 'The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]. Guidance for Industry and Food and Drug Administration Staff. Document issued on July 28, 2014.

appropriately viewed as comparable devices. Direct clinical evidence for the subject device and revision of the CER to include this data should occur as early as is practicable.

> **Example:** Devices A, B and C are all in the same lineage of orthopaedic prostheses. Device C is being assessed. Device B was the most recent predicate, but the main clinical investigation data was derived from an earlier iteration, Device A. Substantial equivalence must be demonstrated between Device C and A to enable this clinical data to be accepted as indirect evidence for demonstrating compliance with the EPs. Substantial equivalence could also be claimed for Device B – this would strengthen the evidential value of its post-market data.

Comparing device characteristics

To determine the degree of comparability of devices, we consider the clinical, technical and biological characteristics. Higher risk devices require a more thorough and comprehensive evaluation of these characteristics. Once each characteristic and its associated elements (see below) have been compared, we can determine the degree of similarity. To demonstrate substantial equivalence, the devices must be similar to such an extent that there would be **no clinically significant difference in clinical safety and performance**.

Comparisons are ideally based on a single device or lineage.

Comparisons that consider multiple devices

In general, you should not provide comparisons that consider multiple devices (unless these are from the same lineage). For instance, it would not be appropriate to compare technical characteristics of a subject device to multiple different devices, without considering that the overall combination of characteristics of the subject device may be novel and hence have new safety and performance implications.

Comparisons may address multiple devices in the following circumstances:

- **Where a subject device is part of a system of devices.** In this instance, comparisons may address the multiple devices within the system, including how the individual components of the system interact and the safety and performance of the system as a whole.
- **Where technical differences between devices are present.** Discussion of the impact of the technical difference may be supported by a relevant example from a third device.

In these instances, the clinical evidence for the comparable devices must allow sufficient conclusions to be drawn regarding the safety and performance of the subject device.

You must identify any safety or performance concerns regarding a comparable device, including matters subject to regulatory review or action (in Australia or another jurisdiction). Whether design and usage issues have been appropriately addressed in the subject device will be an important consideration in determining compliance with the EPs. Sponsors must provide detailed, reasoned arguments supported by appropriate evidence.

Clinical characteristics/intended purpose

Firstly, consider and compare the clinical characteristics which relate to the intended purpose of the devices.

The intended purpose should refer to the clinical condition being treated, the severity and stage of disease, the site of application to/in the body and the patient population. You should clearly state this information in your submission.

The TGA will also assess whether the intended purpose is consistent with information provided with the device, in the IFU, labelling, any advertising material for the devices and technical documentation.

Elements to consider include, but are not limited to, the comparability of the subject device and comparable device with respect to:

- indications for use, including the disease or condition the medical device will diagnose, treat, prevent, cure or mitigate
- patient population (for example, age, gender, anatomy, physiology)
- the site of application to/in the body (organs, parts of the body, tissues or body fluids contacted by the medical device)
- type of contact (for example, contact with mucosal membranes, invasiveness, implantation)
- duration of use or contact with the body
- environment of use (for example, healthcare facility, home)
- intended user (for example, use by health care professional, lay person)
- repeat applications, including any restrictions as to the number or duration of applications.

In general, the intended purpose must be the same for substantial equivalence to be considered. However, if the intended purpose differs (for example if it is narrower than, but encompassed by, the intended purpose for the comparable device), clinical evidence demonstrating safety and performance for the comparable device **specific to the intended purpose for the subject device** may be considered as part of a substantial equivalence claim.

Technical characteristics

Technical characteristics should be broadly similar between the comparable devices, including but not limited to:

- design, for example:
  - dimensions and design tolerances
  - how the different components of the device system work together
- material, for example:
  - chemical formulation
  - additives
  - processing such as forged
  - state such as crystalline
- specifications and properties, for example:
  - physiochemical properties such as type and intensity of energy
  - wavelength

  - porosity
  - particle size
  - viscosity
  - nanotechnology
  - specific mass
  - atomic inclusions such as nitrocarburising
  - oxidability
  - tensile strength and degradation characteristics
- deployment methods (where applicable)
- critical performance requirements
- principles of operation
- software algorithms

Biological characteristics

Biological characteristics should be broadly similar between the comparable devices, including but not limited to:

- biocompatibility of materials in contact with body fluids/tissues
- biological action
- degradation mechanism and profile
- biological response, for example:
  - inflammatory response
  - immune response
  - tissue integration

Presentation of information regarding comparable devices

To make a comprehensive comparison, it is best that you:

- use tables which provide a description of the characteristics for the two devices and note **both** their similarities and differences (see example below)
- clearly and explicitly state **all differences** between the devices
- critically analyse these differences to determine their likely impact on safety and performance.

We highly recommend including illustrations of the devices highlighting similarities and differences.

Your conclusions regarding the impact of differences on device safety and performance must be endorsed by a suitable clinical expert who has:

- relevant medical qualifications

- direct clinical experience in the use of the device or device type in a clinical setting.

A full curriculum vitae of the clinical expert should be provided.

If it can be established that the clinical, technical and/or biological differences would result in no clinically significant difference in device safety and performance, then the comparable device may be considered '**substantially equivalent'** to the subject device.

In order to establish substantial equivalence, the differences between the two devices will need to be minimal. You need to provide evidence to substantiate your claim, such as pre-clinical (bench testing or in vivo studies) and/or clinical (clinical investigation or post-market) data.

Multiple and/or major differences will compromise claims of substantial equivalence. In these scenarios, we may consider the devices '**comparable**' subject to the facts.

It is your responsibility to ensure that all relevant information relating to the comparable device is provided for clinical assessment – in particular the clinical data that demonstrates its safety and performance.

The following flowchart provides guidance on how to demonstrate substantial equivalence:

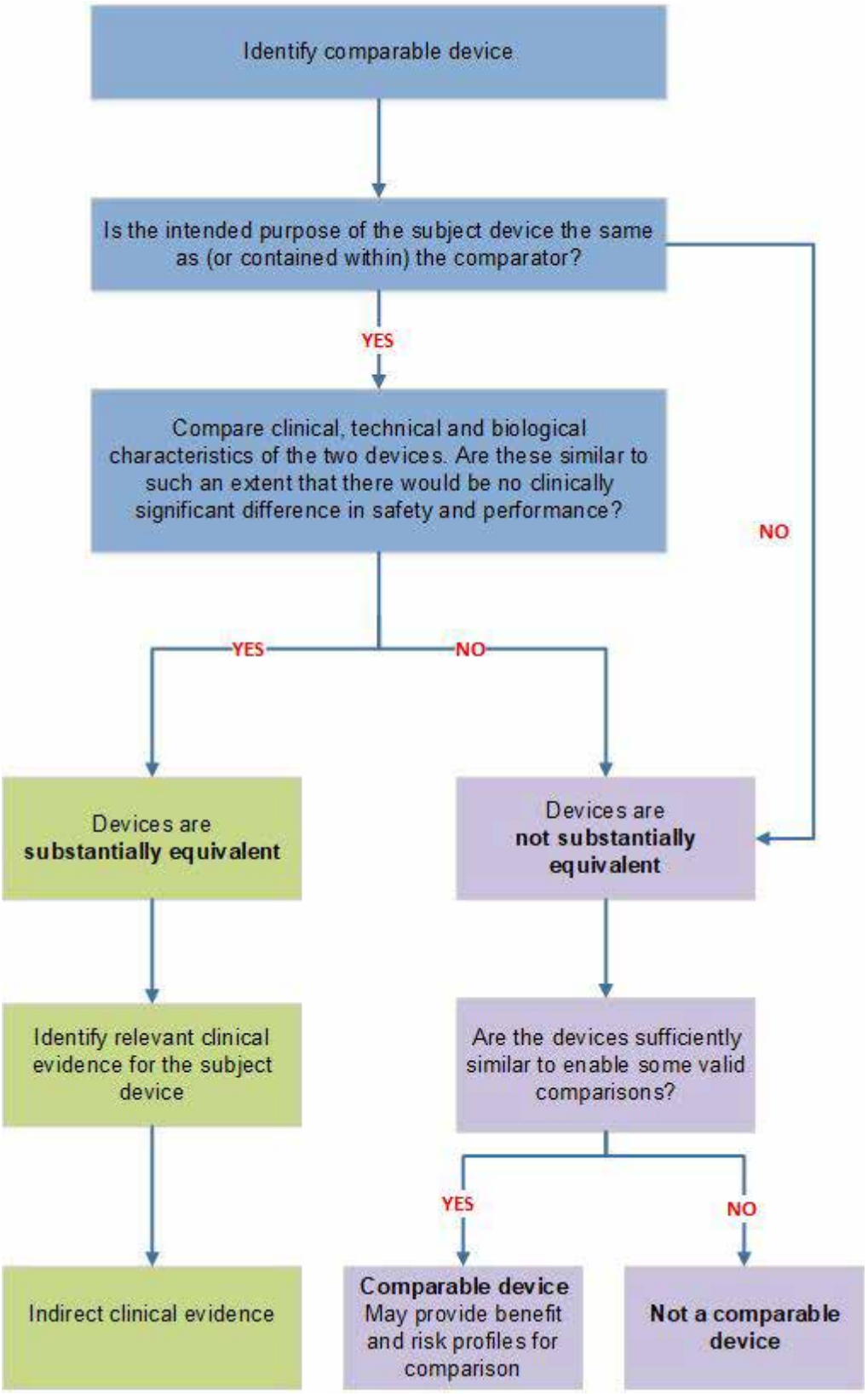

Figure 2. Identifying substantially equivalent and comparable devices

Table 2: Example summary table

The following table template provides an example of how to present information regarding comparable devices.

Evidence presented	The device	Comparable device	Impact of difference on safety and performance
Clinical characteristics			
{e.g. clinical condition treated, intended purpose/ indications, site in body, operational procedures, target population including age, anatomy, physiology}			
Technical characteristics			
{e.g. materials, design, function, energy source etc.} {e.g. deployment methods}			
Biological characteristics			
{e.g. biocompatibility}			

Magnetic resonance imaging (MRI) considerations

Addressed in this section are the clinical and pre-clinical evidence requirements to demonstrate the safety and performance of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment. Active IMDs (AIMDs) are implanted devices that depend on a source of energy for their operation and convert energy, whilst passive IMDs (PIMDs) are those that do not have such a requirement. The evidence considered in this section applies to:

- Active Implantable Medical Devices (AIMDs), including but not limited to:
  - implantable permanent pacemakers (PPM)
  - implantable cardioverter defibrillators (ICD)
  - cardiac resynchronisation therapy (CRT) devices
  - implantable loop recorders (ILR); and
  - the associated leads.

- Passive Implantable Medical Devices (PIMDs), including but not limited to:
  - orthopaedic implants such as hip or knee implants
  - cardiovascular stents
  - heart valves
  - neurovascular aneurysm clips or coils
  - interventional guidewires or catheters

Each unique type of IMD system has its own associated risk-benefit profile that needs to be addressed by the manufacturer.

Summary recommendations

- AIMDs and many PIMDs, for example orthopaedic implants, are complex medical devices forming systems of multiple independent components. The unique configuration of components for each device system may have consequences for the safety of the device system in the MR environment. Therefore, manufacturers are advised to provide appropriate evidence to support the safety and identify the risks and hazards of each unique device system separately. Due to the nature of their materials, currently available AIMDs can only be marked as 'MR conditional' or 'MR unsafe'. PIMDs can be marked as 'MR safe', 'MR conditional' or 'MR unsafe'.
- For IMDs claimed to be 'MR conditional' under specified conditions of use, these conditions must be clearly articulated in the submission and in the IFU, and/or other supporting documents with evidence supporting any reported thresholds.
- For PIMDs, the use of non-clinical data alone suffices to meet the requirements for the applicable EPs. Clinical data are not required.
- A well-documented risk analysis and management system and quality management system should be provided with the CER.
- Provision of clinical data for AIMDs if applicable:
  - Post-market data or clinical investigations from another jurisdiction where the device is already approved can provide useful clinical evidence and are acceptable. This includes clinically indicated MRIs provided that potential sources of bias have been minimised. Studies should be appropriate to inform on the safety and performance of the device for its intended purpose in relation to MR conditional use.
  - examples of appropriate safety outcomes are provided in Table 26 - Safety of active implantable medical devices in the MR environment.
  - when submitting a comprehensive literature review, full details of the method used should be included in the CER in sufficient detail to ensure the literature review can be reproduced.
  - for guidance on the presentation of clinical evidence and conduct of comprehensive literature reviews manufacturers are directed to relevant sections.

Defining 'safety' in the MR environment

The specific terminology used to define the safety of medical devices in the MR environment is outlined in ASTM Standard F2503-13, "*Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment*". In this context, the term "MR

environment" refers to the physical space surrounding a MR magnet, which is affected by the static, gradient and radiofrequency (RF) electromagnetic fields. Standard F2503-13 defines three terms to classify the safety of medical devices in the MR environment:

- **MR safe:** An item that poses no known hazards resulting from exposure to any MR environment. A medical device can only be classified as MR safe if it is composed of materials that are electrically non-conductive, non-metallic, and non-magnetic (e.g. glass, plastic, silicone). Such devices may be determined to be MR safe based on scientific rationale rather than test data;
- **MR conditional:** An item with demonstrated safety in the MR environment within defined conditions. Minimum requirements for demonstrating conditional MR safety requires consideration of the possible interactions between the device and the static, gradient and radiofrequency fields present in the MR environment, and consideration of MR image artefacts from the implants. Known potential hazards related to the use of AIMDs in the MR environment that should be addressed in order to demonstrate conditional safety are outlined in Table 3 (below).
- **MR unsafe:** An item that poses unacceptable risks to patients, medical staff or other persons in the MR environment.

Table 3: Known potential hazards for active implantable medical devices in the MR environment related to the static, gradient and radiofrequency fields

MR hazard/clinical impact	Static field	Gradient field	Radiofrequency field
Force and torque/discomfort, dislodgement	Ÿ		
Vibration/discomfort, device damage	Ÿ	Ÿ	
Device interactions/therapy delivery, device reset, device damage	Ÿ	Ÿ	Ÿ
Device case heating/discomfort, tissue necrosis		Ÿ	Ÿ
Unintended cardiac stimulation/arrhythmia induction, asystole		Ÿ	Ÿ
Lead electrode heating/therapy delivery, sensing			Ÿ

MR = magnetic resonance. Table source: Gold *et al* 2015.

Evidence requirements

Evidence requirements to demonstrate the safety of an IMD system in the MR environment will vary depending on whether the device is labelled as 'MR safe', 'MR conditional', or 'MR unsafe':

- Device systems claimed to be 'MR safe' must be shown to be non-conducting, non-metallic, and non-magnetic in order to satisfy the applicable EPs. A scientifically based rationale to demonstrate that the device poses no known hazards in all possible MR imaging environments may be sufficient. It is unlikely that any AIMD systems currently available would be designated as MR safe.

- Device systems claimed to be 'MR conditional' must be shown to pose no known hazards in the MR environment under specific conditions. For 'MR conditional' PIMD systems, the requirements may be satisfied with non-clinical data alone. In any case, the data should be accompanied by appropriate warnings and specified conditions of use, outlined in the instructions for use (IFU) and/or manual and other easily accessible documents.

Other information that should be provided for IMDs includes:

- the technical specification of the device(s)
- the components to which the device is paired when used clinically, for example the pulse generator with its lead(s)
- scanning exclusion zones implemented
- a risk analysis and management document.

Requirements for PIMDs

For PIMDs claimed to be 'MR conditional', the following experimental data are required using non-clinical testing methods specified in the standards below or equivalent methods.

- Magnetically Induced Displacement Force: ASTM F2052-14, Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment
- Magnetically Induced Torque: ASTM F2213-06 (Reapproved 2011), Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment
- Heating by RF Fields: ASTM F2182-11a, Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging
- Image Artifact: ASTM F2119-07 (Reapproved 2013), Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants

If the testing does not include all sizes of the device, a size or combination of sizes that represent the worst-case scenario for each test should be included in the testing. A rationale should be included for determining why the selected size(s) represent the worst-case scenario for each test.

All testing protocols should be described with the following elements:

- test objective
- equipment used
- acceptance criteria
- rationale for test conditions
- rationale for the acceptance criteria
- number of devices tested
- description of devices tested, including device size
- description of any differences between test sample and final product, and justification for why differences would not impact the applicability of the test to the final product
- results (summarised and raw form).

Regulatory status in other jurisdictions

If the IMD or comparable device is approved for use in another jurisdiction, the manufacturer or sponsor should provide regulatory status, including the certificate number, date of issue and name under which the device is marketed, exact wording of the intended purpose, MR status in key jurisdictions, for example the US, EU, Japan and Canada and IFU used in other jurisdictions.

Post-market data

Information arising from product experience in Australia or other jurisdictions where a device is already in use adds to the clinical evidence for pre- and post-market reviews. The following information should be provided if available:

- all product recalls, including for product correction, suspensions, removals, cancellations and withdrawals, whether withdrawals of indications or the device(s), amendments to the IFU or other key documents such as product manuals, or any other corrective actions in any jurisdiction
- distribution numbers of the device(s) including by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- the number of years of use
- for every year since launch data from post-market vigilance and monitoring reports, adverse events and complaints for IMDs and comparable devices categorised by type (e.g. device reset, device failure, induced arrhythmia, etc.) and clinical outcomes (e.g. death or serious harm, etc.) as reported to regulatory bodies
- post-market data from other jurisdictions can be used to support an application for MR conditional use only if the MR status and MR conditions of use in the other jurisdictions are fully specified including the device combinations used
- explanted devices returned to manufacturers should be accounted for with an explanation of device failures and corrective measures.

Defining active implantable medical devices

An active medical device is a device that uses and converts energy in a significant way in order to operate. Active devices may use any form of energy except for gravitational or direct human energies. Active medical devices can be broadly characterised to serve two main purposes, as defined in the *Therapeutic Goods (Medical Devices) Regulations 2002*:

- ***Active medical devices for diagnosis*** are intended by the manufacturer to be used on a human being, either alone or in combination with another medical device, to supply information for the purpose of detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities.
- ***Active medical devices for therapy*** are intended by the manufacturer to be used on a human being, either alone or in combination with another medical device, to support, modify, replace or restore biological functions or structures for the purpose of treating or alleviating an illness, injury or handicap.

Active **implantable** medical devices are further defined in the Regulations as:

Active implantable medical devices

An active medical device, other than an implantable medical device, that is intended by the manufacturer:

a) either:

i. to be, by surgical or medical intervention, introduced wholly, or partially, into the body of a human being; or

ii. to be, by medical intervention, introduced into a natural orifice in the body of a human being; and

b) to remain in place after the procedure.

Implantable permanent pacemakers (PPM), implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy (CRT) devices, implantable loop recorders (ILR); and their leads are a subclass of active implantable medical devices that are used to monitor and/or regulate cardiac rhythm.

In serving this purpose these devices may simultaneously function as both therapeutic and diagnostic devices. While there are subtle differences in the design and purpose of these different cardiac devices, they typically include:

- ***circuitry*** that controls the timing and intensity of electrical impulses delivered to the heart
- a ***battery*** used to generate electrical impulses and power the circuitry
- a ***case*** that encloses the circuitry and battery
- ***pacing lead(s)*** that deliver electrical impulses between the circuitry and the chambers of the heart
- a ***connector block*** that connects the pacing lead(s) to the case.

Different configurations of the above design characteristics are used to treat different medical conditions:

Permanent pacemakers (PPM) are pacing devices used to regulate abnormal heart rhythm. PPMs deliver low-energy electrical impulses to treat bradyarrhythmias. They may include one pacing lead for single-chamber right ventricular pacing, or two pacing leads for right ventricular and right atrial pacing.

Implantable cardioverter defibrillators (ICD) are capable of delivering both low-energy impulses for pacing, and high-energy impulses for defibrillation. ICDs are typically implanted in patients at risk of life-threatening ventricular arrhythmias, in whom a high-energy impulse is required to restore normal rhythm. ICDs typically have a larger battery than a PPM, and include one lead for right ventricular pacing and defibrillation, +/- another lead for right atrial pacing.

Cardiac resynchronisation therapy (CRT) devices are pacing devices used to regulate the lack of synchrony between the left and right ventricles. CRT devices are typically used to treat patients with advanced heart failure. They include either two or three pacing leads for right ventricle, left ventricle, +/- right atrial pacing. CRT devices may also deliver high-energy impulses to correct life-threatening arrhythmias (CRT-Ds).

Implantable loop recorders (ILR) are single-lead cardiac monitoring devices. They can be used as a temporary tool to diagnose patients with unexplained palpitations or syncope, or for long-term monitoring of patients with unresolved syncope who may be at risk of atrial fibrillation. Unlike other classes of active implantable cardiac devices, they are not capable of pacing or defibrillation.

Regardless of the type of AIMD, it is recommended that manufacturers provide the following information regarding the physical and chemical characteristics of the device. These characteristics include, but are not limited to:

- the materials from which the device components are made, including the chemical composition

- the dimensions and geometry of the device components
- the list of other devices that are likely to be used in conjunction with the device.

Summary of safety and performance data

Selection of included studies

Table 4: Summary of primary studies report in narrative reviews on the safety of AIMDs in the MR environment

Characteristics of included studies	Evidence reported in narrative reviews
Dominant design of included studies	3 RCTs, 1 case-control and 38 case series investigations were included in narrative review articles
Sample size range for included study designs	RCTs: 263-466 Case-control: 65 Case series: 1 to 272
Patient follow-up	Range 0-12 months (median 3 months)
Safety outcomes reported	**Force and torque** • Generator movement • Lead dislodgement • Lead damage • Force (Newtons) **Vibration** • Generator movement • Patient discomfort due to vibration **Device interactions** • Reed switch activation/deactivation • Diminished battery voltage (≥ 0.04 V) • Power-on-reset • Temporary communication failure with device • Device reprogramming • Pause in pacing • Signal (image) artefacts **Device case heating**

Characteristics of included studies	Evidence reported in narrative reviews
	• Detectable heat increase near generator **Lead electrode heating** • Increase in pacing capture threshold (≥ 0.5 V) • Increase in cardiac enzyme level (Troponin-I) • Decrease in atrial sensing amplitude ≥50%, or amplitude lower than 1.5 mV 255 • Decrease in ventricular sensing amplitude ≥ 50%, or amplitude lower than 5.0 mV 256 • Change in pacing lead impedance (≥ 50 Ω) **Unintended cardiac stimulation** • Inappropriate pacing • Induction of arrhythmia • Heart palpitations

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Personalised medical devices (PMDs)

This section provides guidance on expectations in relation to the nature and type of clinical evidence generally necessary for demonstrating the performance and safety of personalised medical devices (PMDs) and meeting the relevant provisions of Essential Principles (EPs). The following section is intended to supplement the general and device-specific recommendations outlined in other parts of these guidelines and any applicable standards. PMDs will generally follow the same regulatory requirements and submission expectations as non-PMDs of the same classification; however, there are some additional considerations that apply to PMDs.

The TGA uses three specific terms to describe the current range of PMDs. These terms are defined in the *Therapeutic Goods (Medical Devices) Regulations 2002*:

- Patient-matched medical devices;
- Adaptable medical devices; and
- Custom-made medical devices.

Note: Medical device production systems (MDPS) are a new regulatory concept (not currently in effect) designed to provide options for healthcare facilities wanting to produce *in-house* medical devices for use in treating their patients. While a definition of MDPS is in the MD Regulations, further processes (including a legislative instrument) are required to be put in place to implement the concept. Further discussion of MDPS is not covered in this section.

The overall framework for the regulation of PMDs is explained in more detail on the TGA website including in relation to the future implementation of MDPS.

Personalised medical devices range from low-risk devices such as personalised shoe inserts and dental aligners to high-risk devices such as permanent orthopaedic implants. A wide range of technologies may be employed in the manufacture of PMDs, and this helps inform the clinical evidence strategy. Since each PMD is manufactured and/or adapted to address unique requirements (e.g. anatomical and/or physiological features of a particular individual), no two PMDs are likely to be identical. The uniqueness in design, manufacture, and/or point-of-care modification of PMDs poses additional challenges in designing and conducting clinical investigations, and for manufacturers conducting clinical evaluation to demonstrate performance and safety and hence compliance with the EPs throughout the device lifecycle.

In particular, this section provides guidance on the clinical evidence requirements for PMDs with reference to their particular type. PMD manufacturers are encouraged to use these recommendations as a guide when developing their strategy for generating clinical evidence.

Summary recommendations

Guiding principle

Whilst generating clinical evidence for PMDs poses additional challenges when designing and conducting clinical studies, due to device heterogeneity, the same principles that apply to clinical study design for non-PMD devices should still be applied to PMDs. For both pre-market approvals, and in addressing post market issues, a legitimate and reasoned approach to clinical data generation, alongside a critical analysis regarding its limitations, will be viewed more favourably than a paucity or absence of clinical data. Whilst post market clinical follow up studies and real world data may form a significant element of a manufacturer's strategy for generating clinical evidence throughout the device lifecycle, especially in relation to addressing residual risks, they do not lessen the need for well-designed clinical investigation studies for pre-market approval of higher risk devices.

Types of PMDs

PMDs are a heterogenous group of devices and are required to comply with the relevant provisions of the EPs. They consist of:

- **Patient-matched medical devices**, which are defined in terms of the 'specified design envelope' (which is also defined in the MD Regulations). Manufacturers should consider generalisability – the extent to which available clinical data can be extrapolated to all potential device specifications within the design envelope – in addition to the clinical evidence requirements discussed in Part 1 – General Requirements. This should include discussions about worst-case and common-use scenarios.
- **Adaptable medical devices**, which are defined in terms of point-of-care modifications. Similar to patient-matched medical devices, the nature and extent of personalisation needs to be considered and the clinical evidence must substantiate the safety and performance of the device as modified, in accordance with the manufacturer's instructions, after the device has been supplied.

- **Custom-made medical devices**, which are produced on a small scale. Whilst these devices are exempted from inclusion on the ARTG (and hence pre-market submission of clinical evidence), consideration should be given to whether unique design parameters are expected to affect the device performance and safety. Custom-made medical devices must still comply with all relevant provisions of the EPs and records must be maintained in relation to performance and safety.

Note: a 'low-volume' exemption from ARTG inclusion also exists for patient-matched medical devices where 5 or less such devices of a kind are manufactured in any financial year. Such devices must still comply with all relevant provisions of the EPs, and records relating to performance and safety be maintained.

Clinical Evidence

Clinical evidence, as discussed in Part 1 – General Requirements, remains an essential aspect of design validation for medical devices and forms an important component of the technical documentation to demonstrate conformity with the EPs.

Given the unique aspects of their design, the Total Product Life Cycle (TPLC) approach is particularly important for PMDs and the clinical evidence should be reviewed and updated periodically throughout the lifecycle of a PMD to ensure continued acceptability of the benefit-risk determination. Claims made by the manufacturer about performance and safety of PMDs, must be supported by the clinical evidence and include consideration for all personalised elements.

In Part 1 of these guidelines, the TGA has provided information regarding key definitions and concepts, clinical evidence requirements, sources of clinical data and clinical evaluation in relation to medical devices, which are also applicable to PMDs.

