Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Draft clinical evidence guidelines - Medical devices

Preliminary draft - Without prejudice

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TGA Health Safety Regulation

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Please note:

- This document is a draft and is circulated for comment and feedback. It represents the TGA's current thinking on the above. It does not operate to bind the TGA or the public.
- A final version of this document will be intended to provide guidance only. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.
- The intended audience for this document is sponsors and manufacturers of medical devices seeking to supply their products in Australia, and is drafted to reflect these users. The TGA recognises that there is a broad range of additional stakeholders who have a legitimate interest in this guidance document, and welcomes feedback from all interested parties.
- This document has been drafted by TGA, based on existing clinical assessment and reports developed by the Royal Australasian College of Surgeons Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S).
- This draft includes academic citations, and the degree of referencing varies in different sections. To make the document easier to maintain in the longer term it is envisaged that the final document will include fewer citations; however feedback on citations (the level of referencing and the individual references cited) would be appreciated.
- Internet links have also been included as full text in footnotes to facilitate paper based review.
- The general guidance included in this document is relevant to medical devices including IVDs. The device specific sections in Chapter 6 do not currently cover specific IVD product groups. Further category specific sections may be developed in future, possibly including for IVD product categories.

Contents

1. Introduction

To provide confidence in the Australian healthcare system and to help ensure the health of the Australian population, all medical devices supplied in Australia must have clinical evidence sufficient to demonstrate an appropriate level of safety and performance when used for the intended purpose(s). Medical devices supplied in Australia must also be included on the Australian Register of Therapeutic Goods (ARTG) (unless exempt or excluded[1]).

Clinical evidence is required not only when a medical device is first included on the register but for the entire period it remains on the register. The TGA may request and review this clinical evidence at any time. Clinical evidence is frequently requested when there is an application for inclusion of a device on the ARTG, a review of conformity assessment procedures or when a safety issue with a medical device has been identified.

Broadly speaking, clinical evidence should provide a clinical assessor with a current and accurate picture of the state of scientific knowledge in relation to the treatment modality in general to which a device relates, and then with respect to the particular device specifically. From this information, an acceptable risk or safety profile is 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 development process, are outweighed by the benefits. The detail and extent of the clinical evidence will depend on the classification of the device, its nature or design and the purpose(s) for which it is intended. This clinical evidence should be updated and systematically reviewed periodically as new information based on post-market surveillance activities and product experience becomes available.

This document is intended to provide guidance to sponsors and manufacturers of medical devices (including IVDs) on what constitutes clinical evidence and the process of clinical data generation and clinical evaluation to produce such clinical evidence. Sections of this document provide specific information on the clinical evidence requirements for the following types of devices:

- Total and partial joint prostheses
- Cardiovascular devices to promote patency or functional flow
- Electrical impulse generators
- Heart valve prostheses
- Supportive devices - meshes, patches and tissue adhesives
- Implantable medical devices in the magnetic resonance environment

The TGA has developed this document in conjunction with the Royal Australasian College of Surgeons Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) to supplement guidance on medical device regulatory requirements in the Australian Regulatory Guidelines for Medical Devices (ARGMD).[2]

This document has been developed taking into account requirements of the *Therapeutic Goods Act 1989* and the Therapeutic Goods (Medical Devices) Regulations 2002. This document

[1] For example, medical devices may be exempt from inclusion on the ARTG under Parts 4-6A and 4-7 of the *Therapeutic Goods Act 1989*, and under Part 7 and Schedule 4 of the Therapeutic Goods (Medical Devices) Regulations 2002
<https://www.comlaw.gov.au/Details/C2015C00086/Html/Text#_Toc414971303>;
<https://www.comlaw.gov.au/Details/C2015C00086/Html/Text#_Toc414971311>;
<https://www.comlaw.gov.au/Details/F2015C00670/Html/Text#_Toc427237978>;
<https://www.comlaw.gov.au/Details/F2015C00670/Html/Text#_Toc427238064>

[2] <https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd>

references and aligns with international guidance documents including those of the Global Harmonization Task Force (GHTF) and the European Commission 'MEDDEVs' which are also based on the GHTF guidelines. The GHTF no longer exists, and has been permanently replaced by the International Medical Device Regulators Forum (IMDRF).

Disclaimer

- This document is a guide only and sponsors and manufacturers are encouraged to familiarise themselves with the legislative and regulatory requirements in Australia. If necessary seek professional advice as it is the responsibility of each sponsor to understand and comply with these requirements.
- The literature search method used by ASERNIP-S to collect and collate the information referenced in this document is described in the appendices relating to the particular types of devices. This document is subject to the limitations of the method and it should be read and relied upon with this in mind.
- This document will evolve over time and updates and clarifications will be included as required.