The depth and extent of the clinical evidence should be appropriate to the risk-based classification, novelty, and parameters involved with personalisation of the device.

Clinical evidence considerations for patient-matched medical devices

A patient-matched medical device is manufactured to match the anatomical and/or physiological features, or to address a pathological condition, of a particular individual. The device is manufactured within the parameters of a specified design envelope using production processes that are capable of being either or both validated and verified, and of being reproduced.

A characteristic feature of a patient-matched medical device type is the specified design envelope.

Specified design envelope

Regardless of the risk-based classification of a medical device, the concept of specified design envelope is applicable to devices coming under the definition of patient-matched medical devices (for example patient-matched plagiocephaly helmets, or patient-matched 3D printed orthognathic surgical plates). A specified design envelope can be conceived of as a set of all relevant parameters (minimum and maximum dimensions, performance limits or other relevant factors) that characterize a patient-matched medical device for production purposes. These parameters or factors may be based on a standard device template (Figure 1 refers). The manufacturer should unequivocally identify all relevant parameters that constitute the specified

design envelope and explicitly establish the boundaries[4] (reference intervals/categories) for each parameter.

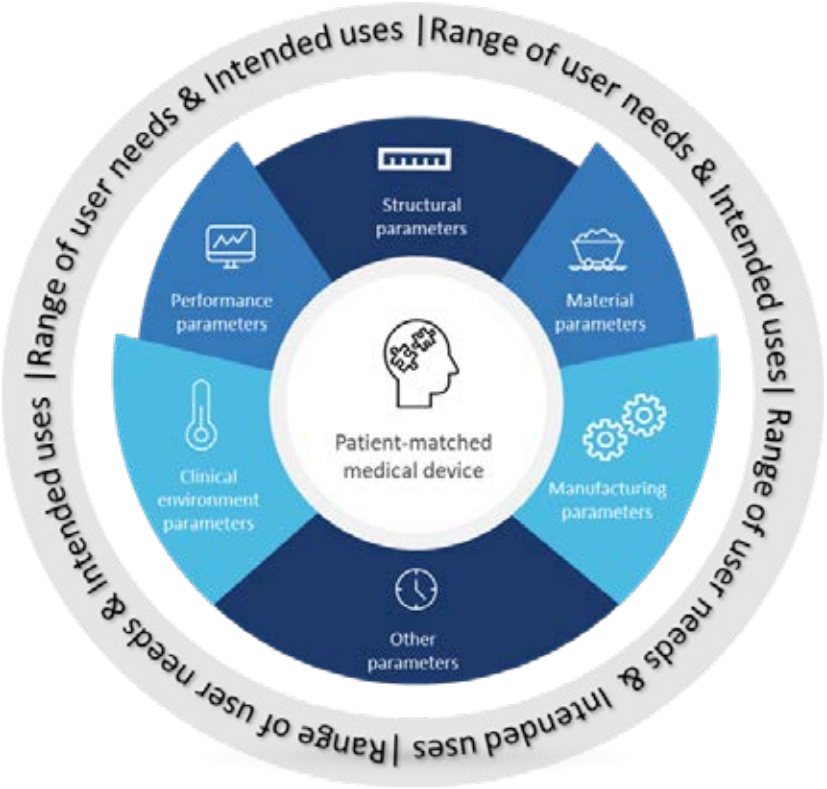

Figure 1. *A template for depicting potential parameters within a design envelope schema*

Parameters that characterise a design envelope may be divided broadly into the six categories set out below. Given the variety of technologies, materials and processes used in the manufacturing of medical devices, not all parameters may apply to every patient-matched medical device.

i. *Structural parameters*
The manufacturer should establish explicit boundaries for the dimensions, area, volume, shape, angles, relative positions, screw hole sizing and number, and other geometrical parameters for the device. In this category, the manufacturer should also include any patient-imaging data used in the device design process. Where the surface morphology of the anatomy is used in the device design process, the manufacturer should specify anatomical landmarks or margins to establish the geometrical limits on the device design.

In addition to the external structural parameters for the device, where applicable, the manufacturer should also establish design limits on the internal structural features of the device, such as porosity, lattice strut size, wall thickness, etc.

ii. *Material parameters*
The manufacturer should identify all raw materials used in the production of the device and their characteristics (biological, physical, chemical), and adhere to relevant material

[4] For the purposes of this document, boundaries mean the reference intervals (for a parameter that only accepts numerical data) and categories (for a parameter that only accepts categorical data).

standards. For example, additively manufactured orthopaedic implants may utilize Ti-6Al-4V Grade 5 and Grade 23 (extra-low interstitial) materials.

iii. Manufacturing parameters

The manufacturer should identify all manufacturing parameters that can be varied during the manufacturing processes and establish explicit boundaries for each parameter. This should include parameters associated with production, post-production processing, fabrication, assembly, cleaning, sterilization (if required), packaging and labelling of the device. For example, a manufacturer may produce two variants of a spinal interbody cage using PEEK (polyetheretherketone), one model with and the other without Ti coating on the superior and inferior surfaces.

iv. Clinical environment parameters
The manufacturer should identify all parameters relating to the clinical environment in which the device is intended to be used, and establish explicit boundaries for each parameter. For example, a manufacturer may produce two different patient-matched maxillofacial bone plates in the same specified design envelope, one intended to be used in the upper jaw and the other intended to be used in the lower jaw where it withstands greater chewing forces.

v. Performance parameters
The manufacturer should identify all parameters relating to the performance of the device when the device is used as intended, and establish explicit boundaries for each parameter. For example, a manufacturer may produce three variants of a spinal interbody cage (for patients with normal bone quality, osteopenia, and osteoporosis) to reduce the risk of subsidence, each with different porosities and compressive stiffness characteristics.

vi. Other parameters
If a parameter is not captured in any of the above categories but will characterize the device for production purposes, the manufacturer should include the parameter in the specified design envelope under this category and establish explicit boundaries for the parameter.

Where the parameter is represented using categorical data, the manufacturer should establish all of the categories that the parameter can accept. Where the parameter is represented using numerical data (continuous or discrete), the manufacturer should establish the reference interval, minimum increment, and unit of measurement for the variable.

Many patient-matched medical devices require the use of imaging data such as 3D printing from computed tomography, magnetic resonance images and other scans (see example below). In these cases, part of defining the parameters of the design envelope should involve particular attention to imaging requirements. This includes but is not limited to a description of all acceptable imaging modalities, minimum imaging quality, maximum timeframe between image acquisition and first use of the device, and software used. These parameters are of clinical importance to ensure patient-matched medical devices are of consistent quality and safety to meet individualised patient care needs.

Clinical evaluation of a patient-matched medical device should consider all devices that can be produced within the specified design envelope and how they relate to their intended patients. In addition, these parameters should be evaluated and discussed by the clinical expert in a manner relevant to the TGA clinical assessment. Given the heterogeneity in the design of patient-matched medical devices, the clinical evidence provided for such devices must demonstrate safety and clinical performance, and acceptability of benefit-risk profile, across the entire design

envelope (or that part of it covered by the intended purpose), in line with the usual requirements for non-PMD devices.

Example – defining the design envelope:

Deformational plagiocephaly is a very common craniofacial problem in babies, which results in a misshapen, flat or asymmetrical head shape. Patient-matched plagiocephaly helmets are a treatment option for this condition in infants as young as six months (and can be used up to 14 months of age).

Michael is an orthotist who manufacturers plagiocephaly helmets using an advanced digital scanning and 3D printing technology. Michael uses validated processes for the design and manufacture of plagiocephaly helmets for head circumference between 38cm and 49 cm. Patient anatomical features are captured via 3D digital scanning to an accuracy of 50 microns. A maximum timeframe of 2 weeks is set between scanning and intended start date for use of the helmet. During device use, further digital scans are to be obtained on at least a monthly basis to ensure the helmet is still appropriate.

Using a dedicated software, the 3D scans are used for digital reconstruction of the patient's cranium. The digitally reconstructed 3D cranium along with the treatment plan provided in the clinician's prescription is used for generating the final design of the helmet, which includes generic but scaled features to apply gradual pressure on the skull in order to achieve the end-state cranial profile. Michael has described all the design features including minimum and maximum helmet dimensions, pressure applied and contour limits.

The final design file is 3D printed using validated production equipment, processes and qualified raw materials. Post-production (cleaning, surface smoothing, finishing, and packaging) is also completed using equipment and processes within validated parameters.

Michael has also conducted a systematic review of the literature to establish the current standards of care for deformational plagiocephaly. Apart from lifestyle measures and higher risk surgical options, he determines that patient-matched helmet therapy is the established state of the art treatment for persistent deformity. Given this device is considered low risk, he decides to conduct a single-arm clinical investigation that will enrol a small number of patients and include helmets that span the entire 38-49cm range covered by the specified design envelope boundaries. The study outcomes will include changes in head shape (with the regular 3D scans) and side effects, such as adverse skin reactions, over a 6-month follow-up period (typical helmet duration of use).

Michael will provide the TGA with all the relevant information relating to the structural, material, manufacturing, clinical, performance and 3D printing parameters in order to clearly articulate the specified design envelope for plagiocephaly helmets. He will also provide evidence from the clinical investigation to establish safety and performance outcomes for this low risk device.

Generalisability of devices within the design envelope (external validity)

A suitably qualified clinical expert/s who has endorsed the CER should determine the extent to which clinical investigation data can be extrapolated to all potential device specifications within the design envelope. Justification of generalisability may involve the use of clinical data, bench testing and/or computer modelling. Each difference in the clinical, technical and biological characteristics between the trialled devices and the extent of the specified design envelope should be discussed, with appropriate assessment of how the differences may impact the safety and performance of the subject device. The clinical expert should comment on worst-case and common-use scenarios in regard to clinical risk(s) when determining the extent of extrapolation, noting that they are not necessarily mutually exclusive (it is possible for worst-case scenarios to also be common-use scenarios).

- **Worst-case scenario(s)**: identified devices with the highest risk features within the design envelope (more than one may exist for patient-matched medical devices within a specified design envelope).

  Lower risk devices may include a discussion from the clinical expert as to why a certain subtype is the worst-case scenario, whereas for higher risk devices, manufacturers should generally provide evidence for worst-case scenarios (with clinical data, bench testing and/or computer modelling).

- **Common-use scenario(s)**: identified devices within the design envelope with the most frequently used design parameters. When defining common-use scenario(s), it may be useful to consider anthropometric differences (e.g. sex, age, ethnicity), as common-use scenario(s) may vary between sub-populations.

Therefore, when compiling and reporting clinical data for a patient-matched medical device, attention should also be given to how the data support the performance and safety of worst-case and common-use scenarios within the design envelope. This may be achieved by reporting data specific to these scenarios, or by providing a robust justification as to why data from other scenarios can be extrapolated to these scenarios (see example below).

Example – generalisability of clinical evidence

Jane is the clinical expert evaluating a clinical evidence report for a 3D-printed patient-matched mandibular advancement splint, used to treat mild sleep apnoea.

In the CER, Jane discusses and critically analyses a clinical study of the device. Even though every patient in the study is treated with a unique patient-matched device, Jane provides a scientific rationale for why the results of the study are generalisable to every patient-matched device potentially produced within the specified design envelope, based on bench testing and/or computer modelling.

This includes a consideration of "worst-case" scenarios captured in the clinical study (the most vulnerable to adverse events and reduced performance) and "common-use" scenarios (the most common device design parameters based on common anatomy and pathology).

The TGA assessor accepts that generalisability has been established. Consequently, this clinical investigation provides support for the safety and performance of the subject device even though every patient receives a slightly different product.

Substantial equivalence

A manufacturer may use clinical data for a comparable medical device (either PMD or non-PMD) to support safety and clinical performance claims for the subject device. The extent to which such evidence may be acceptable will depend on how similar the devices are for relevant aspects, including the intended use and other clinical, technical, and biological characteristics, and manufacturing processes. Consideration should be given to how the differences may affect the safety or clinical performance of the subject device. Where claims of substantial equivalence are made with a device that is either a non-PMD or has a different design envelope, there should be a reasoned argument provided as to why the clinical evidence for the claimed equivalent device can be applied to the entire design envelope (or if this is not claimed, what subset of the design envelope the data is relevant to). This should include discussion of worst-case and common-use scenarios.

Whilst claims of substantial equivalence may be useful (in order to provide indirect clinical evidence for a subject device), in most circumstances this should only represent one component of a strategy to generate sufficient clinical evidence for PMDs. There remains a need for direct clinical evidence, commensurate with the risk of the device, to provide additional assurance that modifications do not affect device safety and/or performance. This is of particular importance when substantial equivalence claims involve a non-PMD device.

Example – substantial equivalence

Jane is the clinical expert evaluating a 3D-printed patient-matched mandibular advancement splint for treatment of mild sleep apnoea. She claims substantial equivalence to a similar patient-matched mandibular advancement splint produced by a different manufacturer.

In the CER, Jane describes all parameters of the design envelope for the subject device, including structural (e.g. minimum and maximum dimensions, attaching mechanism for the maxillary and mandibular components, dental alignment specifications), material, manufacturing, clinical environment, performance and 3D printing parameters (e.g. CT imaging requirements).

From a literature review she determines that mandibular advancement splints are the current standard of care for mild sleep apnoea and provides support for generalisability of devices made within the design envelope through the identification of worst-case and common-use scenarios (from the clinical literature).

She then compares all aspects of the specified design envelope with that of the comparable device and provides a critical analysis describing how any differences could impact the safety and/or performance of the subject device, citing published and original preclinical data.

The TGA assessor accepts that the subject device is substantially equivalent to the proposed comparable device.

The submitted CER contains a mixture of clinical evidence that relates to both the comparable device (indirect evidence) and the subject device (direct evidence), which when combined, is sufficient to support the safety and performance of the 3D-printed patient-matched mandibular advancement splint.

Clinical Investigation

A key challenge in the design of clinical investigation for PMDs, is that the PMD device intervention will be heterogeneous with regards to several of its parameters (compared to non-PMD studies where features such as materials, structure and dimensions are either constant or subject to minor variations). The comparability of subjects within the group receiving the subject device should be optimised through study design, and uncertainties addressed through critical analysis (as discussed in Part 1 of these guidelines).

Despite the uncertainties and limitations in clinical investigations for patient-matched medical devices, it is preferable to undertake a feasible clinical investigation and discuss the limitations (which can then be subject to a risk management framework), rather than seeking approval of devices with a lack of clinical data (which would likely mean non-compliance with the essential principles).

For high-risk devices and those based on technologies where there is little to no prior clinical experience, direct clinical evidence from the use of the patient-matched medical device in humans will generally be required to demonstrate conformity with Essential Principles in the pre-market application. When designing clinical investigation for such devices, consideration should be given to the:

- prevalence and incidence of clinical condition in the general population;
- availability of evidence relating to comparable devices for the same intended purpose;
- standard of care for the clinical condition (based on a literature review);
- availability of evidence relating to comparator devices for the same intended purpose;
- meaningful, measurable, patient-relevant clinical outcome(s);
- follow-up duration and study endpoints to allow for objective assessment of the claimed benefits;
- procedures for recording distinct design and manufacturing features of each device used in the investigation; and
- subgroup analyses of worst-case and common-use scenarios.

The clinical data from a clinical investigation should be collected in a way which permits subgroup analyses of the various parameters of the specified design envelope.

For high-risk devices, if a comparator medical device (PMD or non-PMD) exists for the same intended use, the clinical investigation should be designed on sound scientific principles and methodology, including an appropriate statistical plan, with the comparator device as a positive control. If a single-arm study is the appropriate design for a particular clinical condition or device use, data should be collected in a way that allows for objective comparison with the standard of care. If no treatment exists for the clinical condition, clinical investigation data should be collected in a way that allows for comparison with the natural clinical course of the condition and objective assessment of benefit-risk profile for the device. Clinical investigations should be conducted following relevant standards (ISO 14155) and/or applicable regulatory requirements.

Literature review

Similar to clinical investigations, a literature review will generally only provide appropriate clinical evidence to the extent that the studied devices investigate use over the breadth of the design envelope. Again, the external validity of the trialled devices should be compared to all potential device specifications, with use of both worst-case and common-use scenario analysis.

Post-market data

The TPLC approach is particularly important for PMDs and should be conducted to ensure ongoing acceptability of the residual risks and to identify any new or emerging risks. Manufacturers of patient-matched medical devices are generally expected to submit detailed post-market surveillance (PMS) plans, proportionate to the risk class and the type of device, as part of a pre-market application.

PMS plans should describe PMCF activities to proactively and systematically collect, categorise, and analyse data relevant to the performance and safety of the device periodically throughout its lifecycle. For each PMCF activity, details on the aims, methods of data collection and analyses (including rationales for their appropriateness) should be provided. Data should be collected in a way that allows for subgroup analyses of parameters in the specified design envelope (in particular, worst-case and common-use scenarios) and patient characteristics, to facilitate an objective assessment of claims made by the manufacturer regarding performance and safety.

Other clinical experience data

The systematic collection of other clinical experience data relevant to the PMD (for example, product and/or disease registries) can add to the evidence base. Development of high-quality registries for specific products is encouraged. Data collection should be designed to enhance quality and comparability with other sources of clinical experience data (such as data generated from clinical investigations) and include an explanation of the processes in place to safeguard data quality and integrity.

Ongoing collection and analysis of both post-market and other clinical experience data for a PMD may, over time, support widening of the design envelope.

Clinical evidence considerations for adaptable medical devices

Adaptable medical devices are mass-produced and intended to be assembled or adapted after supply, according to the manufacturer's instructions, to address anatomical and/or physiological features of a particular individual, or a pathological condition (for example devices such as craniofacial implants, dental implants and orthotics that are mass-produced, but adapted by a health professional at the point-of-care). The manufacturer of an adaptable medical device is generally required to supply the device with instructions for use and patient information leaflets (where applicable, e.g. for implantable or active implantable devices) that will ensure the final device complies with all relevant EPs after it has been assembled or adapted.

There should be clear articulation and consideration of the risks relating to usability and appropriateness of the instructions for use and patient information leaflets (where applicable) within the risk management report. A manufacturer of an adaptable medical device should always consider conducting a usability study (consistent with IEC 62366-1) to validate the instructions provided in the IFU for adaptation/assembly of the device.

Similar to patient-matched medical devices, due to heterogeneity in the final form of adaptable medical devices, there are challenges associated with meeting clinical evidence requirements when compared to other non-PMD devices, that should be considered when collecting and discussing clinical data. The principles regarding worst-case and common-use scenarios will generally be applicable to adaptable medical devices and should be considered and discussed. Clinical trials should be designed to consider these variables and allow for subgroup analysis. A well-reasoned and comprehensive risk analysis, including risks relating to parameters for device adaptation, potential device failure modes, and device usability should form the basis for generating the clinical evidence.

Clinical evidence may include data from a comparable device, but direct clinical evidence, particularly with regard to usability, should be provided for higher risk and more novel devices in most circumstances. The design of clinical investigations, including study objectives, use of a

comparator arm, and statistical considerations, should be such that it provides sufficient clinical data to address residual risks and aspects of clinical performance not addressed through the current state of the art for the condition being treated.

In the PMS plan, the manufacturer should include adequate details on PMCF activities to collect, categorise, and analyse the data on the performance and safety of such devices throughout the device lifecycle and update the clinical evidence periodically. Data from PMCF activities should be collected in a way that allows for subgroup analyses of parameters relating to device adaptation, for objective assessment of claims made by the manufacturer on the safety and clinical performance of the devices.

Example – Adaptable medical device

Louise is a dentist and clinical expert for a manufacturer of temporary stainless steel crowns that are used as an interim measure whilst patients await fitting of patient-matched dental crowns. One new device is a mass-produced stainless steel molar crown that comes in a range of sizes. Dentists are required to trim the edges with crown scissors and "crimp" the device with crimping pliers for the individual patient. The device is then cemented to the tooth.

The IFU contains detailed instructions for acceptable point-of-care manipulation of the subject device with respect to sizing. The greatest extent of trimming and crimping supported by the IFU are considered worst-case scenarios (justified through computer modelling).

Louise has conducted a state of the art literature review and from the literature is satisfied that temporary stainless steel and acrylic resin dental crowns are the accepted standard of care when patients are awaiting a more permanent, patient-matched crown.

The manufacturer has conducted detailed useability testing for the subject device with a sample of dentists. Subsequently a clinical investigation was conducted to investigate performance and safety outcomes when compared with another state of the art temporary stainless steel dental crown (with specific regard to worst-case scenarios). Outcomes included validated tools for dental function (performance) as well as adverse events (e.g. infection, migration, early extraction, pain).

Louise has provided a detailed risk management report to appropriately mitigate residual risks, especially those associated with the intended device modifications (trimming and crimping). The residual risks are clearly articulated in the instructions for use.

A detailed ongoing PMCF is planned which will continue to monitor residual risks throughout the device lifecycle.

The clinical evidence provided is considered sufficient to support the safety and performance of the subject device, and the temporary stainless steel molar crown is included on the ARTG.

Clinical evidence considerations for custom-made medical devices

Custom-made medical devices are for the sole use of a particular patient, or health professional (in the course of their practice), and are manufactured in accordance with particular design characteristics specified by a health professional in a written request to the manufacturer. The design characteristics for custom-made medical devices must be intended to address the anatomical and/or physiological features, or the pathological condition, of the intended recipient.

The requesting health professional must also have determined that the device is necessary to address the features or condition of the intended recipient because there is no kind of medical device included in the Australian Register of Therapeutic Goods (ARTG) to address those matters either wholly or to an appropriate level.

These devices are typically required when device specifications are outside the design envelope of a patient-matched medical device. An example is a knee-replacement system required for a rare anatomical variation for which there are no suitable non-PMDs, and which is also beyond the boundaries of specified design envelopes of existing patient-matched medical devices.

Custom-made medical devices are exempt from the requirement to be included in the ARTG, however they are not exempt from the requirement to comply with all applicable Essential Principles including EP 14. They are also not exempt from the need to follow clinical evaluation procedures in Part 8 of Schedule 3 of the MD Regulations.

While clinical evidence for a custom-made medical device may be limited due to the unique nature of the device, the manufacturer should consider the following factors:

- The reasons why a custom-made medical device was requested, including the determination by the requesting health professional that there is no kind of medical device available to address the condition of the intended recipient;
- The design inputs and outputs; and
- Pre-clinical and clinical data to support the claims on safety and clinical performance. *Whilst the presence of any preclinical and clinical data should be considered prior to the issue of a custom-made device, this data will be of particular importance to maintain in the post-market context.*

There should be clear articulation and consideration of risks relating to usability and appropriateness of the instructions for use and patient information leaflet (where applicable) within the risk management report. This is particularly important if the custom-made medical device is based on a non-PMD predicate and/or where a non-PMD version of the device is available.

Example – Custom-made medical devices

Michael, the orthotist that makes plagiocephaly helmets, receives a written request from a paediatrician for a helmet for an 8-month old infant with a head circumference of 50cm. This is outside the reference interval boundary for the specified design envelope, however, there are no devices included on the ARTG that could meet these specifications. A unique device is required to meet the anatomical characteristics of the individual patient and Michael considers the potential effects the larger size may have on the safety and performance of the subject device. Given the low assessed risk and the current clinical need, Michael agrees to make the custom-made medical device. Michael will keep detailed

records of the device specifications, clinical outcomes and adverse events associated with the device use.

Compiling the CER

The recommended approach to clinical evaluation and to compiling the CER (outlined earlier in Part 1 of the guidelines) and principles underpinning the TGA clinical assessment of devices apply to PMDs. The principles around hierarchy of evidence and quality of evidence based on study size and methodology set out in Part 1 are relevant to PMDs. A clinical evaluation should similarly be formed with reference to the manufacturer's risk management strategy.

There should be clear articulation and consideration of the risks relating to usability and appropriateness of the instructions for use and patient information leaflet (where applicable) within the risk management report.

Considerations for patient-matched medical devices

Clinical evaluation of patient-matched medical devices will centre around sufficiency of the clinical evidence to support safety and performance over the entire breadth of the design envelope. Therefore, the design envelope should be characterised in depth with particular reference to worst-case and common-use scenarios. Due to the heterogenous nature of PMDs, the risk management report, instructions for use and patient information leaflets (where applicable) will also be critical.

Considerations for adaptable medical devices

Similar to patient-matched medical devices, clinical evidence should support safety and performance of adaptable medical devices and include an evaluation of point-of-care assembly or modifications. Risk management report, instructions for use and patient information leaflets (where applicable) will carry additional emphasis in assurance for these devices.

Considerations for custom-made medical devices

Whilst custom-made devices are exempt from ARTG inclusion and therefore from pre-market submission of clinical evidence, they are still required to comply with the Essential Principles. Manufacturers must maintain records which include custom-made device specifications, clinical evidence and risk management reports as part of their quality management system. Additionally, custom-made medical devices have the same post-market surveillance requirements as other PMDs.

Defining clinical outcomes

PMDs are inherently a heterogenous group of devices that cover the spectrum of risk. The nature, type and range of clinical evidence that is expected will therefore reflect this spectrum, with greater scrutiny given by the TGA to higher classification devices and devices with novel features. Nevertheless, manufacturers should note the following points:

- Generalisability of PMDs (external validity) within clearly defined parameters will generally need to be established in order to correlate available clinical data to all PMD subtypes.
- Outcome measures used to substantiate safety and performance of a PMD should be the same patient-centred outcomes that define clinical treatment success for a particular condition (i.e. surrogate markers will not generally be sufficient). It is expected that these

outcomes be compared to existing standards of care (or the natural clinical course of the condition where no treatment exists).

- Risk management reports with appropriately detailed Instructions for Use and Patient Information Leaflets (where applicable) and ongoing post-market surveillance are critical to support clinical utility of such devices across their lifecycle.

In situations where uncertainty remains in relation to the acceptability of a strategy for generating clinical evidence, the manufacturer may consider engaging with the TGA for a pre-submission meeting to obtain general feedback.

Example – Premarket application for a subperiosteal mandibular implant

John is an oral surgeon and clinical expert evaluating a new 3D-printed patient-matched subperiosteal titanium mandibular implant that is intended to be used in the treatment of patients with an atrophic mandible (for whom endosseus dental implants are not suitable).

In the CER, John provides a detailed description of the specified design envelope that includes structural, material, manufacturing, performance, clinical environment, and 3D printing parameters. He has discussed how the above parameters relate to individual patient needs. Generalisability of clinical evidence for the subject device across the entire design envelope has been justified through the identification of worst-case and common-use scenarios (with the use of computer modelling and state of the art literature review, respectively).

John claims that the subject device is substantially equivalent to another patient-matched 3D-printed subperiosteal titanium mandibular implant. He compares the clinical, technical, and biological characteristics of the devices across the design envelopes. Clinical reasoning is provided to explain why minor differences are not expected to alter the performance and safety of the subject device (supported by computer modelling).

John discusses the clinical evidence that he has for the comparable device. The manufacturer of the comparable device conducted pre-market clinical investigations for worst-case and common-use scenarios and demonstrated that the comparable device has superior effectiveness for dental function when compared to bone reconstructive treatments used in the dental management of patients with an atrophic mandible (standard of care), and minimal adverse events. Post-market experience with the comparable device demonstrates very low complaint rates. John has provided indirect clinical evidence in support of the safety and performance of subject device within worst-case and common-use scenarios.

John has also conducted a short-term, single-arm clinical study using the subject device for a small sample of patients. Similar positive outcomes (dental function) have been described without any significant adverse events (e.g. pain, infection, explantation).

John has provided a detailed risk management report with appropriate risk mitigation and residual risks are clearly articulated in the instructions for use. He has also included a detailed plan for PMCF to provide ongoing evaluation of the subject device.

Based on the classified risk of the subject device, the TGA assessor accepts that the clinical evidence provided is sufficient to substantiate the safety and performance

of this patient-matched medical device across the specified design envelope. The subject device is included on the ARTG.

Part 3 - Requirements for specific device types

Part 3 provides guidance to assist industry and clinical researchers to understand the TGA's expectations in relation to clinical evidence for particular types of medical devices.

The guidance articulates the nature, type and/or range of evidence that the TGA considers, at a minimum, will generally facilitate an adequate assessment of the benefit-risk profile of the device to be determined, taking into account safety, performance and patient health outcomes. This assessment is part of the process by which the TGA considers compliance of kinds of medical devices against the EPs set out in Schedule 1 of the MD Regulations.

Specific device types currently covered are:

- IVDs
- Total and partial joint prostheses
- Cardiovascular devices to promote patency or functional flow
- Implantable pulse generator systems
- Heart valve replacements using a prosthetic valve
- Supportive Devices - Meshes, Patches and Tissue Adhesives

In vitro diagnostic (IVD) medical devices

In vitro diagnostic (IVD) medical devices (or IVDs) have their own classification system, and must comply with all the EPs, including EP 15 which relates specifically to IVDs.

The Clinical evidence guidelines supplement: In vitro diagnostic (IVD) medical devices provides specific guidance in relation to IVDs.

Total and partial joint prostheses

Joint prostheses include devices used in hip, knee, shoulder, ankle, elbow and wrist joint replacements. Joint replacement (also called arthroplasty) is a commonly performed orthopaedic operation with the objective of relieving pain and improving mobility.

This section outlines what is generally expected regarding appropriate clinical evidence to demonstrate that a joint prosthesis is safe and performs as intended through compliance with the applicable Essential Principles (EPs) of safety and performance in Schedule 1 of the MD Regulations. The section is intended to supplement the general recommendations outlined in other parts of these guidelines.

Note this section provides guidance for all joint prostheses including, but not limited to a 'joint replacement medical device' as defined in the MD Regulations.

Summary recommendations

Joint prostheses are complex medical devices that can be used in combination with other devices or components. Manufacturers are advised to list the common combinations and provide clinical data to support the safety and performance of the device for these nominated configurations. Joint prostheses pose a significant regulatory challenge because these devices need to have a long *in vivo* life without exposing the patient to unduly high risks of adverse events or undesirable effects. In summary, the following is recommended:

- Clinical data is in the form of DIRECT evidence (pertaining to the subject device/system only) or INDIRECT evidence (data pertaining to a substantially equivalent device/system).
- For clinical evidence based on an evaluation of comparable device data, manufacturers are advised to submit all relevant documents with a supporting justification by a clinical expert to:
  - establish substantial equivalence between the device and the nominated comparable device, and
  - confirm that any identified differences will not adversely affect safety and performance of the device.
- Manufacturers should provide details of the clinical context within which the clinical data were obtained. The clinical context of the data should be congruent with the indications for use.
- Provision of clinical data:
  - manufacturers who intend to conduct clinical trials should design trials to the highest practical NHMRC level of evidence and trials should be appropriate to inform on the safety and performance of the device for its intended purpose
  - it is recommended that the minimum period for patient follow-up for clinical trials is two years
  - the main clinical outcomes that determine safety and performance are 'time to first revision' and patient scores such as the Harris Hip Score:
    - for revision data, the manufacturers are advised to benchmark the device against devices of the same class and against a similar patient population as reported by an international joint registry (e.g. OA vs patients prone to dislocation vs trauma vs osteoporosis vs bone resection for tumour etc.)
    - for patient performance data, manufacturers are advised to define the anticipated improvement in patient scores post-surgery (ideally, these should be internationally recognised assessment tool(s) used to measure clinical success)
  - to assess the risk of delayed need for revision surgery (that is in vivo times greater than two years), the manufacturers should consider using surrogate markers that are predictive of prosthesis failure - alternatively, manufacturers may use post-market data if the device is approved and marketed in Australia or elsewhere.
- For guidance on the conduct of comprehensive literature reviews and on the compilation and presentation of clinical evidence, manufacturers are directed to the relevant sections in this document.

Defining joint prostheses

For the purposes of this guidance document a joint prosthesis is an implantable medical device, irrespective of its configuration, that is intended by the manufacturer to replace in full or in part a section of the joint.

Joint prostheses can consist of either monoblock or modular designs. There are practical advantages to modular designs as they allow tailoring of the prosthesis to the patient's anatomy. However, modular devices with multiple components are more complex and may have a different benefit-risk profile when compared with monoblock designs. Each combination is unique and may have its own associated benefit-risk profile that needs to be addressed by the manufacturer.

Limb-preserving devices may also include joint implants. These devices are designed for functional limb reconstructions for patients with significant bone loss usually around the knee and hip. Such bone loss can occur following treatment of malignant bone tumours, aggressive benign bone tumours, infection, multiple revised and failed joint replacements or massive trauma.

Clinical evidence

In Part 1 of these guidelines, the TGA has provided information regarding key definitions and concepts, clinical evidence requirements, sources of clinical data and clinical evaluation in relation to medical devices, which are also applicable to joint prostheses. It is acknowledged that the volume of clinical evidence available may vary between the types of devices under review. For instance, the evidence available for a revision joint replacement system may be limited compared to a primary joint replacement system, and this is considered during the assessment process.

Direct clinical evidence on the actual device is preferred. Otherwise, indirect clinical evidence on a comparable device may be used after substantial equivalence has been established through a comparison of the clinical, technical and biological characteristics as described in Comparable devices including substantially equivalent devices.

Substantial equivalence

A manufacturer may use clinical data from a comparable device to support the performance and safety of the subject device once substantial equivalence has been established. In addition to the guidance provided in Comparable devices including substantially equivalent devices, manufacturers should consider the following when presenting substantial equivalence claims for joint prostheses:

- The sub-classification of the subject device/system. For example:
  - A cemented device will generally not be considered substantially equivalent to an uncemented device given the widely accepted biological and technical differences in fixation mode.
  - A modular device will generally not be considered substantially equivalent to a monoblock device given that modularity introduces additional potential failure modes.
  - A revision device will generally not be considered substantially equivalent to a primary device given differences in clinical characteristics and outcomes, as well as key technical differences.
  - For knee systems, a posterior stabilised knee system will generally not be considered substantially equivalent to a cruciate retaining knee system given the widely accepted biomechanical differences resulting from the design principles of each system, which presents in the form of key technical differences.
- Biological/technical characteristics which should be considered include (but are not limited to) the material of the prostheses, coating, coating thickness, coating porosity, rigidity, fatigability, torsional strength, tensile strength, dimensions, geometry, weight, intended fixation methods, components to which the joint prosthesis may be paired and combinations which may be deployed. It is emphasised that large technical differences, or multiple small technical differences, can negatively impact a substantial equivalence claim.
- Side-by-side technical diagrams of the subject and comparable from multiple perspectives are encouraged as they facilitate the TGA's assessment of substantial equivalence.

- For applications that include multiple device components, substantial equivalence claims presented separately for each device component are preferred (for example, for a knee system application, three separate substantial equivalence claims comparing the femoral components, the tibial baseplates and the tibial inserts).

It is also important to clarify if any changes have been made to the device since the clinical data were gathered and, if so, to document the changes and to clarify the exact version of the device. Where the device and the predicate share a common design origin, particularly when the device is part of a modular system, the lineage of devices with the same intended purpose should be provided as well.

Clinical investigation(s)

Clinical investigations will generally be required for orthopaedic devices with novel features. The design of the clinical investigation(s) should be appropriate to generate valid measures of clinical performance and safety. The preferred design is a randomised controlled clinical trial and conditions should ideally represent those in clinical practice in Australia. The eligible patient groups should be clearly defined with exclusion/inclusion criteria.

Manufacturers are advised to justify the patient numbers recruited according to sound scientific reasoning through statistical power calculation. Some examples of Randomised Controlled Trials (RCTs) involving joint prostheses include the UK Knee Arthroplasty Trial (KAT)[5] and the A JOINTs Canada Project.[6]

The duration of the clinical investigation should be appropriate to the device and the patient population and medical conditions for which it is intended. Duration should always be justified, taking into account the time-frame of expected complications. Clinical trials must be independently audited at key stages throughout the trial to document that the integrity of the trial was maintained. Analysis of clinical events should be blinded and independently adjudicated wherever possible.

Additional resources regarding the design and conduct of clinical investigation(s) are available on the clinical trial pages of the TGA and FDA websites. These guides inform on appropriate numbers of patients to be recruited as well as the necessary patient follow-up for statistically significant and clinically meaningful results. Guidance on the recommended reporting requirements for clinical investigation reports is provided in Reporting standards for clinical investigations.

Literature review

A literature review involves the systematic identification, synthesis and analysis of all available published and unpublished literature, favourable and unfavourable on the device, or, if relying on indirect evidence, the comparable device to which substantial equivalence has been established as described in Comparable devices including substantially equivalent devices.

Data on the materials used to construct the prosthesis, its dimensions and geometry, the number and type of paired components for modular devices and the intended purpose will define the construction of search strategies as well as study selection. This ensures that the searches are comprehensive and the included studies are relevant to the device and/or comparable device. The selection of a comparable device should be made prior to performing the literature

[5] Murray DW, MacLennan GS, Breeman S et al. A randomised controlled trial of the clinical effectiveness and cost-effectiveness of different knee prostheses: the Knee Arthroplasty Trial (KAT). Health Technol Assess. 2014;18:1-235, vii-viii

[6] Litchfield RB, McKee MD, Balyk R et al. Cemented versus uncemented fixation of humeral components in total shoulder arthroplasty for osteoarthritis of the shoulder: a prospective, randomized, double-blind clinical trial-A JOINTs Canada Project. J Shoulder Elbow Surg. 2011;20:529-36.

selection, extraction of the clinical data and analysis of the pooled results. A full description of the device used in any given study or adequate information to identify the device (e.g. manufacturer name and model number) should be extractable from the study report. If this is not possible, the study should be excluded from the review. Manufacturers are referred to Literature review for further information.

Post-market data

Post-market data should be provided for the actual device or for the comparable device to which substantial equivalence has been established, refer to Post-market data.

It is particularly important to include the following:

- information about the regulatory status of the device (or comparable device if relying on this), including name under which the device is marketed in key jurisdictions such as Canada, USA and Japan, certificate number, date of issue, the exact wording of the intended purpose/approved indication and other relevant details such as MRI designation in other jurisdictions
- any regulatory action including withdrawals, recalls, including recalls for product correction (and the reason for these, such as IFU changes) cancellations or any other corrective actions occurring in the market in any jurisdiction as reported or required by regulatory bodies
- distribution numbers[7] of the device(s) including distribution by country and/or geographical region for every year since launch. It is acknowledged that this may not always be appropriate for high volume devices, those with several components and those which have been on the market for many years.
- number of years of use
- for every year since launch, the number of complaints, vigilance and monitoring reports and adverse events categorised by type and clinical outcome (e.g. death, serious harm, revision due to loosening, fracture, implant breakage, etc.)
- explanted joint prostheses returned to manufacturers should be accounted for with an explanation of failures and corrective measures.

Publicly available post-market data such as adverse event reporting on the FDA MAUDE database and the TGA IRIS should be provided including for devices from other manufacturers when demonstrating substantial equivalence with comparable devices.

For reports of adverse events, revisions and complaints to be a useful adjunct to other forms of clinical evidence, the manufacturer should make an active, concerted effort to collect the reports and to encourage users to report incidents. Experience shows that merely relying on spontaneous reports leads to underestimation of the incidence of problems and adverse events.

The post-market data should be critically evaluated by a competent clinical expert to enable an understanding of the safety and performance profile of the device in a 'real-world' setting.

Other clinical experience data (including registry data)

National joint registries have been established in Canada, Denmark, England and Wales, Finland, New Zealand, Norway, Romania, Scotland, Slovakia and Sweden as well as Australia. The quality of data extracted from joint registries may vary. This may be influenced, for example, by the structure of the registries.

[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6554112/

The AOANJRR is highly regarded amongst the international orthopaedic community. So is the UKNJR. These are bodies that collect a large variety of data including but not limited to 'cumulative revision rates (CRR)' or 'cumulative percent revision (CPR)' and 'patient reported outcomes measures (PROMs)'. Good quality registry data (inclusive of these types) is therefore considered a robust source of post-market data.

When utilising registry data, manufacturers are also encouraged to present the data alongside an in-built comparator (for example, the average revision rate across the device type).

Compiling the CER

The approach to clinical evaluation and compiling the CER outlined in Part 1 – General Requirements also applies to joint prostheses. In compiling the clinical evidence the manufacturers must ensure that a competent clinical expert critically evaluates all the clinical data from clinical investigation(s), literature review and/or post-market data and endorses the CER (evidenced by signature and date), when seeking to demonstrate that the clinical evidence is sufficient to comply with the applicable EPs and that the device is safe and performs as intended.

Supportive data and information

The following information on the device must also be provided:

- risk assessment and management document
- IFU, labelling, product manual, PIC/PILs, and all other documents supplied with the device. These must highlight the residual risks and ensure that they are appropriately communicated to the user.

Additional information should be provided as applicable. This may include (but is not limited to):

- additional specifications of the device(s)
- surgical technique guides
- the materials from which the device is made including chemical composition
- other devices that may be used in conjunction with the device
- any aspects of non-clinical testing results that inform the design of the clinical trial should be included in the supporting documents
- biocompatibility testing, bench testing and animal studies where applicable
- specific testing of any adjuvant medicinal components may be necessary especially if these are new chemical entities in the Australian context. This should cover interactions between the device and the medicine, pharmacodynamics and time-release profiles.

Measuring clinical success

Safety

For safety, the primary outcome measure is revision. It is acknowledged that some reoperations which are considered a revision in one registry are not considered a revision in another registry, therefore comparisons of implant performance using data from different registries have to be undertaken with caution. Typically revision is reported as the Cumulative Percent Revision (CPR) based on the time to the first revision. The Australian Orthopaedic Association National

Joint Replacement Registry (AOANJRR) provides annual reports on the performance of joint prostheses for hip, knee and shoulder and provides the CPR for joint prostheses.

The AOANJRR is a comprehensive database providing manufacturers with detailed revision data for devices that are available and used in Australia.

Manufacturers should demonstrate that CPRs for a device or comparable device, if used to substantiate the safety and performance of the device, are equal to or better than published CPRs for joint prostheses of the same class as defined by the AOANJRR or another international joint registry (such as the National Joint Registry [England and Wales]), within the first two years of implantation at a minimum.

If clinical investigations are conducted, it is recommended that the minimum patient follow-up is two years: this is based on the internationally accepted consensus of orthopaedic surgeons and editors of orthopaedic journals. The AOANJRR analysis methods can identify devices that are prone to early failure as indicated by a higher than expected CPR within the first two years of implantation. This supports the concept of the two year minimum patient follow-up in clinical trials. However, manufacturers should be aware that this is the minimum and will not capture information relating to the late failure of a prosthesis. In this situation, manufacturers can assist the clinical assessors by providing adjunct data from surrogate markers. The choice of markers and a justification that these are predictive of future prosthesis failure should be clinically justified.

To assess performance based on rates of revision the manufacturer should:

- identify the published early CPR as documented in the AOANJRR (or other national registries) for devices that are in the same class as the device
- determine whether the device or the comparable device is performing as expected for that class of device as compared to the reference CPR reported by an international joint registry
- document the reason for revision; reasons include, but are not limited to:
  - aseptic and septic loosening for hip, knee and shoulder prostheses
  - dislocation and fracture for hip and shoulder prostheses
  - postoperative alignment for hip and knee arthroplasty
  - wear/erosion for shoulder arthroplasty
- where appropriate provide adjunct data for surrogate markers that may assist in predicting late failure of the device. Examples of surrogate markers:
  - radiological findings e.g. radiolucent lines for hip and knee procedures
  - radiostereometric analysis (RSA) to determine early (within two years) migration of joint components. RSA may be a viable surrogate to identify prostheses that would require early revision due to aspect loosening
  - in the case of metal-on-metal devices, appropriate monitoring of metal ion concentrations in body fluids are a measure of metal exposure and may have merit as a surrogate marker of excessive wear.

Manufacturers, in selecting and reporting surrogate markers of safety, should provide a clinical justification for the selection and where possible should use validated measurement tools.

Performance

Performance related parameters reported in the peer reviewed literature for hip, knee and shoulder prostheses are provided in Table 7.

Clinical success is evaluated by patient-oriented assessment tools that determine functional outcomes. Functional scores provide an aggregate of patient reported domains (e.g. pain, need for support device) with an objective measure of joint motion (e.g. degree of flexion or abduction and alignment) and represent a clinically meaningful grading of joint performance. However, for joint arthroplasty, the short-term performance of a device may be dominated by procedure variables therefore sufficient time should lapse to isolate device specific improvements.

The recommended two year minimum patient follow-up is congruent with the reported time to a stable output for two validated patient scores (these being the Harris Hip Score (HHS) and the Short Form-36 Health Survey (SF 36)). These scores have the greatest change in the first six months post-surgery for patients that have received a unilateral primary total hip replacement and peak or plateau at 18 months and remain high for 5 years.

When documenting patient performance scores, it is recommended that manufacturers provide data with a minimum of two years follow-up post-surgery to reduce the risk of confounding due to procedure variables.

Ideally, manufacturers should define both a Minimum Clinically Important Difference (MCID) and the success margin that can be used to evaluate clinical success. Indicative MCIDs and the expected improvement in function score post-operatively, as well as standardised rating scores are provided for some but not all functional scores, refer to Table 8. When available, these values can inform the design of clinical trials and provide a minimum effect size to determine the necessary statistical power as well as the clinical interpretation of the data.

Summary of safety and performance data

Reported clinical outcomes of hip, knee and shoulder prostheses

Table 7: Summary of performance data extracted from systematic reviews and primary research reports on the safety and performance of hip, knee or shoulder arthroplasty

Performance parameter	Hip	Knee	Shoulder
Revision/reoperation (time to first revision and revision rates)	a	a	a

Performance parameter	Hip	Knee	Shoulder
Function scores	a Harris Hip Score (HHS)	a Hospital for Special Surgery Score (HSSS) Western Ontario and McMaster osteoarthritis index (WOMAC) Bristol Knee Score (BKS) Oxford Knee Score (OKS) Knee Society Score (KSS)	a Western Ontario osteoarthritis of the Shoulder (WOOS) Oxford Shoulder Score (OSS) American Shoulder and Elbow Surgeons Scale (ASESS) Constant score
Quality of Life (QoL) scores		a EuroQoL 5D SF12	a SF36
Minimum Clinical Important Difference (MCID) identified in collating evidence for this guidance report.	a HHS Oxford Hip Score (OHS) WOMAC EQ-5D SF 12	a OKS SF SF 12 WOMAC	a WOOS

Minimum clinically important differences (MCIDs)

If validated MCIDs are available, manufacturers should provide full documentation and justify their utility when assessing the safety of the device. Alternatively, meaningful MCIDs can be established using either an anchor-based or distribution-based approach. In this case, the manufacturer should provide details of the method and assumptions used in determining the MCIDs in the submission.

MCIDs can be used to establish the size of the trial that is necessary to allow statistical verification of clinically meaningful outcomes. These also provide a margin within which a joint prosthesis can be assessed to be as safe as and to perform as well as a currently available device(s).

Table 8: Example MCID and success margins for performance scores identified from systematic reviews and primary research reports on the safety and performance of hip, knee or shoulder arthroplasty

Score	Grading	Success margin post-surgery	Minimum Clinical important Difference (MCID)
Hip			
Harris Hip Score (HHS)	Scale 0 to100 poor <70 fair 70 to 79, good 80 to 89, excellent 90 to 100	> 20 points + radiographically stable implant + no additional femoral reconstruction	range: 7 to 10
Oxford Hip Score (OHS)	Scale 0 to 48 0 to 19 may indicate severe hip arthritis 20 to 29 may indicate moderate to severe hip arthritis 30 to 39 may indicate mild to moderate hip arthritis 40 to 48 may indicate satisfactory joint function	e.g. patients with a pre-surgery score of 0 to 19 and receiving a total hip replacement Absolute change at 6mo post-surgery 19 (95% CI 16.6 to 21.4)	range: 5 to 7
Western Ontario and McMaster Osteoarthritis Index (WOMAC)			8

Score	Grading	Success margin post-surgery	Minimum Clinical important Difference (MCID)
Knee			
Oxford Knee Score (OKS)	Scale 0 to 48 0 to 19 may indicate severe knee arthritis 20 to 29 may indicate moderate to severe knee arthritis 30 to 39 may indicate mild to moderate knee arthritis 40 to 48 may indicate satisfactory joint function	e.g. patients with a pre-surgery score of 0 to 19 and receiving a total knee replacement (39) Absolute change at 6mo post-surgery 14 (95% CI 12.7 to 15.3)	5 [95% CI 4.4 to 5.5]
Western Ontario and McMaster Osteoarthritis index (WOMAC)			for TKR: ~15
Shoulder			
Western Ontario Osteoarthritis of the Shoulder Index (WOOS)			Primary Shoulder replacement: ~ 10%
Constant Shoulder Score	Ratings; >30 poor 21 to 30 fair 11 to 20 good <11 excellent		
Quality of life			
EQ 5D			Hip: 0.074
SF12			4.5 [95% CI 3.9 to 5.2]
SF36			Multiple MCIDs for specific SF 36 domains

Post Market Surveillance of Joint Prostheses

Post market surveillance aims to ensure that compliance with the Essential Principles (EPs) as required by the *Therapeutic Goods Act 1989* is ongoing throughout the lifecycle of a medical device, and to identify any issues that require investigation. The EPs of particular relevance to the clinical assessment are 1, 2, 3, 4, 6 and 14.

However, it should be noted that although a device may have demonstrated compliance with the EPs at the time of premarket assessment, this can change over time, for example, due to the emergence of new safety concerns. If it appears that the benefit risk balance of a device has become unfavourable, the TGA may take action to mitigate the risk to public health.

One source of data the TGA utilises to conduct routine post market surveillance of ARTG-included joint prostheses is the AOANJRR Annual Report.

The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) is a government-funded organisation that collects data on joint replacement (hip, knee and shoulder) and revision procedures performed in Australia. Specifically, the AOANJRR has collected data on 98 to 100% of hip and knee joint replacement procedures performed in Australia since 2003.[8] The information that is collected for the primary joint replacement procedure includes, but is not limited to, de-identified baseline patient demographics, the name and brand of the device implanted, method of prosthesis fixation, surgical technique, the indication for the joint replacement and the date and location of the procedure. When a revision occurs, the same information is collected.

The Registry collates and analyses this data using statistical methods to produce an estimate of the revision rate for each individual prosthesis, enabling comparison between different prostheses to occur. The revision rate is currently the key performance and safety indicator for joint prostheses. The Registry publishes an Annual Report in October that contains detailed information about revision rates and reasons for revision, and also identifies prostheses with a "Higher Than Anticipated Revision Rate".

The TGA utilises this information, in conjunction with other sources of data, for example, post market surveillance data collected by companies and published literature, to monitor the real-world performance and safety of joint prostheses. In addition to the publicly available information from the AOANJRR, the TGA (like manufacturers, hospitals and researchers) can request additional analyses from the AOANJRR where required as part of routine post market surveillance of individual joint prostheses.

Outcomes from post market surveillance may indicate the need for intervention to mitigate the increased risk of revision with a particular prosthesis. There are a number of possible actions that can be initiated by a sponsor or required by the TGA . These include, but are not limited to:

- cancellation from the ARTG
- A product recall
- Product Defect Correction
- Hazard Alert

The Recalls page on the TGA website[9] contains further information about the types and levels of recall and non-recall actions.

[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6554112/
[9] https://www.tga.gov.au/recalls

Below are some hypothetical illustrative examples of the post market surveillance process for joint prostheses, facilitated by the analysis of registry data:

Example 1:

Company A makes a total knee joint replacement 'ABC' that was identified by the AOANJRR as having a higher than anticipated revision rate. . An investigation by the TGA and Company A determined that the revision rate was higher when the patella was not being resurfaced at the time of primary procedure. The revision rate when the patella was resurfaced was within normal limits. The company, in conjunction with the TGA recalls section, issued a Hazard Alert to remind surgeons to resurface the patella at the time of primary procedure to mitigate the risk of revision.

Example 2:

Company X makes a femoral stem 'G' and a compatible acetabular cup 'H'. Company Y makes a femoral stem 'E' and a compatible acetabular cup 'R'. The AOANJRR identified the combination of stem G with cup R as having a higher than anticipated revision rate. A joint investigation by the TGA and Companies X and Y determined that neither company condoned the use of their femoral stem/acetabular cup with those manufactured by different companies. The revision rates of femoral stem G and acetabular cup R were observed to be within normal limits when used appropriately with the same company's respective components. The TGA issued a Medical Device Safety Update that was also distributed to specialty colleges to remind surgeons to avoid combining femoral stem G with acetabular cup R.

Example 3:

Company X , Company Y, Company Z all manufacture a certain type of patellar resurfacing device. The indications for using the device in question have been very broad, covering both primary and revision surgery. An end user has flagged concerns to the TGA regarding the medium to long term performance of this class of device. The 5 to 15 yr CRRs are between 2 to 3 times that of the rest of the class. The TGA contacts the AOANJRR and requests all data pertaining to these devices. Analysis of medium to long term data demonstrated significantly elevated CRRs for these devices compared to the rest of the class. The TGA contacts the manufacturers involved. The manufacturer is asked to withdraw the devices in question or to refine the intended use to very specific clinical indications.

Patient Reported Outcome Measures (PROMs) are expected to become increasingly relevant as a performance and safety indicator, in addition to revision rates. A patient reported outcome is defined as any report of a patient's health status that comes directly from the patient without interpretation by others.[10] PROMs evaluate the patient's perspective in terms of pain, function, health-related quality of life and complications. In this capacity, PROMs may represent a means of identifying patients with joint replacements who have not proceeded to a revision surgery, however have not obtained any benefit in terms of improvement in pain and function.

[10] https://aoanjrr.sahmri.com/documents/10180/681914/AOANJRR+PROMs+Pilot+Final+Report

Cardiovascular devices to promote patency or functional flow

This section provides an overview of the clinical evidence that can be used to establish the safety and performance of cardiovascular (CV) devices to promote patency or functional flow ('CV flow implants').

It provides information on:

- the minimum levels of evidence that are appropriate and useful in assessing the safety and performance of CV flow implants
- the minimum clinical outcomes that define clinical success and demonstrate that a CV flow implant performs as intended.

Summary recommendations

- The CV flow implants discussed here, namely arterial stents-carotid, coronary and peripheral, implants for abdominal aortic aneurysms (AAA) repair, implants for patent ductus arteriosus (PDA) repair, and inferior vena cava (IVC) filters to prevent pulmonary embolism (PE) are complex medical devices that may be used in combination with other devices or components. Manufacturers are advised to list the likely combinations and provide clinical evidence to support the safety and performance of the new device(s) for these nominated configurations.
- For submissions reliant on comparable device data, manufacturers are advised to submit all relevant documents with a supporting justification by a clinical expert to:
  - establish substantial equivalence between the device and the nominated comparable device, and
  - confirm that any identified differences will not adversely affect safety and performance of the device.
- Manufacturers should provide details of the clinical context within which the clinical data were obtained. The clinical context of the evidence base should be congruent with the indication(s) for use.
  - Patient details are critical when comparing pre- and post-market data. Patient selection may differ in these scenarios and result in patients of different risk profiles for failure or adverse events. Risk of such bias should be identified and addressed in the CER.
- Provision of clinical data
  - Manufacturers who intend to conduct clinical trials should design trials to the highest practical NHMRC Level of Evidence. Trials should be appropriate to inform on the safety and performance of the device for its intended purpose
  - Use of the acute (< 48h), sub-acute (< 30days), late (< 1year) or very late (> 1 year) timeline should be considered. However, for temporary devices the timeline should be congruent with the in vivo dwell time
  - The main clinical outcomes that determine safety and performance of CV flow implants vary significantly by device type; for example, (a) a common primary outcome measure for carotid stent studies is a composite of death or stroke (or death, stroke or myocardial infarct (MI)); (b) a common primary outcome measure for coronary stents is target lesion revascularisation (TLR) and/or total vessel revascularisation (TVR); and (c) common primary outcome measures for IVC filters are PE (fatal and non-fatal),

deep vein thrombosis (DVT) and occurrence of a venous thromboembolism (VTE) distal to the filter.

  - It is advised that a clinical justification is provided to support the selection of the primary outcomes and if necessary the use of secondary outcomes or surrogate markers
  - The manufacturer is advised to benchmark the device against devices of the same class as reported in appropriate registers (if available) or provide direct comparative data with a comparable device
  - For patient performance data, manufacturers are advised to define the anticipated improvement in patient scores post-surgery. Ideally, these should be internationally recognised assessment tool(s) used to measure clinical success, e.g. QoL or exercise stress test

- The manufacturers should consider using surrogate markers that are predictive of implant failure when in vivo times are longer than one year. For example, use of endoleak type II with aneurysm expansion to predict late failure of AAA. However, a clinical justification is needed to support the selection of surrogates and the predicative power of surrogates should be validated
- It is recommended that the manufacturer supply post-market data if the device is approved and marketed in another jurisdiction to demonstrate long-term safety and performance outcomes
- When submitting a comprehensive literature review, full details of the search method used should be included in the CER with detail sufficient to enable the review process to be repeated by clinical assessors
- Risks identified in the clinical data should be appropriately mitigated and/or included in the IFU and other information supplied with the device.

- Compilation of the CER
  - in compiling the clinical evidence for a supportive device the manufacturer must ensure that an appropriate clinical expert, that is, someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting, critically evaluates all the clinical data that informs on the safety and performance of the device
  - the clinical expert must then endorse the CER (evidenced by signature and date) containing the clinical evidence to demonstrate that the evidence meets the requirements of the applicable EPs and the device is safe and performs as intended.

Defining CV flow implants

The guidance in this section applies to the following CV flow implants:

- Arterial stents (carotid, coronary and peripheral)
- Implants for abdominal aortic aneurysms (AAA) repair
- Implants for patent ductus arteriosus (PDA) repair
- Inferior vena cava (IVC) filters to prevent pulmonary embolism

Arterial stents-carotid, coronary and peripheral

Arterial stents are metal mesh devices used to correct the pathological narrowing of an artery and to maintain patency e.g., in the neck, heart or vessels of the leg. The aim of a stent is to act as a scaffold to keep the artery open to maintain blood flow and prevent re-stenosis. Using an endovascular approach, a fine wire is inserted into the femoral artery (or other suitable vessel) and passed through the blood vessels into the artery with the blockage. The stent is passed along the wire, often after pre-dilation of the narrowing using a balloon catheter. Stents come in varying diameters, lengths, and shapes and may be self-expandable. They may be “bare metal” (without any coating, often made of stainless steel or cobalt chromium alloy) or “drug eluting” (coated with a drug such as sirolimus or paclitaxel to help prevent restenosis).

Implants for abdominal aortic aneurysm (AAA) repair

While open surgical repair remains the treatment of choice for abdominal aortic repair endovascular repair is becoming more frequently used. AAA grafts have been developed by a number of manufacturers and are generally woven polyester, some with a nitinol exoskeleton. These come in different shapes such as straight, bifurcated and fenestrated devices with various inbuilt systems to attach the device to the patient’s aorta.

Implants for patent ductus arteriosus (PDA) repair

Minimally-invasive transcatheter closure of PDAs has become the preferred method of treatment for children beyond the neonatal period, versus surgical closure with ligation or division of the ductus arteriosus through a thoracotomy incision. PDA implants have been developed by a number of manufacturers with treatment choice based on the size of the PDA, e.g. stainless steel coils which may be used for small PDAs; devices such as a self-expanding device made of nitinol wire mesh and polyester for larger PDAs.

Inferior vena cava (IVC) filters

IVC filters are intended to prevent pulmonary embolism. The filters are metal alloy devices, generally in an umbrella shape, that are inserted into the inferior vena cava in order to mechanically trap fragmented clots from the deep leg veins to prevent their movement to the pulmonary circulation. Filters are designed to be introduced percutaneously. The latest generation of filters are temporary or ’retrievable’ and are designed to be removed 2 to 12 weeks after insertion (as specified by the manufacturer) if their use is no longer required.

Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device and/or comparable device. The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data.

It is important to clarify if any changes have been made to the device since the clinical data were gathered and if so to document the changes and to clarify the exact version of the device. Direct

clinical evidence on the actual device is preferred. Otherwise indirect clinical evidence may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in Comparable devices including substantially equivalent devices.

Where the device and the predicate share any common design origin, the lineage between the devices should be provided as well as a list of other devices that may be used in conjunction with the new device for example the delivery system, such as the catheter system for stents, including any balloons. Manufacturers should refer to Clinical evidence requirements for more information.

Clinical investigation(s)

The design of the clinical investigation should be appropriate to generate valid measures of clinical performance and safety. The preferred design is a randomised controlled clinical trial and conditions should ideally represent clinical practice in Australia. All device characteristics and the intended purpose(s) must be specified when designing clinical investigations including for devices using data from a comparable device as these will determine the criteria for a full and reasoned clinical justification for the selection. The eligible patient groups should be clearly defined with exclusion/inclusion criteria. Manufacturers are advised to justify the number of patients recruited according to sound scientific reasoning through statistical power calculation.

The duration of the clinical investigation should be appropriate to the device and the patient population and medical conditions for which it is intended to be used. Duration should always be justified, taking into account the timeframe of expected complications. CV flow implants must have long in vivo lives without exposing recipients to unduly high risks. Medication which may affect outcomes, for example anticoagulant treatment must be taken into account when determining all endpoints. Analysis of clinical events should be blinded and independently adjudicated wherever possible.

Literature review

A literature review involves the systematic identification, synthesis and analysis of all available published and unpublished literature, favourable and unfavourable, on the device, or, if relying on indirect evidence, comparable device to which substantial equivalence has been established as described in Comparable devices including substantially equivalent devices.

Data on the materials used to construct the device, its dimensions and geometry, the components with which it will be used and the intended purpose will define the construction of search strategies as well as study selection. This ensures that the searches are comprehensive and the included studies are relevant to the device and/or comparable device. The selection of a comparable device should be made prior to performing the literature selection, extraction of the clinical data and analysis of the pooled results. A full description of the device used in any given study must be extractable from the study report or adequate information to identify the device (e.g. manufacturer name and model number). If this is not possible, the study should be excluded from the review.

Literature review describes the process of performing a literature review, summarised briefly below. As a minimum a literature review should include:

- a search protocol: determined prior to implementing the search, that details the aim, search terms, planned steps, inclusion and exclusion criteria
- selection strategy: the citations should be assessed against clearly defined selection criteria documenting the results of each search step with clear detail of how each citation did or did not fit the selection criteria for inclusion in the review.
- a review and critical analysis: the selected literature should be synthesised and critiqued

- a literature report: a report should be prepared which must be critically evaluated and endorsed (evidenced by signature and date) by a competent clinical expert, containing a critical appraisal of the compilation.

It is important that the published literature is able to establish the clinical performance and safety of the device, and demonstrate a favourable benefit-risk profile.

Post-market data

Post-market data can be provided for the actual device or for a comparable device, refer to Clinical evidence requirements. It is particularly important to include the following:

- information about the regulatory status of the device (or comparable device if relying on this), including the certificate number, date of issue and name under which the device is marketed, the exact wording of the intended purpose/approved indication(s) and other details such as MRI status in other jurisdictions
- any regulatory action including CE mark withdrawals, recalls, including recalls for product correction, suspensions, removals, cancellations, voluntary recalls in any jurisdiction (and the reason for these i.e. IFU changes) or other corrective actions occurring in the market as reported to or required by regulatory bodies
- distribution numbers of the device(s) including distribution by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- the number of years of use
- for every year since launch, the number of complaints, vigilance and monitoring reports and adverse events categorised by type and clinical outcome
- explanted devices returned to manufacturers should be accounted for with an explanation of device failures and corrective measures.

For further details refer to Post-market data. Publicly available post-market data such as adverse event reporting on the FDA MAUDE database and the TGA IRIS should be provided for all devices including those from other manufacturers. The manufacturers should include post-market surveillance data from national jurisdictions where the device is approved for clinical use.

For reports of adverse events and complaints and restenosis, for example, to be a useful adjunct to other forms of clinical evidence, the manufacturer should make an active, concerted effort to collect the reports and to encourage users to report incidents. Experience shows that merely relying on spontaneous reports leads to underestimation of the incidence of problems and adverse events.

The post-market data should be critically evaluated by a competent clinical expert to enable an understanding of the safety and performance profile of the device(s) in a 'real-world' setting.

Compiling the CER

Clinical outcomes to define the safety and performance of the CV flow devices were identified from clinical studies published in the peer reviewed literature. In compiling the clinical evidence the manufacturer should ensure that a clinical expert in the relevant field critically evaluates all the clinical data from clinical investigation(s), literature review and/or post-market data (clinical experience) and endorses the CER (evidenced by signature and date), to demonstrate that the clinical evidence is sufficient to comply with the applicable EPs and that the device is safe and performs as intended.

Previous sections outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a CER. These guidance documents apply whether the manufacturer is using direct clinical evidence or relying on indirect clinical evidence from a comparable device. Guidance on defining a comparable device is provided in Comparable devices including substantially equivalent devices.

As per The Clinical Evaluation Report the CER should include the following:

a) General details

b) Description of the medical device and its intended application

c) Intended therapeutic and/or diagnostic indications and claims

d) Context of the evaluation and choice of clinical data types

e) Summary of relevant pre-clinical data

f) Discussion regarding comparable devices including substantially equivalent devices

g) Summary of the clinical data and appraisal

h) Data analysis

i) Conclusions

j) Name, signature and curriculum vitae of clinical expert and date of report

Supportive data and information

The following information on the device must also be provided:

- risk assessment and management document
- IFU, labelling, product manual and all other documents supplied with the device. These must highlight the risks and ensure that they are appropriately communicated to user.

Additional information should be provided as applicable. This may include (but is not limited to):

- additional specifications of the device(s)
- the materials from which the device is made including chemical composition
- other devices that may be used in conjunction with the device
- any aspects of non-clinical testing results that inform the design of the clinical trial should be included in the supporting documents
- biocompatibility testing, bench testing and animal studies where applicable
- specific testing of any adjuvant medicinal components may be required especially if these are new chemical entities in the Australian context. This should cover interactions between the device and the medicine, pharmacodynamics and time-release profiles.
- any further details of post-market data

When relying on a comparable device for CV flow implants with the same intended purpose, a comparison of the technical and physical characteristics of the device and comparable device should be demonstrated through direct testing in order to establish substantial equivalence.

- the technical characteristics of the device include, but are not limited to; the material of the implant including chemical composition; dimensions; geometry; weight; coating; mechanical properties such as tensile strength; integrity including fatigue testing; biocompatibility and behaviour and effects and appearance of the device with magnetic resonance imaging
- the technical characteristics of required delivery systems such as the delivery systems for stents (including balloons). In such cases, sample specifications would cover, for example: diameter and profile; bonding pressure at bonded junctions; maximum pressure for balloons; balloon inflation and deflation times; and stent diameter versus balloon inflation pressure
- a supporting justification by a clinical expert is required to establish substantial equivalence between the device and the comparable device, and confirm that any identified differences in the technical and physical characteristics will not adversely affect safety and performance of the device
- the use of more than one comparable device is discouraged; however, these may be used if each is a valid comparable device and each is found to be substantially equivalent to the new device under consideration
- a clinical justification should be presented as to why direct clinical data are either not required, or only partially required.

The comparable device must have clinical data to support its safety and performance and all supporting data must be provided with the CER. As time since first approval lengthens comparable device data becomes less relevant and should be replaced by data derived from clinical experience with the device.

Defining clinical success

For the selected CV flow devices, the literature did not generally separate outcomes into those related to safety and those related to performance. For that reason, all outcomes are reported together here, separated into the four types of flow devices. Outcomes were often a mix of final outcomes such as MI, stroke and death, and surrogate outcomes such as restenosis, TVR and clinical improvement.

Arterial stents

Table 9 (below) provides a summary of the clinical outcomes used to assess safety and performance of coronary, carotid and peripheral stents as reported in clinical trials included in the identified systematic reviews. These data are indicative of outcome measures commonly reported for these three devices but should not be considered exhaustive.

Table 9: Clinical outcomes for three classes of arterial stents reported in the clinical trials included in the systematic review evidence base

Outcomes reported in studies	Carotid*	Coronary	Peripheral
Composite of death or stroke **OR** death or stroke or MI	a (1* outcome)	a **	
TVR and/or TLR		a (1* outcome)	a (TLR)
Restenosis	a	a	a
Stroke (disabling / major)	a		
TIA	a		
MI	a	a (recurrent)	
Facial neuropathy / cranial nerve palsy	a		
Death	a	a	a
Stent thrombosis (definite or probable; also early or late)		a	
MACE		a	
Technical / procedural success		a	a
Vessel patency assessed via duplex US and/or angiography			a
Reintervention			a
Amputation			a
Clinical improvement as per the Rutherford Scale			a
Hemodynamic improvement			a

Outcomes reported in studies	Carotid*	Coronary	Peripheral
Length of follow-up in included SRs	1 month to 4 years (one to 11 years) The CREST study[109]: Baseline (pre-procedure) then 18 & 54h post-procedure then 1, 6 and 12 months then annually thereafter	6 months to 6 years (most 3-5 or 6 years) Late events up to 1 year but longer timelines may be required**	6 months to 2 or 3 years (one to 8 years)

KEY: MI=myocardial infarction, TLR=target lesion revascularisation, TVR=total vessel revascularisation, TIA=transient ischemic attack, MACE= major adverse cardiac events, US=ultrasound, SR=systematic review
* Outcomes were often divided into <30 day (peri-procedural) or >30 day outcomes
** Outcomes defined in the European Commission MEDDEV 2.7/1 and Academic Research Consortium

Coronary stents

Outcomes were often divided into <30 day (peri-procedural) or >30 day outcomes. Adverse events within the peri-procedural periods may be related to the procedure while those occurring after 30 days are more likely to represent device-related events. Adverse events for coronary stents and the timing of these may be described differently in the literature. Manufacturers are advised to use standardised definitions for clinical endpoints for coronary stents as defined by the Academic Research Consortium (ARC), in 2007. The ARC nominated clinical outcomes have been adopted by the European Commission in their guidance MEDDEV 2.7/1. These include, but are not limited to, outcomes listed in Table 9 (above). The MEDDEV 2.7/1 and ARC also address criteria for collecting clinical data and the use of composite clinical outcomes. These include:

- Composite adverse events divided into device–oriented (cardiac death, MI, TLR) and patient-oriented (all-cause mortality, any MI, any repeat revascularisation)
- Composite acronyms such as MACE (major adverse cardiac events) should be used with caution because of the varied definitions of MACE used clinically and in research
- If MACE is the nominated clinical endpoint, manufacturers are advised to provide a clear definition with clinical justification for the elements included in this composite measure.

Manufacturers should also provide evidence of clinical device success. Typically this will include the successful delivery and deployment of the device, removal of the stent delivery system and final residual stenosis of <50% of the target lesion as assessed by Quantitative Coronary Angiography. Clinical procedural success includes the previous measures associated with stent deployment and stenosis reduction with the additional parameter that there are no ischemia driven adverse events to a maximum of seven days post procedure.

Patient follow-up should be reported for acute (0 – 2 hours), sub-acute (> 24 hours to 30 days), late (> 30 days to 1 year) and very late (> 1 year) events. This timeline is in line with reported patient follow-up times in the peer-reviewed literature (Table 9 & 11).

Carotid stents

Outcomes were divided into <30 day (peri-procedural) or >30 day outcomes, with the main primary outcomes being a composite of meaningful endpoints such as:

- death or stroke or MI
- secondary outcomes included a mix of surrogate and final outcomes such as restenosis, stroke, disabling/major stroke, transient ischemic attack (TIA), MI, facial neuropathy/cranial nerve palsy, and death

> Manufacturers are advised to use a validated stroke assessment tool e.g. the National Institute of Health Stroke Scale to evaluate patients pre- and post-procedure.

Across the research literature the rates at which adverse events occur are highly variable. The diversity is due to differences in patient groups (symptomatic vs. asymptomatic), operator experience and technique, medical management goals and the primary study endpoints.

All will affect the rate at which adverse events occur and whether these rates may be considered clinically acceptable for a given patient cohort.

Examples of indicative rates for death, stroke and MI events are reported for the CREST clinical trial.[109] These are reported as % ± SD:

- Peri-procedure (< 30days)
  - Death; 0.7% ± 0.2
  - Stroke (any) ; 4.1% ± 0.6
  - MI; 1.1 ± 0.3
- After 4 years including peri-procedural period
  - Death; 11.3% ± 1.2
  - Stroke (any) ; 10.2% ± 1.1

However manufacturers are advised to provide a clinical justification of the event rates deemed to be acceptable for the target patient population in which the carotid stent is to be used.

Procedural success requires a successful deployment of stent and withdrawal of delivery system with a < 30% residual stenosis.

Similar to coronary stents, patient follow-up should be reported for acute, sub-acute, late and very late time points as indicated. This timeline is in line with patient follow-up reported in the studies included in the systematic reviews examined for this report and ranged from 1 month to at least 4 years with one study extending to 11 years.

Peripheral stents

Peripheral stents are used for the treatment of peripheral artery disease (PAD). Outcomes included a mix of surrogate and final outcomes including:

- Technical success, vessel patency assessed via duplex ultrasound and/or angiography, TLR, restenosis, reintervention, amputation, clinical improvement as per the Rutherford Scale, hemodynamic improvement, and death (Table 9, 10 & 11).

Examples of safety and performance values for some parameters include, but are not limited to, the following:

- Primary success of 95% with a 5% restenosis at 1 year has been report for nitinol stents. However, restenosis rates at 1 year range from 5% to 25%, depending on lesion length and location;
- For patients included in the Excellence in Peripheral Arterial Disease (XLPAD) registry for the treatment of symptomatic infrainguinal PAD adverse events at 1 year follow-up include:
  - Amputation of target limb; 4.6%
  - MI; 1.9%
  - Target vessel thrombosis; 4.1%
  - Need for surgical revasculisation; 5.9%
- Technical success has been report to be greater than 95%
- Given the physical dimensions of this class of stent, stent fracture may occur at rates in excess of 30% of treated legs.115 Stent fracture significantly impacts primary patency rates and manufacturers are advised to report these rates
- Patency at 1 and 3 years are reported to be 69 to 79% and 59 to 70% respectively.

Generalised safety and performance values cannot be provided because of the heterogeneity in lesion anatomy and location, stent size, materials and associated stent technologies. Therefore manufacturers are advised to:

- define the patient cohort and provide a clinical justification for selected safety and performance parameters
- define the lesion anatomy according to a recognised classification system e.g. TransAtlantic Inter-Society Consensus.

Follow-up in the studies included in the systematic reviews examined for this report ranged from 6 months to 2 or 3 years with one study extending to 8 years. These are in line with patient follow-up based on the acute (< 48h), sub-acute (< 30days), late (< 1year) or very late (> 1 year) timeline.

Implants for AAA repair

Much of the evidence focussed on adverse events (AEs) and post-operative complications, as well as mortality (30-day, aneurysm-related and all-cause) - Table 11. Additional outcomes were a mix of surrogate and final outcomes and include:

- Reintervention rates (including conversion from endovascular aneurysm repair [EVAR] to an open procedure), MI, stroke, renal failure and aortic rupture
- Secondary outcomes focussed on practical and logistical issues such as procedure time, blood loss, fluoroscopy time, contrast load, recovery time, need for blood transfusion, days in an intensive care unit (ICU) and length of hospital stay (LOHS).

Clinical success is defined by a consideration of both clinical and radiological criteria and standards. These include:

- Deployment of the device at the intended location without death as a result of the intervention.
- Absence of Type I and Type III endoleaks.

- Aneurysm expansion of ≤ 5mm in diameter or ≤ 5% volume.
- Absence of aneurysm rupture or need to convert to open surgery.

In contrast clinical failure is defined as:

- Graft dilation of > 20% in diameter or persistent increase in aneurysm size.
- Graft migration or failure of device to integrate.
- Type II endoleak with an aneurysm expansion.

Manufacturers should specify the time period for clinical success. Life table or Kaplan Meier estimates should not have standard deviations of greater than 10%.

Any changes in lesion anatomy during follow-up should be referenced to measures taken immediately post-procedure.

Technical success is defined as the successful deployment and removal of the delivery device without the need for surgical conversion or mortality. Chaikof *et al* further qualified technical success to include:

- Access to arterial system using a remote site (e.g. femoral artery) with or without a permanent conduit to access the site
- Deployment of endoluminal graft with secure proximal and distal fixation
- Absence of type I or type III endoleak
- Patent endoluminal graft without twists, kinks, or obstruction (> 30% stenosis or pressure gradient of > 10 mmHg).
- The need for additional modular components, stents and adjunctive surgical procedures should be reported.

Follow-up in the studies included in the systematic reviews examined for this report ranged from 30 days (peri-procedural) to 9 years. Again these are in line with patient follow-up based on the acute (< 48h), sub-acute (< 30days), late (< 1year) or very late (> 1 year) timeline.

Implants for PDA repair

Outcomes of primary interest were adverse events and the surrogate outcomes of primary success, residual shunt and need for blood transfusion. Manufacturers need to provide clear patient characteristics and lesion anatomy. Clinical evidence should be provided for all lesion types that are included in the indication(s) for use of the implant. The diversity of lesion size and heterogeneity of currently marketed devices for PDA repair limits the generation of generalised safety and performance values. Manufacturers are advised to provide a justification for the selected clinical outcomes and values that define clinical and technical success.

The following values have been reported in the literature and serve as a guide to acceptable safety and performance for a PDA device:

- Clinical success based on the absence of non-trivial residual angiographic shunt is report to be 90 to 96% for two commercially available devices
- Manufacturers are advised to demonstrate PDA closure rate at implant, 24 hours post-procedure and at appropriate clinical follow-up. Follow-up has been reported at 1, 2 and 5 years. Patient follow-up and assessment method should be supported with a clinical justification

- Major adverse events (e.g. device embolization, device malposition) have been reported to occur at 2.2% (95% CI 1.0 to 3.7).

Follow-up in the studies included in the systematic review examined for this report was unclear but was possibly 6 months. However, manufacturers are advised that follow-up should be reported for the peri–procedure period as well as late (≤1 year) and very late (≥ one year) time points.

IVC filters to prevent PE

Of primary interest were adverse events, PE (including fatal PE), DVT, and occurrence of a VTE distal to the filter. Manufacturers are advised to provide details of target patient baseline risk for PE, operator experience and technique, medical management goals and the primary study endpoints. These have been shown to be independently associated with adverse events.

The following safety and performance values are indicative and are provided to assist the manufacturer in the preparation of submissions. The list is not exhaustive and should be considered as a guide only.

- Fatal PE is not frequently reported and manufacturers should use appropriate study designs with sufficient power to detect such events when possible. If meta-analysis is performed, then the Peto Odds methods for rare events should be considered.
- Based on the IVC filter registry maintained by British Society of Interventional Radiology (BSIR) more than 96% of filters were deployed as intended. However, manufacturers should report the filter orientation on deployment (i.e. centralised, tilted or abutting the IVC wall).
- Manufacturers should report the dwell time for the device and the impact on retrieval for temporary devices.
- Any structural failure should be reported.
- Manufacturers are advised that DVT was reported to be lower than the 1% in BSIR registry data. However, the clinical profile of the patient cohort may affect this adverse event. Therefore, manufacturers are advised to provide a clinical justification for expected DVT rates in the target population.
- Perforations are the most common long-term adverse event occurring in 0.3 to 14% of filter deployments; the range may reflect differences in IVC filter type.
- The BSIR IVC registry requires notification of filter migration of > 10mm. Manufacturers are advised to report any filter migrations.
- Mortality rates reported for the BSIR IVC registry ranged from 4.3 to 12.3% depending on filter type, dwell time and clinical condition of the patient. Manufacturers are advised to provide a clear clinical context for the use of the IVC filter to assist the clinical assessor to determine whether the device has a favourable benefit-risk profile.

Similar to other CV devices, technical success is based on the successful deployment of the IVC filter in the correct orientation and location as well as the removal of the delivery system.

Follow-up in the studies included in the systematic reviews examined for this report ranged from in-hospital only to 8 years. Follow-up periods should be congruent with the in vivo life span for temporary devices. For permanent devices the acute (< 48h), sub-acute (< 30days), late (< 1 year) or very late (> 1 year) timeline should be considered.

- Manufacturers, in selecting and reporting surrogate markers of safety and performance (as described in the previous section) should provide a clinical justification for the selection and, where possible, should use validated measurement tools.
- When documenting patient performance scores, it is recommended that manufacturers provide data with a minimum of one year follow-up post-surgery to reduce the risk of confounding due to procedure variables.

Summary of safety and performance data

Characteristics of clinical studies of CV flow implants

Table 10: Study characteristics extracted from systematic reviews and primary research reports on the safety and performance of selected CV flow implants

Characteristics of included studies	Arterial stents: Carotid (6 SRs) Coronary(6 SRs) Peripheral (5 SRs)			Implants for AAA repair (4 SRs) (1 retrospective comparative cohort)	Implants for PDA repair (1 SR) (1 retrospective cohort study)	IVC filters (2 SRs) (1 RCT)
	Carotid	Coronary	Peripheral			
Number of included studies per SR	11 to 41	10 to 28	4 to 14	5 to 32	7	2 and 8

Characteristics of included studies	Arterial stents: Carotid (6 SRs) Coronary(6 SRs) Peripheral (5 SRs)			Implants for AAA repair (4 SRs) (1 retrospective comparative cohort)	Implants for PDA repair (1 SR) (1 retrospective cohort study)	IVC filters (2 SRs) (1 RCT)
	Carotid	Coronary	Peripheral			
Dominant design of included studies	3 SRs were limited to RCTs; 3 included a mix of MAs, RCTs, cohort studies, case series & registry studies	5 SRs were limited to RCTs; 1 included RCTs & observational studies	3 SRs were limited to RCTs; 1 included SRs & RCTs; 1 included RCTs & case series	2 SRs were limited to RCTs; 1 included RCTs & registries; 1 included RCTs, observational cohort studies & registries	SR: All Level IV Primary study: Level IV	SRs: Levels II-IV RCT=Level II

Characteristics of included studies	Arterial stents: Carotid (6 SRs) Coronary(6 SRs) Peripheral (5 SRs)			Implants for AAA repair (4 SRs) (1 retrospective comparative cohort)	Implants for PDA repair (1 SR) (1 retrospective cohort study)	IVC filters (2 SRs) (1 RCT)
	Carotid	Coronary	Peripheral			
Sample size (range) for included studies	3 SRs with RCTs: total enrolled = 4,796 to 7,572 patients 3 SRs with various study designs: total enrolled = up to 575,556	5 SRs with RCTs: total enrolled = 6,298 to 14,740 patients 1 SR with RCTs and observational studies: total enrolled = 10,447	3 SRs with RCTs: total enrolled = 627 to 1,387 patients 1 SR with SRs and RCTs; total enrolled = unclear 1 SR with RCTs and case series: total enrolled = 1,628	2 SRs with RCTs: total enrolled = 1,594 to 3,194 patients 1 SR with RCTs & registries; total enrolled = 52,220 patients 1 SR with RCTs, observational studies & registries: total enrolled = 72,114 Primary study: total enrolled = 2,198	SR 2014: n=259 patients in device group; n=551 in control group Primary study: Level III-2 retrospective cohort with concurrent controls; n=51 in device group; n=130 in control group	SR 2010: 2 RCTs of 129 and 400 patients (division between arms NR) SR 2014: n=432 in filter groups; n=4160 in historical control groups RCT 2012: total n=141 (70 in device group, 71 in control group)
Reported comparisons	Carotid artery stenting vs. endarterectomy (one study also included medical therapy)	4 assessed DES versus BMS; 2 assessed DES versus BMS or another type of DES	Balloon angioplasty with stents (BMS or DES) versus balloon angioplasty alone (one compared BMS versus DES)	Primarily EVAR versus open repair; also EVAR versus watchful waiting in candidates deemed not fit for surgery	Implanted device versus surgical closure	IVC filter versus no filter

Characteristics of included studies	Arterial stents: Carotid (6 SRs) Coronary(6 SRs) Peripheral (5 SRs)			Implants for AAA repair (4 SRs) (1 retrospective comparative cohort)	Implants for PDA repair (1 SR) (1 retrospective cohort study)	IVC filters (2 SRs) (1 RCT)
	Carotid	Coronary	Peripheral			
Quality of included evidence as reported	2 SRs did not report quality assessment; 1 developed a custom tool but did not report results; 3 used a tool developed by the Cochrane Collaboration and found risk of bias generally low	1 SR did not report quality assessment; 1 developed a custom tool but did not report results; the other 4 used various tools and determined studies were generally high quality with low risk of bias	All 5 SRs assessed study quality using a variety of tools (e.g., Cochrane Collaboration, Jadad, custom); quality was generally assessed as moderate to high	SRs assessed via Jadad or Cochrane Collaboration tool. Other study types used NOS. RCT quality usually high; others low to moderate	SR: With the NOS, assessed studies as having low-risk bias; funnel plot for primary outcome showed no obvious publication bias	SR 2010: With D&B, assessed studies as low quality SR 2014: With the Jadad scale, assessed studies as scoring 2/5 & 3/5 (low)
Patient Follow-up	From 1 month to 5 years	Generally 3 to 5 years	6 months to 8 years; generally 6-24 months	From post-op course in hospital up to 9.1 years	SR: 6 months Primary study: 24 months	SR 2010: NR SR 2014: 34 days to 8 years RCT 2012: 15 (± SD 2) months

KEY: SD=Standard deviation; SR=Systematic review; RCT=randomized controlled trial KEY: AAA=Abdominal aortic aneurysm; BMS=Bare metal stents; D&B=Downs & Black; DES=Drug eluting stents; EVAR=endovascular aneurysm repair; IVC=Inferior vena cava; MA=Meta-analysis; NOS=Newcastle-Ottawa scale; NR=not reported; PDA=Patent ductus

Reported clinical outcomes on selected CV flow implants

Table 11: Summary of types of safety and performance data extracted from SRs and additional primary research on CV flow implants

Type of CV flow implant	Outcomes reported in included research
Arterial stents: • **Carotid** (6 SRs) • **Coronary** (6 SRs) • **Peripheral** (5 SRs)	• Carotid: often divided into <30 day (peri-procedural) or >30 day outcomes – Primary: Composite of (a) death or stroke OR (b) death or stroke or MI – Secondary: Death, stroke / disabling / major stroke, TIA, MI, facial neuropathy / cranial nerve palsy – Restenosis • Coronary – TVR and / or TLR – Death – Recurrent MI – Stent thrombosis (definite or probable; also early or late) – Various composite endpoints such as MACE • Peripheral – Death, reintervention, amputation – Technical success, vessel patency, TLR, restenosis – Clinical improvement as per Rutherford Scale, hemodynamic improvement, QOL
Implants for AAA repair (4 SRs) (1 retrospective comparative cohort)	• AEs / postop complications, e.g., MI, stroke, renal failure, aortic rupture • Mortality (30-day, aneurysm-related, all-cause) • Reintervention rates including conversion from EVAR to open procedure • Secondary endpoints, e.g., QOL, procedure time, blood loss, blood transfusion, fluoroscopy time, contrast load, recovery time, days in ICU & LOHS

Type of CV flow implant	Outcomes reported in included research
Implants for PDA repair (1 SR) (1 retrospective cohort study)	• AEs • Primary success • Residual shunt • Blood transfusion • LOHS
IVC filters (2 SRs) (1 RCT)	• AEs • DVT • Fatal PE • PE • VTE distal to the filter

KEY: AAA=Abdominal aortic aneurysm; AE=Adverse events; CTA=computed tomography angiography; DVT=Deep vein thrombosis; EVAR=Endovascular aneurysm repair; ICU=Intensive care unit; IVC=Inferior vena cava; LOHS=Length of hospital stay; MACE=Major adverse cardiac events; MI=myocardial infarction; NR=not reported; PE=Pulmonary embolus; PDA=Patent ductus arteriosus; QOL=Quality of life; SD=Standard deviation; SR=Systematic review; TIA=transient ischemic attack; TLR=target lesion revascularisation; TVR=total vessel revascularisation; VTE=Venous thromboembolism

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Implantable pulse generator systems

Implantable pulse generator systems are active medical devices that produce electrical discharges. This section specifically covers cardiac active implantable devices and implantable electrical nerve stimulation devices.

Summary recommendations

- Implantable pulse generator systems (pacemakers including cardiac resynchronisation therapy with or without defibrillation (CRT, CRT-D), implantable cardiac defibrillators (ICDs) and implantable electrical nerve stimulation devices), are complex medical devices that may be used in combination with other devices or components. Manufacturers are advised to list all components and combinations and provide clinical evidence to support the safety and performance of the new device for these nominated configurations.
- Provision of clinical investigation data: Manufacturers who intend to conduct clinical investigations should use study designs to the highest practical NHMRC Level of Evidence, and trials should be appropriately designed to inform on the safety and performance of the device for its intended purpose.
    - For Active Implantable Cardiac Devices (AICDs), patient follow-up in clinical trials should include the peri-operative, acute (≤ 3 months) and chronic (> 3 months) phases, with the patient then monitored during yearly follow-up visits. Follow-up time should be sufficient to identify late adverse events. The nominated follow-up periods should be supported by clinical justification.
    - For implantable devices for pain and other neurological symptom control, patient follow-up for clinical trials should include the peri-operative, acute (≤ 3 months) and chronic (> 3 months) phases. Due to the chronicity of pain and other neurological symptoms, performance should be studied for 1 year or longer post device implantation.
- The clinical outcomes that determine safety and performance of implantable pulse generator systems vary significantly by device type:
    - The manufacturer is advised to benchmark the new device against devices of the same class as reported by an international registry, if available.
    - Nominated values that indicate safety and performance should be appropriate to patient health status and indicated use and justified by a clinician who is an expert in the field.
    - For patient performance data manufacturers are advised to define the anticipated improvement in patient scores post-surgery or post-treatment. Ideally, these should be by an internationally recognised assessment tool(s) used to measure clinical success e.g. pain assessment via a visual analogue scale.
    - When submitting a comprehensive literature review, full details of the method used should be included in the CER in sufficient detail to ensure the literature review can be reproduced.
    - A well-documented risk assessment and management system should also be provided. All clinical risks identified in the clinical investigation data, literature review and post-market clinical experience should inform and be reflected in the risk assessment documentation. These risks should be appropriately rated and quantified, before assigning risk reduction activities such as statements in the IFU and training materials to reduce inherent risks.

- For guidance on the conduct of comprehensive literature reviews and presentation of clinical evidence, manufacturers are directed to the relevant sections and appendices.
  - In compiling the clinical evidence for an implantable pulse generator system, the manufacturer should ensure that a clinical expert, that is, someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting, conducts a critical evaluation of all the clinical data that informs the safety and performance of the device.
  - The clinical expert must determine whether the clinical evidence is sufficient to demonstrate that the device meets the requirements of the applicable EPs, including that it is deemed to be safe and to perform as intended, and that there is a positive benefit-risk ratio with regard to its use. The clinical expert should then endorse the CER (by signature and date).
- A full curriculum vitae of the clinical expert should be included in the CER.

Defining implantable pulse generator systems

These are active medical devices that produce electrical discharges as required for a variety of treatments, and include (but are not limited to) the following two categories.

- Active Implantable Cardiac Devices (AICD) including:
  - single and dual chamber pacemakers
  - cardiac resynchronisation therapy pacemakers, with or without defibrillation (i.e. CRT-D and CRT respectively)
  - implantable cardiac defibrillators (ICDs)
- Electrical nerve stimulation devices
  - only implantable electrical nerve stimulation devices will be covered in this guidance; transcutaneous electrical nerve stimulation (TENS) devices are not included.

Implantable pulse generator systems can pose a significant regulatory challenge as they are active devices that must have long in vivo lives without exposing recipients to unduly high risks of adverse events.

Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device (direct evidence) and/or a comparable device (indirect evidence). The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data. Manufacturers should refer to Clinical evidence requirements for further information.

Direct clinical evidence on the actual device is preferred. Otherwise indirect clinical evidence may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in Comparable devices including substantially equivalent devices.

It is important to indicate if any changes have been made to the device since the clinical data were gathered and to document these changes and clarify the exact version of the device. The manufacturer should ensure that combinations of components that are to be included in the IFU are tested.

Clinical investigation(s)

Regardless of design, clinical studies should provide unbiased results that allow an objective comparison of implantable pulse generators with respect to their safety and performance. To achieve this for new device applications based on direct clinical data the manufacturers should ensure that clinical trials are conducted according to internationally recognised standards for a given trial design, e.g., follow the ISO standard 14155.

Clinical trials must be independently audited at key stages throughout their conduct to document that the integrity of the trial(s) was maintained. Clinical trial data should be reported using an internationally recognised standard for a given study design, e.g., the CONSORT reporting standards for RCTs.

For AICDs patient follow-up in clinical trials should include the peri-operative, acute (≤ 3 months) and chronic (> 3 months) phases, with the patient then monitored during yearly follow-up visits. Follow-up time should be sufficient to identify late adverse events. The nominated follow-up periods should be supported by clinical justification.

For implantable devices for pain and other neurological symptom control, patient follow-up for clinical trials should include the peri-operative, acute (≤ 3 months) and chronic (> 3 months) phases. Due to the chronicity of pain and other neurological symptoms, performance should be studied for 1 year or longer post device implantation.

For applications based on clinical data from a comparable device, the manufacturer should demonstrate that clinical data are derived from methodologically sound clinical studies and describe any direct relationship that exists between the comparable device and the new device with respect to the clinical data. Where the device and the predicate share any common design origin, the lineage between the devices should be provided. Manufacturers are advised to provide all relevant documents with a justification by a clinical expert to establish substantial equivalence and to confirm that any identified differences between the device and the nominated comparable device will not adversely affect the safety and performance of the device.

For further information on demonstrating substantial equivalence refer to Comparable devices including substantially equivalent devices.

Literature review

The manufacturer should ensure that an internationally recognised method is followed when conducting a systematic literature review. A literature review involves the systematic identification, synthesis and analysis of all available published and unpublished literature, favourable and unfavourable, on the device when used for its intended purpose as outlined in the literature review section. The data can be generated from the use of the device or, if relying on indirect evidence, the comparable device to which substantial equivalence has been established. All included studies on the device and/or comparable device should have been appraised for reporting quality and potential bias.

If the literature review is to include equivalent device/s, such devices should be identified beforehand after substantial equivalence has been demonstrated. Clinical evidence provided in the form of a literature review will be in support of safety and performance for the subject device only if the reviewed studies relate to the device itself or device/s demonstrated to be substantially equivalent. However, a literature review relating to a class of device, i.e. relating to similar but not substantially equivalent devices, may provide supporting evidence of safety and performance for the device type, to which the data for the subject device or substantially equivalent device/s may be compared. For each study included in the literature review, the device used must be clearly identified by manufacturer name and model, and studies relating to the subject device or devices demonstrated to be substantially equivalent should be identified as such and analysed separately to those for other devices.

Post-market data

Post-market data should be provided where available for the device itself, as well as for the comparable device. For implantable pulse generators, the regulatory status of the device should include the MR designation in each jurisdiction where it is approved for use. It is particularly important to include the following:

- distribution numbers of the device(s) by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- safety data including medical device vigilance reports, adverse events, and complaints categorised by type and clinical outcome for every year since launch should be reported, including all deaths (all cause, cardiac and sudden cardiac death). Mortality data should include clear definitions of patient death categories and overall mortality rate, and all patient deaths should be supported by sufficient documentation.
- the number of years of use
- Examples of registry data for implantable pulse generator systems have been reported in peer reviewed studies from Spain, Denmark, Sweden, France, Italy, China, Germany, Poland, the United States, and Australia.
- Any explanted pulse generators returned to manufacturers should be accounted for with an explanation of failures and corrective measures.

For reports of adverse events (AEs) and complaints etc., to be a useful adjunct to other forms of clinical evidence, the manufacturer must make a positive, concerted effort to collect the reports and to encourage users to report incidents. Experience shows that merely relying on spontaneous reports leads to an underestimation of the incidence of complaints, vigilance and adverse event reports.

Compiling the CER

In compiling the clinical evidence the manufacturer should ensure that an expert in the relevant field critically evaluates all the clinical data from clinical investigation(s), literature review and/or post-market data (clinical experience). The clinical expert should demonstrate substantial equivalence for comparable devices where applicable and then endorse the CER (evidenced by signature and date) that establishes whether the clinical evidence is sufficient to demonstrate the requirements of the applicable EPs, in particular that the device is safe, performs as intended, and has a favourable risk-benefit profile.

Previous sections outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a CER. These guidance documents apply whether the applicant is using direct clinical evidence or relying on indirect clinical evidence from a comparable device. Guidance on defining a comparable device is provided in Comparable devices including substantially equivalent devices.

As per The Clinical Evaluation Report the CER should include the following:

a) General details

b) Description of the medical device and its intended application

c) Intended therapeutic and/or diagnostic indications and claims

d) Context of the evaluation and choice of clinical data types

e) Summary of relevant pre-clinical data

f) Discussion regarding comparable devices including substantially equivalent devices

g) Summary of the clinical data and appraisal

h) Data analysis

i) Conclusions

j) Name, signature and curriculum vitae of clinical expert and date of report

Supportive data and information

The following information on the device must also be provided:

- risk assessment and management document
- IFU, labelling, product manual and all other documents supplied with the device. These must highlight the risks and ensure that these are appropriately communicated to user.

Additional information should be provided as applicable. This may include (but is not limited to):

- additional specifications of the device(s)
- the materials from which the device is made including chemical composition
- the components to which the device is paired when used clinically
- the technical characteristics of the leads and electrodes
- other devices that may be used in conjunction with the device
- any aspects of non-clinical testing results that inform the design of the clinical trial
- biocompatibility testing, bench testing and animal studies where applicable
- specific testing of any adjuvant medicinal components may be required especially if these are new chemical entities in the Australian context. This should cover interactions between the device and the medicine, pharmacodynamics and time-release profiles.

Defining clinical success

General

Safety and performance data should be provided for the peri-operative, acute (≤ 3 months post-implant) and chronic phases (> 3 months post-implant). Ideally, patients should be assessed with planned yearly follow-up visits. Given the long-term in vivo life of these implantable devices and the potential permanent implantation of some components e.g. leads, manufacturers are advised that long-term follow-up is required. According to peer reviewed literature, typical follow-up periods are three or more years.

Manufacturers are advised to consult ISO 14708 “Implants for surgery – Active implantable medical devices”, part 2 (pacemakers), part 3 (neurostimulators) and part 6 (ICDs). These ISO standards detail requirements that must be met to provide basic assurance of safety for both patients and users, by ensuring protection from:

- unintended biological effects
- external energy sources for example: electric currents, electrostatic discharge
- external cardiac defibrillators

- temperature and pressure
- electromagnetic fields including MR environment
- ionising radiation

Novel features or pacing modes not previously evaluated in comparable devices should be allocated more extensive study and assessment in the submitted clinical evidence to demonstrate safety and performance.

Irrespective of their placement, implantable pulse generators can be affected by electromagnetic interference (EMI). The risks of altered device function on exposure to electromagnetic fields that are produced either intentionally or as by-products of use of other devices should be assessed. Typical EMI sources include cardioversion, RF ablation, electrosurgery, radiotherapy, use of TENS devices, metal detectors, wireless services (including cellular phones) and MRI environments. Manufacturers are advised to refer to MRI considerations and the current version of ISO 14117 (electromagnetic compatibility test protocols for active implantable medical devices) in conjunction with this section.

The American Society of Anaesthesiologists, in collaboration with American Heart Association and the Society of Thoracic Surgeons, have provided a consensus statement on postoperative evaluation of AIMDs following procedures that expose patient to EMI (excluding MRI) and appropriate recommendations should be included in the IFU.

- Manufacturers should define the electromagnetic fields and the duration of exposure to such fields within which the device performs as intended i.e. the tolerance to electromagnetic field exposure.
- This information is necessary to inform the content of IFU and manuals provided with the device.

Active implantable cardiac devices

Safety

Systematic reviews on single, dual-chamber and CRT pacemaker systems either with or without defibrillation capability and ICD systems included the following peri-procedure events and longer term outcomes that were tracked as safety measures:

- procedural complications e.g. pneumothorax, haemothorax, pocket haematoma and infection
- device pocket erosion
- coronary sinus dissection or perforation, damage to arteries and nerves, air embolism, venous thrombosis, cardiac perforation
- pericardial effusion
- device migration
- toxic or allergic reaction, e.g. nickel allergy, silicone allergy
- CRT-D and ICDs; arrhythmia and inappropriate shocks
  - A Health Canada guidance report (Health Canada. Guidance Document: Medical Device Applications for Implantable Cardiac Leads. File No. 11-113340-236; 2011) also lists changes to defibrillation thresholds and lead impedances
- device-related problems

  - leads: dislodgement, reposition, difficult placement, malfunction or fracture
  - sensing problems (loss, oversensing or undersensing)
  - loss of capture
- extracardiac stimulation
- CRT and CRT-D: progression to pacemaker syndrome, atrial fibrillation, heart failure or stroke
- hazards related to use in the MRI environment (refer to Section10: Demonstrating the safety of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment)
- death

Performance

In guidance documents on pacemakers and their associated leads issued by Health Canada and US FDA, and systematic reviews (SRs) related to CRT-D and ICD evidence, the key performance outcomes were listed as:

- implantation success
- sensing characteristics
- battery longevity
- QoL measures using a validated tool e.g. the New York Heart Association Classification or SF-36 scores
- reduced mortality (all cause, cardiac and sudden cardiac deaths)
  - mortality data should include clear definitions of patient death categories and overall mortality rate, and all patient deaths should be supported by sufficient documentation
- avoidance of rehospitalisation (for any reason) after device placement, including heart transplant
- for CRT and CRT-D devices the pacing impedances (low [< 200 ohms] or high [> 3000 ohms] measured using a recognised standard method [ISO 14708-2]) are within the ranges specified by manufacturer
- voltage stimulation threshold (CRT, CRT-D)
- improved cardiac function (CRT, CRT-D) e.g. left ventricle ejection fraction (LVEF), reduced incidences of atrial fibrillation (AF), stroke, heart failure
- improvement in clinical symptoms

Implantable electrical nerve stimulation devices

Implantable electrical nerve stimulators (including such devices as deep brain and vagal nerve stimulators) are a treatment modality for patients who suffer chronic pain e.g. neuropathic, nociceptive and non-cancerous pain and other disabling neurological symptoms.

The different aetiologies of pain and other neurological symptoms can impact on the performance of neurostimulators. Therefore manufacturers are advised to clearly define the target symptom and stimulation loci to assist clinical assessors to evaluate the safety and performance of implantable neurostimulators for pain or the management of other neurological symptoms. Devices can be categorised as either intracranial (e.g. deep brain stimulation) or extracranial (e.g. spinal cord, vagal nerve or peripheral nerve stimulators).

Safety: intracranial neurostimulators

Adverse events are variously reported and include:

- usual risks associated with major surgery
- infection
- intracerebral or extra-axial haematomas
- seizure (intraoperative or trial stimulation period)
- seizure long-term
- neurological deficit (short-term < 1 mo)
- neurological deficit long-lasting
- local pain/headache
- hardware maintenance e.g. shortened battery life, failed leads
- MRI environment safety concerns including heating (which has been reported to have caused permanent neurological impairment and is of greatest concern for various neurostimulator devices)

Safety: extracranial neurostimulators

Adverse events are variously reported and include:

- device-related complications e.g. electrode migration, lead fracture
- distorted or loss of sensation (paraesthesia or numbness)
- dural puncture (spinal cord stimulators)/CSF leak
- infection
- discomfort or pain
- undesired stimulation
- hardware maintenance e.g. shortened battery life, failed leads
- MRI environment safety concerns - including heating (which has been reported to create the greatest concern for various neurostimulator devices)

Performance: intracranial and extracranial neurostimulators

The evidence reviewed reported on various outcomes including:

- pain (pain reduction, pain intensity scores, pain coping ability, reduction or cessation in use of pain medication, pressure pain threshold, time to first reduction in pain, and maximum reduction in pain) as well as anxiety score
  - measured using validated scales e.g. visual analogue scales (VAS) or numerical rating scales
  - reported success criterion e.g. more than 50% of patients achieve a greater than 50% reduction in VAS of pain intensity on follow-up, usually at 6 to 24 months

- symptom reduction or improvement for non-analgesic neurostimulator indications (e.g. movement disorders such as Parkinsonian tremor, essential tremor, dystonia; urinary or faecal incontinence; epilepsy)
- patient function e.g. QoL, mood, sleep and function scores should be assessed using validated tools such as:
  - Oswestry Disability Index and the Low Back Pain Outcome Scale
  - SF-36
  - Zung Self-Rating Depression Scale
- return to work
- hospital attendance
- patient satisfaction and experience

Manufacturers are advised that ranges for stimulation parameters of frequency (Hz), Amplitude (V) and pulse-width (ms) should be provided and included in IFU documentation.

Summary of safety and performance data

Studies from the peer reviewed literature

Table 12: Study characteristics extracted from SRs on the safety and performance of selected implantable pulse generators

Characteristics of included studies	Pacemakers (including CRT) (2 SR)	ICDs (5 SRs)	Pain management devices (5 SRs or narrative reviews)
Number of included studies per SR	Dominant design RCT total included studies n = 45	4 SRs / MAs only included RCTs: range 3 to 8; 1 SR only included cohort studies: n=18	Mixed evidence base with the number of included studies ranging from 11 to 62
Clinical situation(s)	Dual-chamber versus single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome	(a) Primary prevention of SCD in patients w/ CKD at risk of life-threatening ventricular arrhythmias; (b) patients w/ HF; (c) patients w/ ARVD/C; (d) primary prevention of SCD in older patients	(a) Complex regional pain syndrome (b) neuropathic or ischaemic (c) low-back disorders (d) nociceptive or neuropathic pain (e) headaches
Dominant design of included studies	1 SR including 4 RCTs of parallel group design and 28 randomised crossover comparisons	4 SRs included only RCTs; 1 SR included only observational studies	Case series and RCT
Sample size (range) for included studies	RCTs: 58 to 2568 Crossover studies: 8 to 48	Total N in SRs ranged from 610 to 5674	Total N in the SR ranged from 210 to 509
Reported comparisons	Dual-chamber versus single chamber ventricular pacing	(a) Usual medical therapy, placebo or amiodarone; (b) CRT-D (ICD + CRT); (c) "appropriate control" (not specified but could not include ICD or CRT-D)	Medical and/or surgical treatment (appropriate to condition) that does not include SCS.
Patient follow-up	RCTs: 1.5 to 5 years Crossover studies: 48 hours to 8 weeks	Means of 3 months to 3.8 years	Ranged from 1 month to 7.2 years

KEY: ARVD/C= arrhythmogenic right ventricular dysplasia / cardiomyopathy; CKD=chronic kidney disease; CRT=cardiac resynchronisation therapy; CRT-D=cardiac resynchronisation therapy plus ICD; HF=heart failure; ICD=implantable cardiac defibrillator; MA=meta-analysis; RCT=randomised controlled trial; SCD=sudden cardiac death; SR=systematic review; w/=with

Table 13: Reported clinical outcomes in the peer reviewed literature on selected implantable pulse generators

Type of pulse generator	Outcomes reported in the included research or resources
Pacemakers (including CRT) (2 SR)	Safety: implantation success, lead fracture, lead dislodgement, conductor failure, extracardiac stimulation, insulation failure, loss of capture, sensing problems (loss, oversensing or undersensing), perforation and other lead-related AEs, including death • Voltage stimulation thresholds • Sensing characteristics • Pacing impedances (Low or high) • Battery longevity
ICDs (5 SRs)	Safety (AEs / postop complications): pneumothorax, haemothorax, pocket haematoma, lead dislodgement or reposition or difficult placement or malfunction or fracture, ICD migration, impending ICD pocket erosion, infection, ICD-related infection, pericardial effusion or tamponade, coronary sinus dissection or perforation, damage to arteries and nerves, air embolism, venous thrombosis, cardiac perforation, arrhythmia, inappropriate shocks • Mortality (all-cause and ICD-related) • Rehospitalisation (for any reason) after ICD placement including heart transplant • Improvement in clinical conditions • QoL • From Health Canada: defibrillation thresholds and lead impedances (since the device is designed for cardioversion or defibrillation)
Pain management (5 SRs)	• Safety intracranial (AEs / postop complications): l risks associated with major surgery, infection, intracerebral or extra-axial haematomas, subdural or epidural haemorrhage, seizure (intraoperative or trial stimulation period), seizure long-term, neurological deficit (short-term < 1 mo), neurological deficit long-lasting, local pain/headache, hardware maintenance e.g. shorten battery life, failed leads, MR environment safety concerns e.g. heating leading to neurological damage • Safety extracranial (AEs / postop complications): device-related complications e.g. electrode migration, lead fracture, loss of paraesthesia, dural puncture (spinal cord stimulators), infection, hardware maintenance e.g. shortened battery life, failed leads, MR environment safety concerns • Pain (pain reduction, pain intensity scores, pain coping, pressure pain threshold, time to first reduction in pain, and maximum reduction in pain) as well as anxiety score

Type of pulse generator	Outcomes reported in the included research or resources
	• Patient function e.g. QoL, mood, sleep and site specific function scores should be assessed using validated tools such as: – return to work – patient satisfaction and experience – analgesic consumption – hospital attendance

KEY: AE=adverse events; FVC=forced vital capacity; ICD=implantable cardiac defibrillator; ROM = range of motion; QOL=quality of life; SR=systematic review

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Heart valve replacements using a prosthetic valve

Heart valve replacement using a prosthetic valve is performed to reduce the morbidity and mortality associated with native valvular disease or to replace a malfunctioning prosthetic valve.

Summary recommendations

- Prosthetic heart valves are complex medical devices which are currently made of either synthetic material (mechanical valves) or biological tissues (bioprosthesis) or a combination of both and inserted via open surgery or percutaneously. Manufacturers are advised to provide clinical evidence to support the safety and performance of the particular device and any accessories used to deliver the device.
- Provision of clinical investigation data:
  - manufacturers who intend to conduct clinical trials should design trials to the highest practical NHMRC level of evidence and trials should be appropriate to inform on the safety and performance of the device for its intended purpose
  - to comply with ISO 5840, clinical trials should continue until the minimum number of patients with each valve type have each been followed for a minimum of one year and there are at least 400 valve years of follow-up of each valve type. For modification of an existing valves already on the ARTG the patient years deemed acceptable may in some circumstances be adjusted based on a risk analysis of the changes
  - for evaluating the performance of prosthetic heart valves it is recommended that the Objective Performance Criteria (OPC) as listed in ISO 5840 (and updates) be reported including early (within 30 days post implantation), mid- term outcomes (after 30 days post implantation) and at one year (or two years for reimbursement). The selection should be supported by a clinical justification
  - typical safety and performance values are provided in Table 15, Table 16, Table 17, Table 18 and Table 19 and Table 20.
- Pre-clinical data demonstrating the mechanical and physical characteristics should be consistent with the intended purpose and anticipated in vivo lifespan of the heart valve replacement.
- Documentation demonstrating biocompatibility of the device should be provided.

- For submissions reliant on comparable device data, manufacturers are required to submit all relevant documents with a supporting clinical justification by the clinical expert that establishes substantial equivalence between the device and the nominated comparable device.
- When submitting a comprehensive literature review full details of the method, search strategy, inclusion/exclusion criteria for selection of studies and analysis should be included in the CER with sufficient detail to ensure the search can be reproduced.
- In addition, a well-documented risk analysis and management system must be provided with the CER. The clinical investigation data, literature review and post-market clinical experience should inform the risk assessment documentation. All clinical risks identified in the clinical data should be reflected in the risk assessment documentation. These risks should be appropriately rated and quantified and ideally be presented as risk matrices, before assigning risk reduction activities such as statements in the IFU and training materials to reduce residual risks. The residual risk following risk mitigation implementation should be estimated.
- Manufacturers should provide details of the clinical context within which the clinical data was obtained. The clinical context of the evidence should be consistent with the indications for use.
- Compilation of the clinical evidence
  - in compiling the clinical evidence for a prosthetic heart valve the manufacturer should ensure that a competent clinical expert critically evaluates all the clinical data that informs on the safety and performance of the device
  - the competent clinical expert must then endorse the CER (evidenced by signature and date) which demonstrates that the clinical evidence is sufficient to meet the requirements of the applicable EPs and the device is deemed to be safe and to perform as intended
- The full CV of the clinical expert should be provided

Defining heart valve prostheses

This section includes both conventional heart valves (those that are implanted using open heart surgery) and percutaneous heart valves (those that are collapsed into a catheter and are expanded at the time of implantation). The guidance also applies to 'sutureless' (meaning heart valves with fewer sutures, not without sutures) valve technology whereby the valve is mounted on a self-expanding nitinol frame that is implanted into the aortic annulus following resection of the diseased tissue. Each type of valve has its own associated risk benefit profile that needs to be addressed by the manufacturer.

Currently there are three main types of prosthetic heart valves, mechanical, biological and valves that combine mechanical and biological components (using hybrid valve technology).

The main designs of mechanical (synthetic) valves include:

- the caged ball valve
- the tilting disc (single leaflet) valve
- the bileaflet valve.

Biological valves (bioprosthesis or tissue valves) are classified into two major categories:

- xenografts made from bovine, porcine, or equine tissue

- homografts obtained from cadaveric donors.

Xenografts may have a supporting frame (stent) or no supporting frame (stentless).

Manufacturers and applicants are advised to read this guidance section in conjunction with other relevant sections and ISO documentation, ISO 5840:2021 and ISO 5840-3:2021.

Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or post-market data (clinical experience) from the use of the device (direct) and/or comparable device (indirect). Direct clinical evidence on the actual device is preferred. It is important to clarify if any changes have been made to the device since the clinical data were gathered and if so to document the changes and to clarify the exact version of the device. Otherwise indirect clinical evidence from a comparable device may be used after substantial equivalence has been demonstrated through a comparison of the clinical, (intended purpose) technical and biological characteristics as described in Comparable devices including substantially equivalent devices. Where the device and the predicate share any common design origin, the lineage between the devices should be provided as well.

The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data and documented in the IFU and other information supplied with the device. Manufacturers should refer to Clinical evidence requirements for more information.

Clinical investigation(s)

The design of the clinical investigation(s) should be appropriate to generate valid unbiased measures of clinical performance and safety. If clinical studies on cardiac valve prostheses are conducted it is recommended that manufacturers refer to ISO 5840-1:2021; ISO 5840-2:2021 and ISO 5840-3:2021 as guides to study design.

Additional resources regarding clinical study design and conduct are available on the TGA and FDA websites. The preferred design is a randomised controlled clinical trial and conditions should ideally represent clinical practice in Australia. The eligible patient groups should be clearly defined with exclusion/inclusion criteria.

It is recommended that the clinical study continue until the minimum number of patients of each valve type has each been followed for a minimum of one year (two years if seeking reimbursement). There must be at least 400 valve years of follow-up of each valve type. This is based on guidance in ISO 5840:2021. For modification of an existing valve on the ARTG the patient years deemed acceptable may in some circumstances be adjusted based on a risk analysis of the changes. The manufacturer is responsible for providing justification of the study protocol. The number of patient years should also be documented.

Medication which may affect outcomes, for example anticoagulant treatment, must be taken into account when determining all endpoints. Analysis of clinical events should be blinded and independently adjudicated wherever possible.

Literature review

A literature review involves the systematic identification, synthesis and analysis of all available published and unpublished literature, favourable and unfavourable, on the device when used for its intended purpose or, if relying on indirect evidence, the comparable device to which substantial equivalence has been established.

Data on the materials used to construct the prosthesis, its dimensions and geometry and the intended purpose and population will define the construction of search strategies as well as study selection when conducting a comprehensive literature review. This ensures that the

searches are complete and the included studies are related to the device and/or comparable device. The search strategy should be made prior to performing the literature review, extraction of the clinical evidence and analysis of the pooled results. A full description of the device used or adequate information to identify the device (e.g. manufacturer name and model number) in any given study must be extractable from the study report. If this is not possible, the study should be excluded from the review.

Post-market data

Post-market data can be provided for the actual device or for the comparable device. It is particularly important to include the following:

- information about the regulatory status of the device(s) (or comparable device(s) if relying on this), including the certificate number, date of issue and name under which the device is marketed, the exact wording of the intended purpose/approved indication(s), any conditions and other information which may be relevant such as MRI designation in other jurisdictions.
- any regulatory action including CE mark withdrawals, recalls, including recalls for product correction (and the reason for these i.e. IFU changes), removals, suspensions and cancellations and any other corrective actions anywhere in the world
- distribution numbers of the device(s) including distribution by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- the number of years of use
- for every year since launch, the number of complaints, vigilance and monitoring reports and adverse events categorised by type and clinical outcome
- explanted devices returned to manufacturers should be accounted for with an explanation of device failures and corrective measures.

Publicly available post-market data such as adverse event reporting on the FDA MAUDE database and the TGA IRIS may be used for devices from other manufacturers. The manufacturer should include post-market surveillance data from national jurisdictions where the device is approved for clinical use. Registries for different prosthetic heart valves have been established in Belgium, France, Germany, Italy, New Zealand and the United Kingdom as well as Australia.

For reports of adverse events and device failures to be useful clinical evidence, the manufacturer must make a positive, concerted effort to collect the reports and to encourage users to report incidents. Experience shows that merely relying on spontaneous reports leads to an underestimation of the incidence of failures and adverse events.

The post-market data should be critically evaluated by a competent clinical expert to enable an understanding of the safety and performance profile of the device(s) in a 'real-world' setting.

Compiling the CER

Previous sections outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a CER. This guidance applies whether the applicant is using direct clinical evidence or relying on indirect clinical evidence from a comparable device. As time since first approval lengthens comparable device data becomes less relevant and should be replaced by data derived from clinical experience with the device.

As per The Clinical Evaluation Report the CER should include the following:

a) General details

b) Description of the medical device and its intended application

c) Intended therapeutic and/or diagnostic indications and claims

d) Context of the evaluation and choice of clinical data types

e) Summary of relevant pre-clinical data

f) Discussion regarding comparable devices including substantially equivalent devices

g) Summary of the clinical data and appraisal

h) Data analysis

i) Conclusions

j) Name, signature and curriculum vitae of clinical expert and date of report

Supportive data and information

The following information on the device must also be provided:

- risk assessment and management document
- IFU, product manual and all other documents supplied with the device. The clinical evidence must highlight the risks and ensure that these are appropriately communicated to user.

Additional information should be provided as applicable. This may include (but is not limited to):

- additional specifications of the device(s)
- the materials from which the device is made including chemical composition
- other devices that may be used in conjunction with the device
- any aspects of non-clinical testing results that inform the design of the clinical trial should be included in the supporting documents
- biocompatibility testing, bench testing and animal studies where applicable
- specific testing of any adjuvant medicinal components may be required especially if these are new chemical entities in the Australian context. This should cover interactions between the device and the medicine, pharmacodynamics and time-release profiles.

Current heart valve prostheses vary in their composition, method of insertion and way in which they are fixed.

In submissions to the TGA, it is recommended that manufacturers of heart valve prostheses refer to ISO documents for guidance on the type of information that should be provided with respect to the characteristics of the device, for example 5840-1: 2015, Cardiovascular implants -- Cardiac valve prostheses -- Part 1: General requirements; 5840-2:2015 Cardiovascular implants -- Cardiac valve prostheses -- Part 2: Surgically implanted heart valve substitutes and 5840-3:2013 Cardiovascular implants -- Cardiac valve prostheses -- Part 3: Heart valve substitutes implanted by transcatheter techniques.

For **mechanical** heart valve prostheses these include, but are not limited to:

- the materials used in the valve
- the design of the valve
- the size of the valve
- assembly technique
- testing and quality control procedures
- haemodynamic properties
- packaging and sterilisation procedures.

For **biological** heart valve prostheses these include, but are not limited to:

- the material used in the valve
- the design of the valve
- the size of the valve
- assembly technique
- testing and quality control procedures
- haemodynamic properties
- tissue preservation and/or cross-linking technique(s)
- anticalcification treatment(s)
- packaging and sterilisation procedures.

All device characteristics and the intended purpose(s) are essential prerequisites for the design of clinical studies to demonstrate the clinical safety and performance of devices with no equivalent comparable device(s).

If a comparable device is available and data from that device is used to support a submission, the device characteristics and intended purpose will determine the criteria for a full clinical justification for the selection of the comparable device. The following should be included when relying on a comparable device for heart valve prostheses:

- A comparison of the technical and physical characteristics of the new and comparable device(s) should be demonstrated through direct testing in order to establish substantial equivalence
  - direct comparisons of the technical and physical characteristics include, but are not limited to; the composition of the prostheses, hydrodynamic performance, biocompatibility, accessories such as implantation tools, corrosion resistance, shelf life, fatigability, durability, dimensions, geometry and weight. Refer to ANNEX D and I in ISO 5840:2021 for a more comprehensive list
  - any differences in the technical and physical characteristics should be addressed in the clinical justification to determine whether the difference will affect the benefit-risk profile when the device is used for its intended purpose
  - the use of more than comparable device is discouraged; however, these may be used if each comparable device is found to be substantially equivalent to the device under consideration

  - a clinical justification should be presented when using a comparable device as to why direct clinical data are either not required, or are only partially required

- The comparable device(s) must have clinical data to support safety and performance.
- The clinical expert should critically evaluate all the clinical data for the device and comparable device and then endorse the CER (evidenced by signature and date) that establishes whether the clinical evidence is sufficient to demonstrate the requirements of the applicable EPs and that the device is safe and performs as intended.

Defining clinical success

The studies identified for these guidelines identified appropriate clinical outcomes to establish the safety and performance of prosthetic heart valves however outcomes were sometimes classified differently. For example, mortality and stroke were referred to as safety outcomes in some studies and performance outcomes in others, or included under both headings. For this reason outcomes are reported together here, separated into early and late outcomes post treatment.

It is recommended that early outcomes are reported at 30 days post treatment and include the following:

- all-cause mortality
- valve related mortality
- thromboembolism
- valve thrombosis
- all cause reoperation
- explant
- all stroke (disabling and non-disabling)
- life threatening bleeding (note: bleeding should be classified as either ‘all haemorrhage’ or ‘major haemorrhage’)
- acute kidney injury (stage 2 or 3, including need for haemodialysis)
- peri-procedural myocardial infarction
- endocarditis
- major vascular complication
- coronary obstruction requiring intervention
- valve-related dysfunction (note: valve regurgitation should be reported as ‘all paravalvular leaks’ and ‘major paravalvular leaks’)

In addition, it is recommended the following outcomes be reported after 30 days:

- all-cause mortality
- all stroke (disabling and non-disabling)
- hospitalisation for valve-related symptoms or worsening congestive heart failure
- a quality of life measure e.g. the New York Heart Association Classification (NYHA) or the Minnesota Living with Heart Failure Questionnaire (MLHF)

- prosthetic valve endocarditis
- prosthetic valve thrombosis
- bleeding, unless unrelated to valve therapy (e.g. trauma) (note: bleeding should be classified as either 'all haemorrhage' or 'major haemorrhage' 'anticoagulant-related haemorrhage'
- reoperation
- thromboembolic events (e.g. stroke)
- structural valve deterioration
- non-structural valve dysfunction/valve related dysfunction (note: valve regurgitation should be reported as 'all paravalvular leaks' and 'major paravalvular leaks' and it should be noted if the dysfunction required a repeat procedure)

At one year the following should be reported:

- Structural valve deterioration
- Thromboembolism
- Major, reversible ischemic neurological deficit (RIND)
- Valve thrombosis
- Anticoagulant-related haemorrhage
- Prosthetic valve endocarditis
- Non-structural valve dysfunction/paravalvular leak
- Re-operation

It is recommended that the following outcomes; valve related dysfunction, prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events and bleeding, be reported in a time-related manner as described in Guidelines for reporting mortality and morbidity after cardiac valve interventions.

The outcomes listed above are a recommended minimum based on a consensus report produced by the Valve Academic Research Consortium. For appropriate definitions, diagnostic criteria and measurement of the above outcomes manufacturers should consult the following documents:

- the Valve Academic Research Consortium Consensus Documents on standardised endpoint definitions for transcatheter aortic valve implantation
- guidelines by Akins *et al* (2008) for reporting mortality and morbidity after cardiac valve interventions
- guidelines on the evaluation of prosthetic valves with echocardiography
- the update of objective performance criteria for clinical evaluation of new heart valve prostheses by ISO (Wu *et al* 2014)

For valve function, including transcatheter and surgically implanted valves, indicative values on what is considered a normal functioning valve and what is considered a dysfunctional valve are reported in documents by VARC and guideline documents on the evaluation of prosthetic valves with echocardiography (Table 15, Table 16, Table 17, Table 18 and Table 19).

For surgically implanted valves other than those implanted through the transcatheter technique, specific objective performance criteria (OPC) for thromboembolism, valve thrombosis, all and

major haemorrhage, all and major paravalvular leaks and endocarditis have been determined by ISO and reported in Wu *et al* (2014) (Table 20). A new valve should have complications rates lower than twice the OPC. For transcatheter valves the number of events for each of the listed outcomes should be similar to or less than those reported in studies published in peer reviewed journals or heart valve registries for a similar type of prosthetic heart valve in the same valve position. Values that are reported need to be supported by clinical justification.

Manufacturers should report early (within 30 days post implantation) and late valve outcomes (after 30 days post implantation) with a follow-up of one year or more (two years if seeking reimbursement) and a minimum of 400 valve years of follow-up for each valve type.

Outcomes are comprised of the most relevant patient endpoints as defined by the Valve Academic Research Consortium (VARC).

For surgically implanted valves, manufacturers should refer to the objective performance criteria determined by the ISO for what is considered an acceptable number of events for different outcomes.

For transcatheter valves the number of events for each outcome should be similar to or less than those reported in studies published in peer reviewed journals or heart valve registries for a similar type of prosthetic heart valve in the same valve position.

Summary of safety and performance data

Reported clinical outcomes on prosthetic heart valves

Table 14: Summary of outcome data extracted from health technology assessments on prosthetic heart valves

Safety parameter	Surgical Aortic Valve Replacement	Transcatheter Aortic Valve Implantation	Sutureless valve replacement
Death (any cause)	a	a	a
Death (cardiovascular cause)	a	a	
Repeat hospitalisation		a	
Myocardial infarction		a	
Strokes		a	a
Transient ischemic attack		a	
kidney injury/need for haemodialysis		a	a
Vascular complications		a	
Bleeding/haemorrhage	a	a	a
Endocarditis	a	a	a

Safety parameter	Surgical Aortic Valve Replacement	Transcatheter Aortic Valve Implantation	Sutureless valve replacement
Atrial fibrillation		a	a
Tamponade/pericardial effusion		a	
Life threatening arrhythmias/arrhythmias requiring intervention		a	
Haemodynamic collapse/need for haemodynamic support		a	
New pacemaker		a	a
Device malfunction, misplacement or migration		a	a
Non-structural dysfunction	a		
Structural valvular deterioration	a		
Injury to valve or myocardium		a	
Valve-in-valve or second valve required		a	
Conversion to sutured valve			a
Conversion to surgical valve replacement		a	
Thromboembolism	a		a
Valve thrombosis	a		
Reintervention/reoperation or freedom from reoperation	a		a
Aortic regurgitation/paravalvular regurgitation		a	a
Atrioventricular block			a

Safety parameter	Surgical Aortic Valve Replacement	Transcatheter Aortic Valve Implantation	Sutureless valve replacement
Cross-clamp time	a		a
Bypass time	a		a
Left ventricular mass regression index	a		
Life expectancy based on microsimulation	a		
Event-free life expectancy based on microsimulation	a		
Successful implantation		a	
Length of stay in intensive care		a	
Length of hospital stay		a	
Haemodynamic parameters			
Post-operative mean and peak aortic pressure gradient	a	a	a
Effective orifice area index	a		a
Left ventricular ejection fraction		a	
Mean aortic valve area		a	a
Change in NYHA* class	a	a	a
6-minute walk test		a	

*NYHA: New York Heart Association

Table 15: Parameters used to assess transcatheter valve function and a guide to what are considered normal values as defined by the Valve Academic Research Consortium

Parameter	Prosthetic Aortic Valve Stenosis		
	Normal	Mild Stenosis	Moderate/Severe Stenosis
Quantitative parameters (flow dependent)†			
Peak velocity (m/s)	<3m/s	3–4 m/s	>4m/s
Mean gradient (mm/Hg)	<20 mm Hg	20–40 mm Hg	>40 mm Hg
Quantitative parameters (flow-independent)			
Doppler velocity index‡	>0.35	0.35–0.25	<0.25
Effective orifice area§	>1.1 cm^2	1.1–0.8 cm^2	<0.8 cm^2
Effective orifice area‖	>0.9 cm^2	0.9–0.6 cm^2	<0.6 cm^2

Parameter	Prosthesis-Patient Mismatch		
	Insignificant	Moderate	Severe
Indexed effective orifice area¶ (cm^2/m^2)	>0.85 cm^2/m^2	0.85–0.65 cm^2/m^2	<0.65 cm^2/m^2
Indexed effective orifice area# (cm^2/m^2)	>0.70 cm^2/m^2	0.90–0.60 cm^2/m^2	<0.60 cm^2/m^2

Parameter	Prosthetic Aortic Valve Regurgitation		
	Mild	Moderate	Severe
Semi-quantitative parameters			
Diastolic flow reversal in the descending aorta-PW	Absent or brief early diastolic	intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)**	<10%	10–29%	≥30%
Quantitative parameters‡			

Parameter	Prosthetic Aortic Valve Regurgitation		
	Mild	Moderate	Severe
Regurgitant volume (mL/beat)	<30 mL	30–59 ml	≥60 ml
Regurgitant fraction (%)	>30%	30–49%	≥50%
EROA (cm^2)	0.10 cm^2	0.10–0.29 cm^2	≥0.30 cm^2

†These parameters are more affected by flow, including concomitant aortic regurgitation
‡For left ventricular outflow tract (LVOT) >2.5 cm, significant stenosis criteria is <0.20
§Use in setting of Body Surface Area (BSA) ≥1.6 m2 (note: dependent on the size of the valve and the size of the native annulus).
‖Use in setting of BSA <1.6 m2, ¶ Use in setting of BMI <30 kg/m2, # Use in setting of BMI ≥30 kg/m2
**not well-validated and may overestimate the severity compared with the quantitative Doppler
EROA: effective regurgitant orifice area; PW: pulsed wave

Table 16: Guide to normal values, intermediate values for which stenosis may be possible and values that usually suggest obstruction in mechanical and stented-biological prosthetic aortic valves* from Zoghbi et al (2009)

Parameter	Normal	Possible stenosis	Suggests significant stenosis
Peak velocity (m/s)†	<3	3-4	>4
Mean gradient (mm Hg)†	<20	20-35	>35
DVI	≥0.30	0.29-0.25	<0.25
EOA (cm^2)	>1.2	1.2-0.8	<0.8
Contour of the jet velocity through the PrAV	Triangular, early peaking	Triangular to intermediate	Rounded, symmetrical contour
AT (ms)	<80	80-100	>100

AT: acceleration time; DVI: Doppler velocity index; EOA: effective orifice area; PrAV: prosthetic aortic valve;
*In conditions of normal or near normal stroke volume (50-70 mL) through the aortic valve
†These parameters are more affected by flow, including concomitant aortic regurgitation

Table 17: Parameters for evaluation of the severity of prosthetic aortic valve regurgitation from Zoghbi et al (2009)

Parameter	Mild	Moderate	Severe
Valve structure and motion			
Mechanical or bioprosthetic	Usually normal	Abnormal†	Abnormal†
Structural parameters			
LV size	Normal	Normal or mildly dilated‡	Dilated‡
Doppler parameters (qualitative or semiquantitative)			
Jet width in central jets (% LVO diameter): colour*	Narrow (≤25%)	Intermediate (26-64%)	Large (≥65%)
Jet density: CW Doppler	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms):CW doppler§	Slow (>500)	Variable (200-500)	Steep (<200)
LVO flow vs. pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in the descending aorta: PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Doppler parameters (quantitative)			
Regurgitant volume (mL/beat)	<30	30-59	>60
Regurgitant fraction (%)	<30	30-50	>50

CW: continuous wave; LV: left ventricular; LVO: left ventricular outflow; PHT: pressure half-time; PW: pulsed wave
*Parameter applicable to central jets and is less accurate in eccentric jets: Nyquist limit of 50-60 cm/s.
†Abnormal mechanical valves, for example, immobile occlude (valvular regurgitation), dehiscence or rocking (paravalvular regurgitation); abnormal biologic valves, for example, leaflet thickening or prolapse (valvular), dehiscence or rocking (paravalvular regurgitation).
‡Applies to chronic, late postoperative AR in the absence of other aetiologies.
§Influenced by LV compliance.

Table 18: Doppler parameters for assessment of stenosis in prosthetic mitral valves from Zoghbi et al (2009)

Parameter	Normal	Possible stenosis	Suggests significant stenosis
Peak velocity (m/s)	<1.9	1.9-2.5	≥2.5
Mean gradient (mm HG)	≤5	6-10	>10
VTIPrMv/VTI_{LVO}†§	<2.2	2.2-2.5	>2.5
EOA (cm^2)	≥2.0	1-2	<1
PHT (ms)	<130	130-200	>200

PHT: pressure half time; PrMV: prosthetic mitral valve.
*Best specificity for normality or abnormality is seen if the majority of the parameters listed are normal or abnormal, respectively.
†Slightly higher cut off values than shown may be seen in some bioprosthetic valves.
‡values of the parameters should prompt a closer evaluation of valve function and/or other considerations such as increased flow, increased heart rate, or prosthesis-patient mismatch.
§These parameters are also abnormal in the presence of significant prosthetic mitral regurgitation.

Table 19: Echocardiographic and Doppler criteria for severity of prosthetic mitral valve regurgitation using findings from transthoracic echocardiograms and transesophogeal echocardiogram from Zoghbi et al (2009)

Parameter	Mild	Moderate	Severe
Structural parameters			
LV size	Normal*	Normal or dilated	Usually dilated‡
Prosthetic valve‖	Usually normal	Abnormal¶	Abnormal¶
Doppler parameters			
Colour flow jet area‖#	Small, central jet (usually < 4 cm^2 or <20% of LA area)	Variable	Large central jet (usually >8 cm^2 or >40% of LA area) or variable size wall-impinging jet swirling in left atrium
Flow convergence**	None or minimal	Intermediate	Large
Jet density: CW Doppler‖	Incomplete or faint	Dense	Dense
Jet contour: CW Doppler‖	Parabolic	Usually parabolic	Early peaking, triangular
Pulmonary venous flow‖	Systolic dominance	Systolic blunting§	Systolic flow reversal†
Quantitative parameters††			
VC width (cm) ‖	<0.3	0.3-0.59	≥0.6
R vol (mL/beat)	<30	30-59	≥60
RF (%)	<30	30-49	≥50
EROA (cm^2)	<0.20	0.20-0.49	≥.50

EROA: effective regurgitant orifice area; LA: left atrial; RF: regurgitant fraction; R vol: regurgitant volume; VC: vena contracta.
*LV size applied only to chronic lesions.
†Pulmonary venous systolic flow reversal is specific but not sensitive for severe MR.
‡In the absence of other aetiologies of LV enlargement and acute MR.
§Unless other reasons for systolic blunting (e.g., atrial fibrillation, elevated LA pressure).
‖Parameter may be best evaluated or obtained with TEE, particularly in mechanical calves.
¶Abnormal mechanical valves, for example, immobile occlude (valvular regurgitation), dehiscence or rocking (paravalvular regurgitation); abnormal biologic valves, for example, leaflet thickening or prolapse (valvular), dehiscence or rocking (paravalvular regurgitation).
#At a Nyquist limit of 50 to 60 cm/s.
**Minimal and large flow convergence defined as a flow convergence radius<0.4 and ≥0.9 cm for central jets, respectively, with a baseline shift at a Nyquist limit of 40 cm/s; cut-offs for eccentric jets may be higher.
†† These quantitative parameters are less well validated than in native MR.

Table 20: Objective performance criteria (OPC) from the ISO for valve-related complications for new valves or newly modified valves implanted surgically (% per patient-year)*

Adverse event	Mechanical Valve		Bioprosthetic Valve	
	Aortic	Mitral	Aortic	Mitral
Thromboembolism	1.6	2.2	1.5	1.3
Valve thrombosis	0.1	0.2	0.04	0.03
Major haemorrhage	1.6	1.4	0.6	0.7
Major paravalvular leak	0.3	0.5	0.3	0.2
Endocarditis	0.3	0.3	0.5	0.4

*Not for transcather valves. A new valve is required to have complication rates lower than twice the OPC

Characteristics of clinical studies on heart valve prostheses

Table 21: Summary of study characteristics of six systematic reviews on surgical aortic valve replacement identified in a health technology assessment

Review	Design of included studies	Numbers of studies and patients	Follow-up	Comparison
Kassai *et al* 2000	RCTs	3 studies (2 in adults) 1,229 patients (1,011 adult)	Mean of 11–12 years for adults	Aortic and/or mitral: mechanical vs. bioprosthetic
Kunadian *et al* 2007	RCTs	11 studies 919 patients	NR	Aortic: Stented vs. non-stented bioprosthetic
Lund and Bland, 2006	Observational	32 articles describing 38 case series 17,439 patients	Mean 6.4 years for mechanical (range, 3.9 to 10.8) and 5.3 years (2.6 to 10.1 for bioprosthetic)	Aortic: Mechanical vs. bioprosthetic
Puvimanasghe *et al* 2004 Puvimanasinghe *et al* 2003	Observational	22 studies 13,281 patients	Total follow-up in patient-years was 25,726 for St Jude mechanical and 54,151 for porcine bioprosthesis	Aortic: St. Jude mechanical vs. porcine bioprosthetic
Puvimanasinghe *et al* 2006	Observational	13 studies 6,481 patients	18 years for Carpentier-Edwards pericardial valves and up to 20 years for Carpentier-Edwards porcine supraanular valves	Aortic: Carpentier-Edwards pericardial aortic vs. Carpentier-Edwards supra-annular bioprosthetic
Rizzoli *et al* 2004	Observational	11 studies 1,160 patients	Mean duration: 6.8 years	Tricuspid: Bioprosthetic vs. mechanical valves

NR: not reported

Table 22: Summary of study characteristics of 57 RCTs* on surgical aortic valve replacement identified in a Health Technology Assessment.

Total number of patients: 12,379

Valve types studied	Valve comparisons	Average follow-up time
Aortic (n=43)	Most common comparison was bioprosthetic stented vs. bioprosthetic unstented (n=15)	1 year or sooner (69% of studies) >1 to 5 years (24% of studies) > 5 to 10 years (7% of studies
Aortic and mitral (n=11)	Homograft vs. mechanical (n=1) Mechanical vs. mechanical (n=7) Mechanical vs. bioprosthetic (n=2) Bioprosthetic vs. bioprosthetic (n=1)	>1 to 5 years (36% of studies) > 5 to 10 years (45% of studies) >10 years (18% of studies)
Mitral (n=3)	All compared mechanical valves	Mean of 5 years

*Note: Sixteen of the 57 trials were included in the systematic reviews in Table 21

Table 23: Summary of study characteristics of two Health Technology Assessments on transcatheter aortic valve implantation

Study	Study details	Numbers of patients	Follow-up	Comparison
NICE (2011)	HTA including 1 systematic review (all Level IV studies)*, 2 level II studies, 1 Level III study and 6 Level IV studies	Systematic review: n=2,375 Level II studies: n=358 and n=699 Level III study: n=175 Level IV studies: n=ranged from 70 to 1,038	Systematic review: greater than 1 year in 7 case series and 30 days in 22 case series Level II studies: maximum of 2.8 years and 1.4 years (median) Level III study: median of 466 days Level IV studies: ranged from 30 days to a median of 3.7 years	Level II studies: TAVI vs. standard therapy and TAVI vs. surgical implantation
Tice (2014)[205]	HTA including 2 Level II studies†, 10 Level III studies‡ and 16 Level IV studies§	Level II studies: n=358 and n=699 Level III studies: ranged from n=51 to n=8,536 Level IV studies: ranged from n=130 to n=10,037	Level II studies: 19 months and 24 months Level III studies: ranged 1 month to 24 months Level IV studies: ranged from 1 month18 months	Level II studies: TAVI vs. standard therapy and TAVI vs. surgical placement Level III studies: all TAVI vs. surgical implantation except one TAVI vs. surgical implantation vs. medical therapy
Registries	NA	132 to 4,571	Major events generally reported at 30 days and then yearly after that. Maximum follow-up of 3 years for the registries identified	NA

HTA: Health Technology Assessment; NA: not applicable
*Note: given the systematic review is not on Level II studies it does not meet the Level I study classification as prescribed by the NHMRC
†Same Level II studies as included in NICE (2011)
‡ Includes one Level III study which is a meta-analyses
§ Includes two Level IV studies which are meta-analyses

Table 24: Summary of study characteristics of two Health Technology Assessments and one multicentre case series on sutureless aortic valve replacement

Study	Study details	Numbers of patients	Follow-up	Comparison
NICE (2012)	HTA including 7 studies* (1 Level III and 6 Level IV)	Range from 30 to 208	Range from duration of hospital stay (NR) to 16 months	1 Level III study compared S-AVR to TA-TAVI
Sinclair *et al* (2013)	HTA including 6 studies† (all Level IV)	Range from 6 to 140	Range from a mean of 313 days to up to 3 years	NA
Englberger *et al* (2014)	Single Level IV (multicentre) study	141	5 years	NA

HTA: Health Technology Assessment; NA: not applicable; S-AVR: sutureless aortic valve replacement; TA-TAVI: transapical-transaortic valve implantation

*This Health Technology Assessment also included one case report which was not included in data extraction

†The Health Technology Assessment included nine case series in total but three were only in abstract form so were not included in data extraction. One of the six case series in this Health Technology Assessment was also included in the Health Technology Assessment by NICE 2012

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Supportive Devices - Meshes, patches and tissue adhesives

Supportive devices act as scaffolds, reinforcement or buttressing and include all devices that hold, fix or sustain body organs or incisions. The majority of supportive devices are surgical meshes for hernia and gynaecological repair, central nervous system (CNS) patches, and tissue adhesives, but sheeting of various origins is also included.

These devices can be made from biologic and non-biologic materials and be permanent or absorbable in various combinations. Each type of supportive device has its own associated benefit-risk profile that needs to be addressed by the manufacturer.

Summary recommendations

- Manufacturers are advised that pre-clinical data demonstrating that the mechanical, biocompatibility and physical characteristics of the device are congruent with the intended purpose and anticipated in vivo lifespan of the surgical support.
- Provision of clinical investigational data:
  - manufacturers who intend to conduct a clinical trial should design the trial using the highest practical NHMRC Level of Evidence and trials should be appropriate to inform on the safety and performance of the device for its intended purpose
  - it is suggested that the minimum period for patient follow-up for clinical trials is 24 months for permanent and biological meshes. At the time of writing there is no agreed recommended follow up for patches or tissue adhesives.
  - across the surgical supports the main clinical outcomes that determine safety and performance for hernia repair are recurrence rate, reoperation rate, function and QoL scores, adhesions (particularly for intraperitoneal mesh), mesh degradation, seroma and pain, and for pelvic organ prolapse (POP) and stress urinary incontinence (SUI), cure of stress incontinence and patient scores such as the Pelvic Organ Prolapse Quantification System (POP-Q)
    - for revision data, the manufacturer is advised to benchmark the device against devices of the same class as reported by an international registry, if available
    - for patient performance data, manufacturers are advised to define the anticipated improvement in patient scores post-surgery. Ideally, these should be internationally recognised assessment tool(s) used to measure clinical success, e.g., QoL or cough stress test
  - when submitting a comprehensive literature review, full details of the method used should be included in the CER in sufficient detail to ensure the literature review can be reproduced.
  - for guidance on the conduct of comprehensive literature reviews and presentation of clinical evidence manufacturers are directed to relevant sections in this document.
- For submissions reliant on comparable device data, manufacturers and sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between a device and the nominated comparable device(s).
- In addition, a well-documented risk analysis and management system should also be provided with the CER.

- Manufacturers should provide details of the clinical context within which the clinical data were obtained. The clinical context of the evidence base should be congruent with the indications of use for which the manufacturer seeks TGA approval.
- Compilation of the CER:
  - in compiling the clinical evidence for a supportive device the manufacturer should ensure that a clinician who is an expert in the field and experienced in the use of the device critically evaluates all the clinical data that informs on the safety and performance of the device
  - the clinical expert must then endorse the CER containing the clinical evidence (evidenced by signature and date) to demonstrate that the evidence meets the requirements of the applicable EPs and the device is deemed to be safe and to perform as intended.

Defining supportive devices

The TGA describes supportive devices as devices in the following sub-groups.

- **Surgical mesh:** this is a textile-based sheet (typically knotted or warp knitted) used as a temporary or permanent support for organs or other tissues. It is used for hernia repair, POP, SUI and many other purposes. The main classes of surgical mesh are biological and synthetic or a combination of these. Types of mesh include bio-mesh, polypropylene, expanded polytetrafluoroethylene (ePTFE), composite polypropylene-PTFE, polyester, composite meshes that combine permanent and absorbable materials such as collagen, polyglactin, polylactic acid and polyglycolic acid and in combination with materials such as titanium. More than one type can be used at once and they can be absorbable, semi-absorbable and non-absorbable. The configuration of mesh varies. Fixation methods include staples, sutures, tackers and glue.
- **Patches:** specifically CNS patches, both absorbable and non-absorbable, are impermeable adhesive membranes used in intradural neurosurgical procedures, as an alternative to using autologous grafts or cadaveric implants. These patches are used to reinforce dural closure when there is the risk of postoperative cerebrospinal fluid (CSF) leak.
- **Tissue Adhesives:** these are an alternative to sutures and staples used for closure of wounds and fixation of devices such as surgical mesh, patches and scaffolding to tissues. They may also be used as a sealant for closure, for example, of colostomies. Tissue adhesives are defined as any substance with characteristics that allow for polymerization. This polymerization must either hold tissue together or serve as a barrier to leakage or to control bleeding. Fibrin sealants are the most commonly used adhesives. Other adhesives include cyanoacrylates, albumin-based compounds, collagen-based compounds, glutaraldehyde glues and hydrogels. Tissue adhesives can act as a barrier to microbial penetration as long as the adhesive film remains intact.

Any of the supportive devices can include biocompatible coated materials such as silver coating, titanium dioxide, hydroxyapatite, hyaluronate, monocryl, paclitaxel and many other materials.

Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or post-market data (clinical experience) on the device (direct) and/or the comparable device (indirect). Direct clinical evidence on the actual device is preferred. It is important to clarify if any changes have been made to the device since the clinical data were gathered and if so to document the changes and to clarify the exact version of the device. Otherwise indirect clinical evidence on a comparable device may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in Comparable devices including substantially equivalent devices.

Where the device and the predicate share any common design origin, the lineage of the devices should be provided as well. The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data. Manufacturers should refer to Clinical evidence requirements for more information.

Clinical investigation(s)

The design of the clinical investigation(s) should be appropriate to generate valid measures of clinical performance and safety. The preferred design is a randomised controlled clinical trial and conditions should ideally represent clinical practice in Australia.

The eligible patient groups should be clearly defined with exclusion/inclusion criteria, patient profiles and morbidity as well as specific indications. In addition the risks, techniques, design of implants and accessories and experience of users should be taken into account. Manufacturers are advised to justify the patient numbers recruited according to sound scientific reasoning through statistical power calculation. Registry data from jurisdictions where the device is marketed may provide useful clinical evidence.

The duration of the clinical investigation should be appropriate to the device, the patient population and medical conditions for which it is intended. Duration should always be justified, taking into account the time-frame of expected complications. Analysis of clinical events should be blinded and independently adjudicated wherever possible.

Literature review

A literature review involves the systematic identification, synthesis and analysis of all available published and unpublished literature, favourable and unfavourable, on the device or comparable device when used for its intended purpose(s).

The literature search protocol should be determined prior to implementing the search, detailing the aim, search terms, planned steps and inclusion and exclusion criteria. Data on the materials used to construct the device, their biocompatibility, the device dimensions and geometry and the intended purpose will determine the construction of search strategies as well as study selection. The selection of comparable device should be made prior to performing the literature selection, extraction of the clinical evidence and analysis of the pooled results. The search output should be assessed against clearly defined selection criteria documenting the results of each search step with clear detail of how each citation does or does not fit the selection criteria for inclusion in the review. This ensures that the searches are comprehensive and the included studies are related to the device in question or substantially equivalent device(s).

A full description of the device used or adequate information to identify the device (e.g. manufacturer name and model number) must be extractable from study report. If this is not possible, the study should be excluded from the review. The overall body of evidence from the literature should be synthesised and critically evaluated by a competent clinical expert and a literature report prepared containing a critical appraisal of this compilation. The full details of the search can be provided in the supporting documents and should be sufficient to allow the search to be reproduced.

Post-market data

Post-market data can be provided for the actual device or for the comparable device.

It is particularly important to include the following:

- information about the regulatory status of the device(s) or comparable device, including the certificate number, date of issue and name under which the device is marketed, the exact wording of the intended purpose/approved indication(s) and any conditions in other jurisdictions
- any regulatory action such as CE mark withdrawals, recalls (including recalls for product correction, and the reason for these i.e. IFU change), suspensions, removals, cancellations, any other corrective action) anywhere in the world as reported to or required by regulatory bodies
- distribution numbers of the device(s) including by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- the number of years of use
- for every year since launch, adverse events, complaints and vigilance data categorised by type and clinical outcome (adhesion, tissue damage (erosion, dehiscence etc.), chronic pain, bacterial infection and toxicity due to chemical components of the device)
- the post-market surveillance data from national registries in jurisdictions where the device is approved for clinical use if available
- explanted devices returned to manufacturers should be accounted for with an explanation of device failures and corrective measures.

Publicly available post-market data such as adverse event reporting on the FDA MAUDE database and the TGA IRIS may be used for devices from other manufacturers.

For reports of adverse events and device failures to be useful clinical evidence, the manufacturer must make a positive, concerted effort to collect the reports and to encourage users to report incidents. Experience shows that merely relying on spontaneous reports leads to an underestimation of the incidence of devices failures and adverse events.

The post-market data should be critically evaluated by an appropriately qualified clinical expert, that is, someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting. The CER should then be endorsed by the clinical expert (evidenced by signature and date) to enable an understanding of the safety and performance profile of the device(s) in a ‘real-world’ setting.

Compiling the CER

In compiling the clinical evidence the manufacturer should ensure that a clinical expert in the relevant field critically evaluates all the clinical data from clinical investigation(s), literature review and/or post-market data (clinical experience) and provides a written report, the CER, to allow the clinical assessor to determine whether the clinical evidence is sufficient to demonstrate that the requirements of the applicable EPs have been met and the device is safe and performs as intended.

Sources of clinical data and The Clinical Evaluation Report outline the components that may comprise clinical evidence for a medical device, and the process to compile a CER, respectively. These apply whether the manufacturer is using direct clinical evidence or relying on indirect clinical evidence based on a comparable device. Guidance on defining a comparable device is provided in Comparable devices including substantially equivalent devices.

The device description should include sufficiently detailed information to satisfy the requirements of Appendix 3 of MEDDEV 2.7.1 Rev 4 on "Device description – typical contents". For supportive devices this may include, but is not limited to; the material type, chemical composition, biological compatibility testing, coating, porosity, flexibility, tensile strength, durability and dimensions. If biological actives are impregnated the in vitro activity should be demonstrated and documented in the submission.

The design of clinical studies to demonstrate the clinical safety and performance of devices that have no equivalent comparable device must include all device characteristics and all intended uses. If a comparable device is available and data from that device is used to support a submission, the device characteristics and intended purpose will determine the criteria for a full and reasoned clinical justification for the comparable device selection.

As per The Clinical Evaluation Report the CER should include the following:

a) General details

b) Description of the medical device and its intended application

c) Intended therapeutic and/or diagnostic indications and claims

d) Context of the evaluation and choice of clinical data types

e) Summary of relevant pre-clinical data

f) Discussion regarding comparable devices including substantially equivalent devices

g) Summary of the clinical data and appraisal

h) Data analysis

i) Conclusions

j) Name, signature and curriculum vitae of clinical expert and date of report

Supportive data and information

The following information on the device must also be provided:

- risk assessment and management document
- IFU, labelling, product manual and all other documents supplied with the device. The clinical evidence must highlight the risks and ensure that these are appropriately communicated to user.

Additional information should be provided as applicable. This may include (but is not limited to):

- additional specifications of the device(s)
- the materials from which the device is made including chemical composition
- other devices that may be used in conjunction with the device
- any aspects of non-clinical testing results that inform the design of the clinical trial should be included in the supporting documents

- biocompatibility testing, bench testing and animal studies where applicable
- specific testing of any adjuvant medicinal components may be required especially if these are new chemical entities in the Australian context. This should cover interactions between the device and the medicine, pharmacodynamics and time-release profiles.
- any further details of post-market data

Defining clinical success

Meshes

Hernia repair surgery is the most common application for surgical meshes followed by reconstructive surgery for POP and SUI.

Meshes can be used for either a primary or secondary repair or as suture line reinforcement material. It is imperative that the clinical evidence reflects the indication for use of the mesh under review. Measures such as de novo or worsening prolapse in a non-treated compartment and urinary symptoms may be reported as both safety and performance measures.

Safety

Post-operative complications and/or reoperation are the primary safety outcome measures although subjective measures of success should also be included.

Complications associated with surgical mesh for hernia repair reported in the literature include adhesions, fistula, bowel obstruction, mesh erosion, bleeding, infection, haematoma, seroma and chronic pain. Bowel obstruction is not seen in extra peritoneal mesh placement. Some of these complications may occur with surgery and are not due to the mesh per se.

Complications associated with surgical mesh for POP and SUI reported in the literature include pain, bleeding, organ perforation (such as bladder and urethral perforation), dyspareunia, visceral injury, urinary issues (including retention, voiding dysfunction, urge incontinence, overactive bladder) as well as late events such as mesh erosion and exposure. A summary of the safety data extracted from systematic reviews is provided in Table 25. Clinical experts have reported additional complications associated with the use of surgical mesh for POP and SUI which include inflammation, seroma, haematoma, infection, fistula, urinary tract infection, bowel dysfunction, nerve injury, chronic pain and de novo or worsening prolapse in a non-treated compartment.

The manufacturer should report all post-surgical complications and serious adverse events or failures that have been found with the use of the mesh or comparable device(s) if used for comparison. Registers also collect valuable information on surgical outcomes and some public measures of performance and adverse outcomes.

One direct register for meshes used in POP repair was identified:

- Austrian Urogynecology Working Group registry for transvaginal mesh devices for POP repair

In addition a number of registers for surgeries that involve meshes for hernia repair were identified:

- Swedish hernia register
- Herniamed, a German internet-based registry for outcome research in hernia surgery
- Americas Hernias Society Quality Collaborative (AHSQC) in the USA
- European Registry of Abdominal Wall Hernias (EuraHS)
- ClubHernie

The Environmental Protection Agency's Integrated Risk Information System (IRIS) is a US safety database for toxicology and human effects data from chemical substances which may in some cases provide information on products used in or with meshes.

Based on the literature reviewed for these guidelines, if clinical studies are conducted, the minimum patient follow-up should be 24 months for hernia and gynaecological repair. However, manufacturers should be aware that late adverse events of a device can occur many years after implantation.

Safety parameters should be established *a priori* with nominated values clinically justified by a clinical expert experienced in the use of the device.

Performance

It is useful to divide success into objective success measures and subjective success measures, such as clinician reported outcomes and patient-reported outcomes. Performance related parameters reported in the peer reviewed literature for surgical meshes include recurrence rates, reoperation rates, functional scores, quality of life scores and pain. For absorbable devices, clearance and metabolism times are also provided in Table 25. Other measures for performance are objective success measures (including anatomic success measure such as POP-Q) and subjective success measures such as quality of life outcomes. An important outcome is de novo or worsening prolapse in a non-treated compartment and, specifically in regards to SUI, de novo or worsening urinary symptoms should be included as a measure of performance.

Primary repair

Recurrence and reoperation rates can be used to measure clinical success in primary repair surgery.

Recurrence rates of 15-25% are frequently reported after mesh repair of a hernia. The rates of reoperation vary based on the indication, patient characteristics and surgical procedure undertaken, therefore, depending on these characteristics, rates within this range may be considered acceptable. A satisfactory result of biologic mesh application is a recurrence rate of 18% or below and seroma formation of 12% or less.

Importantly, patient follow-up periods must be comparable to accurately compare recurrence rates as a function of supportive devices.

Primary and secondary outcomes

Clinical success is often evaluated by patient-oriented assessment tools that determine functional outcomes. It can also be evaluated by primary outcomes or secondary outcomes, and it is important to make a distinction between these two. Functional scores provide an aggregate of patient reported domains (e.g. pain) with an objective measure of mesh success (e.g. current size of hernia) and represent a clinically meaningful grading of mesh performance. However, for procedures using surgical mesh, the short-term performance of a device may be dominated by procedural variables; therefore sufficient time should lapse to isolate device-specific improvements.

Measures of performance that may be of use include the Ventral Hernia Working Group (VHWG) grading system and the Pelvic Organ Prolapse Quantification System (POP-Q). POP-Q is a validated staging system for pelvic organ prolapse and currently the most quantitative, site-specific system with high reported inter-observer reliability. The VHWG has a staging system which predicts both risk and likely outcome in terms of both recurrence and SSO. It is made up of the VHWG grading system plus a defect size component to predict SSO and recurrence and has been validated for clinical application.

Where validated measurement tools are not used, manufacturers can assist the clinical assessor by providing data based on surrogate markers. The choice of surrogate markers and the validation of these to predict future complications or failure should be clinically justified and consistent with the proposed therapeutic indications.

Examples of surrogate markers for mesh performance are:

- Reoperation for recurrence in hernia surgery
- For hiatal hernia, radiological or endoscopic absence of a recurrent hernia (defined as >2cm in size)[211]
- For POP, examples of surrogate markers of performance include: recurrent prolapse, ongoing pain including dyspareunia, de novo urinary or bowel symptoms.
- For SUI, de novo or worsening urinary symptoms

Manufacturers should, where possible, use validated measurement tools. When selecting and reporting surrogate markers of performance manufacturers should provide a clinical justification for the selection.

Minimum benchmarks that need to be reached to demonstrate the device is performing as expected and is equivalent to already marketed products should be used. For prolapse, at one year POP-Q stage II or greater is considered to be surgical failure and POP-Q stage I was considered a surgical cure. For hernia, at the time of writing, there are no benchmarks for performance.

Patches

Central Nervous System (CNS) patches, both bioabsorbable and non-absorbable, are impermeable adhesive membranes used in (intradural) neurosurgical procedures, as an alternative to using autologous grafts or cadaveric implants. These patches are used to reinforce dural closure when there is the risk of postoperative cerebrospinal fluid (CSF) leak.

Safety

For safety, the primary outcome measures are CSF leak, CSF fistula and deep wound infection. Other complications associated with CNS patches (studies reviewed tested for these effects but their occurrence was very rare) include adverse or allergic effects, hydrocephalus, brain tissue scarring, new epileptic seizures and mortality, refer to Table 26. The manufacturer should report all of the above and any other serious post-surgical events for the patch or comparable device if used for comparison.

Based on the literature reviewed for these guidelines, the minimum possible patient follow-up for studies conducted on CNS patch surgery is three months. However, manufacturers should be aware that 3 months is the minimum and will not capture information relating to the late failure of a patch. At the time of writing there are no benchmarks for CNS patches. Manufacturers should define a minimum performance marker based on the literature and clinical expertise, providing a clinical justification for the parameters and values that have been selected.

Performance

Performance related parameters reported in the peer reviewed literature for patches are provided in Table 27.

Clinical success is often evaluated by patient-oriented assessment tools that determine functional outcomes. With regards to mesh, functional scores provide an aggregate of patient reported domains (e.g. pain) with an objective measure of mesh success (e.g. improvement in POP-Q stage) and represent a clinically meaningful grading of mesh performance. No such tool has been found for application of CNS patch. The most useful functional measure for CNS patches is the existence of cerebrospinal fluid leakage. Manufacturers should define a minimum performance marker based on the literature and clinical expertise, providing a clinical justification for the parameters and values that have been selected.

Tissue adhesives

Safety

Chronic pain, infection, inflammation, tissue damage, bleeding and leakage of bile and other fluids are primary outcome measures for tissue adhesive surgeries, refer to Table 26. Chronic pain can be measured with Visual Analogue Score (VAS) as mild, moderate or severe persisting from 3 months to 1 year. Secondary outcomes reported in the literature are numbness, discomfort, patient satisfaction, QoL (measured with SF12), length of hospital stay, and time to return to normal activities. The manufacturer should report any post-surgical complications and failure of the adhesive or comparable adhesive device.

Articles reporting on tissue adhesives rarely report follow up times, rather they refer to post-operative outcomes. Recurrence rates considered acceptable for surgeries using tissue adhesives are important in measuring success. In the literature, recurrence was found to be 1.5% at 17.6 months in a study on hernia repair using fibrin glue. Another study found a recurrence rate of 2.3% at 15 months. Thus a recurrence rate <2.3% in 15-18 months may be acceptable. Rates for tissue adhesives other than those containing fibrin glue are not readily evident, at time of writing. Patient follow-up periods must be comparable when using recurrence rates as a measure of performance of tissue adhesives. Nominated recurrence rates need to have a rigorous clinical justification provided by a clinical expert with experience in the use of the device or device types who takes into account current research when evaluating all of the clinical data in the CER.

Performance

Recurrence is one performance related parameter reported in the peer reviewed literature for tissue adhesives (Table 27).

Clinical success of surgery is often evaluated by patient-oriented assessment tools that measure functional outcomes. Functional scores would provide an aggregate of patient-reported domains (e.g. pain) with an objective measure of success (e.g. fluid leakage) and represent a clinically meaningful grading of performance. A functional measure for tissue adhesives is wound closure. It is recommended that the manufacturers define a minimum performance marker based on the literature and clinical expertise and provide a clinical justification for the parameters and values that have been selected.

When documenting patient performance scores for tissue adhesives, it is recommended that manufacturer provide a clinical justification for the follow-up period used. At the time of writing 15-18 months follow-up has been reported in the literature.

As assessment tools of device performance may not be available, manufacturers can assist the clinical assessors by providing data on direct markers.

Examples of direct markers for performance of adhesives are:

- achievement of haemostasis/ increased number of patients reaching haemostasis – measured as no evidence of bleeding from exposed surfaces
- presence of haematoma/ seroma during study, visual perception of oedema 1-7 days post-operatively
- fluid drainage 24h post-operatively, volume of blood loss or transfusion, and resection surface complications such as intra-abdominal fluid collections detected by CT scan
- reduction in drainage volume
- morbidity defined as all complications arising directly related to the procedure
- mortality defined as death within 30 days of the procedure or within the same hospital admission

Manufacturers should, where possible, use validated measurement tools. If selecting and reporting surrogate markers of performance manufacturers should provide a clinical justification for the selection and validation of these to predict device complications or failure.

Summary of safety and performance data

Characteristics of clinical studies on supportive devices

Table 25: Summary of study characteristics extracted from systematic reviews and primary research reports on safety and performance of supportive devices

Characteristic of included studies	Meshes - Hernia	Meshes - Gynaecological	Patches	Tissue Adhesives
Systematic reviews	11	5	0	4
Number of included studies per systematic review	4 - 40	20 - 45	NA	4 - 10
Sample size (range) for included studies	14 - 1120	63 - 95	NA	20 - 255
Dominant design of included studies	RCT, observational, case control, prospective cohort	RCTs	NA	RCTs, observational studies

Characteristic of included studies	Meshes - Hernia	Meshes - Gynaecological	Patches	Tissue Adhesives
Reported comparisons	Lightweight v. heavy mesh Lichtenstein repair v. mesh plugs Sutures v. glue for mesh fixation Sublay v. onlay for mesh position Laporascopic v. open surgery Comparing mesh materials Biologic v. non biologic mesh Human-derived v. porcine-derived biologic mesh Self-gripping mesh or suture fixation	Mesh v. conventional repair Mesh v. vaginal colpopexy Mesh v. anterior or posterior colporrhaphy	NA	Fibrin sealant v. staples Fibrin sealant v. Tranexamic acid Fibrin sealant v. control
Quality of included evidence as reported	Poor to satisfactory	Low to high	NA	Inadequate to good
Patient Follow-up Comparative trials e.g. RCTs	1 month to 10 years	3 months to 3 years	NA	7 months to 4 years

Reported clinical outcomes in the peer reviewed literature

Table 26: Summary of safety data extracted from systematic reviews on supportive devices

Safety parameter	Vaginal surgical mesh	Hernia surgical mesh	Patches	Tissue adhesives
Death			ü	ü
Urinary issues	ü		*N/A*	*N/A*
Pain	ü	ü		
Chronic pain		ü	*N/A*	ü
Infection		ü	ü	ü
Bleeding	ü	ü		ü
Organ perforation	ü			*N/A*
Dyspareunia	ü		*N/A*	*N/A*
Material exposure	ü		*N/A*	*N/A*
Visceral injury	ü		*N/A*	*N/A*
Mesh erosion	ü	ü	*N/A*	*N/A*
Haematoma		ü	*N/A*	ü
Seroma		ü	*N/A*	ü
Bile leak	*N/A*	*N/A*	*N/A*	ü
Cytotoxicity	ü		*N/A*	ü
CSF leakage	*N/A*	*N/A*	ü	
Adhesions	*N/A*	ü	*N/A*	*N/A*
Fistula	*N/A*	ü	*N/A*	*N/A*
Bowel obstruction	*N/A*	ü	*N/A*	*N/A*
Hydrocephalus	*N/A*	*N/A*	ü	*N/A*

Greyed cells (N/A) indicate that the safety parameter is not applicable to that device class

Table 27: Summary of performance data extracted from systematic reviews, RCTs and primary research reports on the safety and performance of supportive devices

Performance parameter	Surgical Mesh - Gynaecological	Surgical Mesh - Hernia	Absorbable devices	Patches	Tissue Adhesives
Revision/ reoperation (recurrence rates)	ü	ü	ü	ü	ü
Function scores	Pelvic Organ Prolapse Quantification System (POP-Q) Incontinence Impact Questionnaire Short-form prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) Patient Global Impression of Change (PGIC) Pelvic Floor Distress Inventory (PFDI-20) Pelvic Floor Impact Questionnaire (PFIQ-7) Surgical Satisfaction Questionnaire (SSQ)			Existence of CSF leakage	
Quality of Life (QoL) scores		SF-36 SHS SF-12 EuroQol EQ-5D			

Performance parameter	Surgical Mesh - Gynaecological	Surgical Mesh - Hernia	Absorbable devices	Patches	Tissue Adhesives
Pain		VAS post-herniorrhaphy pain questionnaire McGill pain Questionnaire Inguinal Pain Questionnaire Cunningham classification of post-herniorrhaphy pain			
Clearance			Days to clear the body, days metabolised, excretion route		

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Software as Medical Device

Introduction

Software use is increasingly common in medical devices. The guidance provided in this chapter describes the clinical evidence that should be provided for devices in which the claim of clinical benefit is attributed to the software itself. (Software that is used to support the intended purpose of the device is not covered in this chapter.)

In the context of software, clinical benefit may be considered slightly differently from that for pharmaceuticals or other medical devices. The clinical benefit of software as a medical device most commonly lies in obtaining or collating clinical information which assists with clinical decision making. If a software device is making the claim of clinical benefit, this must be supported by clinical evidence including safety, effectiveness and performance data.

Summary recommendations

The TGA is a member for the International Medical Device Regulators forum and follows the recommendations for evaluation outlined at

Software as a Medical Device (SaMD): Clinical Evaluation (IMDRF/SaMD WG/N41): https://www.imdrf.org/documents/software-medical-device-samd-clinical-evaluation

and

Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software (MDCG 2020-1): https://ec.europa.eu/health/system/files/2020-09/md_mdcg_2020_1_guidance_clinic_eva_md_software_en_0.pdf

Glossary and abbreviations

Glossary

Adverse event: Any untoward medical occurrence in patients/subjects, users or other persons. In the context of clinical investigation, for patients/subjects, this would include all untoward medical occurrences, whether or not related to the device that is the subject of the investigation, that occurred in the course of the investigation. In the context of clinical experience, this would only include untoward medical occurrences that may be related to the medical device.

Application audit: The Act enables the Regulations to prescribe certain kinds of applications that are to be selected for audit. These kinds of applications must be selected for audit by the Secretary. However, the Secretary may also select for auditing any other application under section 41FH of the Act. The TGA has established two levels of application audit, Level 1 and Level 2:

- ***Level 1:*** Targeted for completion within 30 days - The TGA will consider:
  - the original or correctly notarised copy of the manufacturer's Australian Declaration of Conformity
  - Copy of the latest and current conformity assessment evidence for the medical device
  - Information about the device, including copies of the label, instructions for use and advertising material such as brochures, web pages and advertisements

- ***Level 2:*** Targeted for completion within 60 days – The TGA will consider all of the documentation considered in a Level 1 audit. In addition, the TGA will consider:
  - the risk management report
  - the clinical evaluation report
  - efficacy and performance data for medical devices that disinfect including those that sterilise other medical devices.

Assessor: A medically qualified person who reviews the clinical evaluation report and supporting documents provided to the TGA with applications for inclusion, review of conformity assessment procedures and post-market reviews of medical devices.

Australian Register of Therapeutic Goods (ARTG): The ARTG is the register of information about therapeutic goods for human use that may be imported, supplied in or exported from Australia. All medical devices, including Class I, must be included in the ARTG before supply in Australia. There are limited exceptions to this requirement specified in the legislation.

Biological characteristics: Relate to use of the materials or substances in contact with the same human tissues or body fluids. Evaluators should consider biological safety (e.g. in compliance to ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference.

Clinical data: Safety and/or performance information that is generated from the clinical use of a device.

Note: Under the clinical evaluation procedures in Part 8 of Schedule 3 of the MD Regulations, the manufacturer must obtain clinical data in relation to the device in the form of clinical investigation data or a literature review, or both.

Clinical evaluation: A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety and/or performance of a medical device when used as intended by the manufacturer.

Note: the clinical evaluation procedures (in the MD Regulations) set out requirements in relation to the obtaining and evaluation of clinical data.

Clinical evidence: The clinical data and the clinical evaluation pertaining to a medical device.

Note: EP 14 provides that every medical device requires clinical evidence demonstrating that the device complies with applicable EPs.

Competent clinical expert: Generally expected to be someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting.

Note: the clinical evaluation procedures (in the MD Regulations) require the manufacturer to ensure that the clinical data is evaluated by competent clinical experts.

Clinical Evaluation Report (CER): A report by an expert in the relevant field outlining the scope and context of the evaluation, the inputs (clinical data), appraisal and analysis stages, and conclusions about the safety and performance of the device. The clinical evaluation report should be signed and dated by the clinical expert.

Clinical investigation: Systematic investigation or study in one or more human subjects, undertaken to assess the safety and/or performance of a medical device.

Note: 'clinical trial' or ' clinical study' is synonymous with 'clinical investigation' and these terms are used interchangeably in this document.

Clinical investigation data: Safety and/or performance information that is generated from the use of a medical device (based on the definition above this information is generated in or on one or more human subjects).

Clinical investigation plan: Document that states the rationale, objectives, design and pre-specified analyses, methodology, monitoring, conduct and record-keeping of the clinical investigation.

Clinical performance: The ability of a medical device to achieve its intended clinical purpose as claimed by the manufacturer.

Clinical safety: Acceptability of risks as weighed against benefits, when using the medical device according to the manufacturer's labelling.

Clinical use: Use of a medical device in or on living human subjects.

Note: Includes use of a medical device that does not have direct patient contact.

Comparable device: A medical device with related function chosen by the manufacturer to inform the clinical evaluation of the device in question.

Note: A 'comparable device' is distinct from a 'comparator', which is the state of the art/standard of care against which a medical device may be compared (for example, in a clinical study).

Conformity Assessment: The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles.

Conformity assessment is the name given to the processes that are used to demonstrate that a device and manufacturing process meet specified requirements. In Australia this means that the manufacturer must be able to demonstrate that both the medical device and the manufacturing processes used to make the device conform to the requirements of the therapeutic goods legislation.

Conformity assessment is the systematic and ongoing examination of evidence and procedures to ensure that a medical device complies with the Essential Principles. It provides objective evidence of the safety, performance, benefits and risks for a specified medical device and also enables regulatory bodies to ensure that products available in Australia conform to the applicable regulatory requirements.

The Conformity Assessment Procedures allow risk based premarket assessment for devices. All manufacturers of all medical devices are required to meet manufacturing standards and all manufacturers, except those manufacturing the lowest risk devices, are audited and are required to have their systems certified. The level of assessment is commensurate with the level and nature of the risks posed by the device to the patient, ranging from manufacturer self-assessment for low risk devices through to full TGA assessment with respect to high-risk devices.

Conformity assessment certificate: A certificate to demonstrate that the conformity assessment procedure has been assessed.

Critical analysis: The process of the careful and systematic examination, appraisal and evaluation of both favourable and unfavourable data.

Essential Principles: The Essential Principles (EPs) provide the measures for safety and performance and are set out in Schedule 1 of the MD Regulations. For a medical device to be supplied in Australia, it must be demonstrated that the relevant EPs have been met.

Hazard: Potential source of harm.

Incident: Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Indications for use: The disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

Intended purpose: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.

In-Vitro Diagnostic (IVD): A medical device is an IVD if it is a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with other diagnostic goods for in vitro use. It must be intended by the manufacturer to be used in vitro for the examination of specimens derived from the human body, solely or principally for the purpose of giving information about a physiological or pathological state, a congenital abnormality or to determine safety and compatibility with a potential recipient, or to monitor therapeutic measures. The definition of an IVD does not encompass products that are intended for general laboratory use that are not manufactured, sold or presented for use specifically as an IVD.

Kind of medical device: A single entry in the ARTG may cover a range of products that are of the same kind rather than individual devices. At present, medical devices (with the exception of Class III and Active Implantable Devices (AIMDs) and Class 4 IVDs and Class 4 in-house IVDs) are included as a group in the ARTG under a single entry if they: have the same sponsor; have the same manufacturer; have the same medical device classification; have the same nomenclature system code (GMDN code).

Manufacturer: Refer to section 41BG of the Act.

Medical device: A medical device is:

(a) any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

   i. diagnosis, prevention, monitoring, treatment or alleviation of disease;

   ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;

   iii. investigation, replacement or modification of the anatomy or of a physiological process or state;

   iv. control or support of conception;

   v. in vitro examination of a specimen derived from the human body for a specific medical purpose;

   and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means; or

(aa) any instrument, apparatus, appliance, material or other article specified under subsection (2A); or

(ab) any instrument, apparatus, appliance, material or other article that is included in a class of instruments, apparatus, appliances, materials or other articles specified under subsection (2B); or

(b) an accessory to an instrument, apparatus, appliance, material or other article covered by paragraph (a), (aa) or (ab).

Refer to section 41BD of the Act for remainder of the definition.

Medical device classifications: Medical devices are classified according to their risk. The device classifications are determined using a set of rules contained in the Regulations that take into account the degree of invasiveness in the human body, the duration and location of use and whether the device relies on a source of energy other than the body or gravity. There are two sets of classification rules; one based on the above and the other based on IVDs as medical devices.

Predicate: A previous iteration of the device, within the same lineage of devices, with the same intended purpose and from the same manufacturer, in relation to which a manufacturer is seeking to demonstrate substantial equivalence.

Post-market surveillance: Once a device has been included in the ARTG, the sponsor has ongoing responsibilities. These include monitoring and reporting to the TGA adverse events, vigilance reports, complaints, performance issues and regulatory actions in other jurisdictions. Please refer to Sections 22 and 23 of the ARGMD.

Risk: Combination of the probability of occurrence of harm and the severity of that harm.

Risk management: Systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.

Serious adverse event: An adverse event that led to a death or led to a serious deterioration in health (one that results in a life-threatening illness or injury; results in a permanent impairment of a body structure or body function; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; led to foetal distress, foetal death or a congenital abnormality/ birth defect).

Sponsor: Refer to Section 3 of the Act.

Substantial equivalence: A finding that comparable devices are similar to such an extent that there would be no clinically significant difference in safety and performance, taking into account the intended purpose and clinical, technical and biological characteristics of the devices.

Technical characteristics: These relate to the design, specifications, physicochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use.

Abbreviations

Abbreviation	Meaning
AAA	Abdominal aortic aneurysm
AE	Adverse event
AICD	Active implantable cardiac device
AIMD	Active implantable medical device
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ARGMD	Australian Regulatory Guidelines for Medical Devices
ARTG	Australian Register of Therapeutic Goods
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (Royal Australasian College of Surgeons)
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
BMS	Bare metal stent
BSIR	British Society of Interventional Radiology
CAPA	Corrective and preventive action
CE	Conformité Européenne (European Conformity)
CEBM	Centre for Evidence-Based Medicine
CDMSNet	Canadian Medical Devices Sentinel Network
CDRH	Center for Devices and Radiological Health [USA]
CER	Clinical Evaluation Report
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPR	Cumulative Percent Revision
CRT	Cardiac Resynchronisation Therapy
CSR	Clinical Study Report

Abbreviation	Meaning
CTA	Computed tomography angiography
D&B	Downs & Black [quality assessment tool]
DES	Drug-eluting stent
DVT	Deep vein thrombosis
EHR	Electronic Health Record
EPs	Essential Principles
EU	European Union
EUDAMED	European Databank on Medical Devices
FDA	Food and Drug Administration [USA]
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GMDN	Global Medical Device Nomenclature [System]
HBD	Harmonisation By Doing
HDE	Humanitarian device exemption
ICMJE	International Committee of Medical Journal Editors
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IDEAL	Innovation, Development, Exploration, Assessment, Long-term study [Collaboration]
IFU	Instructions For Use
ILR	Implantable Loop Recorder
IMDRF	International Medical Device Regulators Forum
IRIS	Medical device Incident Reporting and Investigation Scheme (TGA)

Abbreviation	Meaning
ISO	International Standards Organization
IVD	In vitro diagnostic
KAT	Knee Arthroplasty Trial
LOHS	Length of hospital stay
MA	Meta-analysis
MACE	Major adverse cardiac events
MAUDE	Manufacturer and User Facility Device Experience database
MCID	Minimum clinically important difference
MDPS	Medical device production systems
MD Regulations	Therapeutic Goods (Medical Devices) Regulations 2002
MDR	Medical Device Reporting (Program) [USA]
MedSun	Medical Device Surveillance Network [USA]
MHLW	Ministry of Health, Labour & Welfare [Japan]
MHRA	Medicines and Healthcare Products Regulatory Authority [UK]
MI	Myocardial infarction
MLHF	Minnesota Living with Heart Failure Questionnaire
MPMDB	Marketed Pharmaceutical and Medical Devices Bureau [Canada]
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NB	Notified Body [EU]
NCAR	National Competent Authority Report
NHMRC	National Health and Medical Research Council
NHS	National Health Service [UK]

Abbreviation	Meaning
NICE	National Institute for Heath and Care Excellence
NOS	Newcastle-Ottawa scale [quality assessment tool]
NR	Not Reported
NYHA	New York Heart Association Classification
OPC	Objective Performance Criteria
PAL	Pharmaceutical Affairs Law [Japan]
PCT	Pacing Capture Threshold
PDA	Patent Ductus Arteriosus
PE	Pulmonary Embolus
PMA/PMAS	Pre-Market Approval or Pre-Market Approval Supplement [USA]
PMCF	Post-Market Clinical Follow-up
PMD	Personalised medical device
PMDA	Pharmaceuticals and Medical Devices Agency [Japan]
PPM	Permanent Pacemaker
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PMS	Post-market Surveillance
POP-Q	Pelvic Organ Prolapse Quantification System
QMS	Quality Management System
QOL	Quality Of Life
QUADAS	Quality Appraisal of Diagnostic Accuracy Studies
RANZCR	Royal Australian and New Zealand College of Radiologists
RCT	Randomized controlled trial
RF	Radiofrequency

Abbreviation	Meaning
RIND	Reversible Ischemic Neurological Deficit
RSA	Radiostereometric analysis
RWD	Real World Data
RWE	Real World Evidence
SAR	Specific Absorption Rate
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guidelines Network
SSO	Surgical Site Occurrence
SR	Systematic Review
STARD	Standards for Reporting of Diagnostic Accuracy
STED	Summary Technical Document
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient Ischemic Attack
TGA	Therapeutic Goods Administration
TLR	Target Lesion Revascularisation
TPLC	Total product life cycle
TVR	Total Vessel Revascularisation
UK	United Kingdom
USA	United States of America
VARC	Valve Academic Research Consortium
VHWG	Ventral Hernia Working Group
VTE	Venous Thromboembolism
WHO	World Health Organisation

Source material

Search Method: Identification and selection of clinical studies

The search method used by ASERNIP-S to identify, retrieve and review the evidence that supports this guidance document was a pragmatic adaption of a rapid systematic review.[11]

Selection criteria were established *a priori* and include publication type, type of medical device under review, intended purpose of the medical device, adverse events (safety), and clinical outcomes related to device performance.

Using the PubMed Clinical queries tool, representative articles were identified through scoping searches. These results informed the selection of appropriate text words and subject headings.

All searches were executed using the Ovid platform for Medline, Embase and the Cochrane library and Evidence-based medicine databases. Through the application of search filters for study type (Systematic Reviews, Randomised Controlled Trials and Registry trials) search results were restricted to appropriate level evidence.

For joint prostheses - Search title: Total and partial joint arthroplasty: Search terms: Shoulder surgery[MeSH], Shoulder Joint/surgery[MeSH]; Knee surgery [MeSH]; 'knee Joint' surgery[MeSH]; hip Joint surgery [MeSH]; arthroplasty[MeSH]; ((shoulder OR hip OR Knee) adj2 replacement). [text word]; ((shoulder OR hip OR Knee) adj2 joint).[text word]; ((shoulder OR hip OR Knee) adj3 arthroplasty)[text word]; ((shoulder OR hip OR Knee) adj3 surger?)[text word].

For cardiovascular devices for patency and functional flow- Search title: Cardiovascular devices for patency and functional flow: Search terms: Heart [MeSH]; aneurysm [MeSH]; aorta[MeSH]; Venae cavae[MeSH]; 'Ductus Arteriosus, Patent'[MeSH]; vascular.[text word]; endovascular.[text word]; cardiovascular. [text word]; heart.[text word]; cardiac.[text word]; ; 'vena cava'.[text word]; aorta.[text word]; 'Patent ductus arteriosus'.[text word] ; aneurism.[text word]

Selected CV flow implants included the following types:

- Arterial stents (carotid, coronary and peripheral)
- Implants for AAA repair
- Implants for PDA repair

For implantable pulse generators - Search title: electrical impulse generators: Search terms: Pacemaker, Artificial[MeSH]; Biological Clocks[MeSH]; Tachycardia, Ectopic Atrial[MeSH]; implantable cardioverter-defibrillators[MeSH]; Defibrillators, Implantable[MeSH]; Tachycardia, Ventricular[MeSH]; Ventricular Fibrillation[MeSH]; Pain Management[MeSH]; Postoperative pain[MeSH]; Analgesia, Patient-Controlled[MeSH]; Magnetic Field Therapy[MeSH]

Selected implantable pulse generators of the following types:

- Active Implantable Cardiac Devices (AICD) including:
  - single and dual chamber pacemakers
  - cardiac resynchronisation therapy pacemakers, with or without defibrillation (i.e. CRT-D and CRT respectively)

[11] Watt A, Cameron A, Sturm L et al. Rapid reviews versus full systematic reviews: an inventory of current methods and practice in health technology assessment. Int J Technol Assess Health Care. 2008;24:133-9.

  - implantable cardiac defibrillators (ICDs)
- Electrical nerve stimulation devices

For heart valve prostheses- Search title: Heart valve replacement using a prosthetic valve: Search terms: Heart valve prosthesis [MeSH]; heart valve prosthesis implantation[MeSH]; (valv$ adj3 prosthe$).[text word]; (valv$ adj3 bioprosthe$).[text word]; (artificial adj3 valv$).[text word]; (mechanical adj3 valv$).[text word]; (bioprosthe$ OR prosthe$ OR mechanical).[text word]; (aortic adj3 valv$).[text word]; (mitral adj3 valv$).[text word]; (pulmon$ adj3valv$).[text word].

For supportive devices- Search title: Supportive devices – meshes, patches and tissue adhesives: Search terms: Surgical mesh [MeSH]; Bioabsorbable Implants; Absorbable Implants [MeSH]; Coated Materials. Biocompatible [MeSH]; Tissue scaffolds [MeSH]; Tissue adhesives [MeSH]; Fibrin Tissue Adhesive [MeSH]; Blood patch, Epidural [MeSH].

For active implantables in the magnetic resonance environment - Search title: safety of active implantables in the magnetic resonance environment: Search terms: Magnetic Resonance Imaging[MeSH]; magnetic resonance [text word]; MRI [text word]; MR [text word]; Cardiac Pacing, Artificial[MeSH]; Pacemaker, Artificial[MeSH]; defibrillators, implantable[MeSH]; safe*[text word]; performance [text word]; efficacy [text word]; heat* [text word]; scar*[text word]; burn*[text word]; artefact* [text word]; ;dislodge*[[text word]; interference [text word]; ICD [text word]; Defibrillator [text word]; pacemaker* [text word] ; resynch* [text word]; cardiac monitor [text word] ; loop recorder [text word]; ICM [text word].

A focused internet search was conducted to identify recent and relevant legislation, current guidance documents and other standards/documents to assist in the compilation and presentation of clinical evidence. Only documents that are publicly available to manufacturers were included. For regulatory documents, the scope of the search was confined to Australia and the comparable jurisdictions of Canada, the EU/UK, Japan and the USA.

Evidence from both the targeted internet searches and peer reviewed literature focused on study designs that are based on solid scientific principles which generate clinical evidence on the safety and performance of the device. Such evidence sources include, but are not limited to, controlled clinical trials, case control studies, case series and post-market registry data.

Summaries of exemplar articles documenting clinical research on the safety and performance of the device types have also been presented. Reports were selected based on recency and relevance and to be representative of those currently used in clinical practice in Australia.

Searches were restricted to English language articles published between January 2009 and June 2014 with updates for some topics to January 2015. All citations were retrieved and initial selection was based on title and abstract with potentially relevant articles retrieved in full text for final selection.

Identified study designs

Based on the NHMRC levels of evidence study, designs used to evaluate the safety and performance of high risk medical devices range from systematic reviews of RCTs to case-series reports (Level IV). Irrespective of level of evidence the quality of reporting varied from low to high as assessed by validated quality tools.

In summary, the clinical evidence in this document includes:

- systematic reviews of RCTs, comparative cohort trials and cases-series
  - given the diversity of included evidence these systematic reviews do not meet the Level I classification as prescribed by the NHMRC
- RCTs (Level II)
  - when practical, this should be the preferred study design
  - clinical trials of a RCT design are reported for the high risk devices and included in the evidence base
- observational studies (Level III)
  - these are a valid alternative to RCTs[12] provided appropriate matching of treatment groups is performed, e.g. through the application of propensity scores[13]
- case series (Level IV)
  - these can inform on the safety and performance of the high risk devices and have a high sensitivity for adverse events
- post-market registries
  - these are established for some of the high risk devices and provide a valuable resource for post-market safety and performance data from other jurisdictions that can be used to support a pre- or post-market review of safety and performance of a high risk device

[12] Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency medicine journal. 2003;20:54-60

[13] Yue LQ. Statistical and regulatory issues with the application of propensity score analysis to nonrandomized medical device clinical studies. J Biopharm Stat. 2007;17:1-13; discussion 5-7, 9-21, 3-7 passim

Yue LQ. Regulatory considerations in the design of comparative observational studies using propensity scores. J Biopharm Stat. 2012;22:1272-9

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Medical Devices Branch, Therapeutic Goods Administration	February 2017
V1.1	Minor updates to reflect CTA name change	Biological Science Section	November 2020
V2.0	Updated section on Comparable devices including substantially equivalent devices. Updated links and footnotes.	Devices Clinical Section	March 2021
V3.0	Updated Part 1 – General Requirements and overall structure. Updated links.	Devices Clinical Section	November 2021
V3.1	Updated Part 1 – General Requirements – The Essential Principles New chapter - Personalised medical devices (PMDs) Updated - Total and partial joint prostheses New chapter - Software as Medical Device Updated - Abbreviations	Devices Clinical Section	June 2022

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