Appendix 1: Glossary and abbreviations provides a listing of technical terminology and acronyms used throughout this document.

2. Legislative basis

Overview

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

- *Therapeutic Goods Act 1989* (the Act),[3] particularly Chapter 4[4] of the Act; and
- Therapeutic Goods (Medical Devices) Regulations 2002 (the MD Regulations).[5]

Medical devices are classified according to the intended purpose of the device which generally correlates with the level of risk:

- Medical devices are classified under Schedule 2[6] of the MD Regulations from lowest to highest risk into Classes I (which includes Im, with a measuring function and Is, supplied sterile), IIa, IIb, III and Active Implantable Medical Devices (AIMD)
- *In vitro* diagnostic medical devices (IVDs) are classified under Schedule 2A[7] of the MD Regulations from lowest to highest risk Classes 1 to 4.

Section 4 of the ARGMD[8] provides guidance on medical device classifications, and Classification of IVD medical devices[9] provides guidance for IVD classifications.

The classification of a medical device determines the options available to the manufacturer for demonstrating compliance with regulatory requirements prior to market authorisation, and to an extent the level of review by the TGA or certification bodies (e.g. European Notified Bodies) in the conformity assessment process.

A medical device must comply with the Essential Principles [10] ((EPs) outlined below) which set out the requirements relating to safety and performance. The Act and MD Regulations also require that the sponsor must have **available sufficient information to substantiate compliance** with the EPs or have procedures in place that will allow them to obtain such information and provide this information to the TGA if required.

The obligation to have information that demonstrates compliance with the EPs is with the manufacturer and the sponsor must be able to provide information to demonstrate such compliance.[11] This applies to all medical devices regardless of risk class.

[3] <http://www.comlaw.gov.au/Details/C2015C00086/Html/Text>
[4] <http://www.comlaw.gov.au/Details/C2015C00086/Html/Text#_Toc414971187>
[5] <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text>
[6] <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028042>
[7] <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028048>
[8] <https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd>
[9] <https://www.tga.gov.au/publication/classification-ivd-medical-devices>
[10] Therapeutic Goods (Medical Devices) Regulations 2002, Schedule 1 <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028039>
[11] *Therapeutic Goods Act 1989*, section 41FN <http://www.comlaw.gov.au/Details/C2015C00086/Html/Text#_Toc414971275>

The sponsor and/or manufacturer must (among other matters) provide clinical evidence to demonstrate compliance of the devices with the EPs if requested.[12]

Working with the Essential Principles

Compliance with Essential Principles

For a medical device to be supplied in Australia it must be demonstrated that the relevant EPs have been met to ensure the device is safe and performs as intended.

Schedule 1[13] of the MD Regulations outlines the EPs which discuss safety and performance. Compliance with the EPs is required for all devices included on the ARTG. The principles do not set out categorically how manufacturers should comply with these but leave some room for flexibility. One of the ways to demonstrate compliance with the EPs is to conform to relevant standards published by an Australian or International Standards Agency.

There are six general and eight specific principles and one for IVDs, paraphrased below.

General:

- Principle One: Use not to compromise health and safety
- Principle Two: Design and construction to conform with safety principles
- Principle Three: Must perform the way the manufacturer intended
- Principle Four: Must be designed and manufactured for long-term safety
- Principle Five: Must not be adversely affected by transport or storage
- Principle Six: Benefits must outweigh undesirable effects

Specific:

- Principle Seven: Chemical, physical and biological properties
- Principle Eight: Infection and microbial contamination
- Principle Nine: Construction and environmental properties
- Principle Ten: Principles for devices with a measuring function
- Principle Eleven: Protection against radiation
- Principle Twelve: Medical devices connected to or equipped with an energy source
- Principle Thirteen: Information to be provided with a medical device
- Principle Fourteen: Clinical evidence
- Principle Fifteen applies to IVDs only.

[12] *Therapeutic Goods Act 1989*, section 41JA <http://www.comlaw.gov.au/Details/C2015C00086/Html/Text#_Toc414971320>
[13] <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028039>

The Essential Principles

Principle fourteen: Clinical evidence

EP 14 states:

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

In addition to other procedures, manufacturers must apply clinical evaluation procedures to the medical devices they supply.[14]

These clinical evaluation procedures must be implemented in accordance with the requirements specified in Schedule 3 Part 8[15] of the MD Regulations.

Specifically 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); and
- ensure that all the clinical data held in relation to the device is critically evaluated by a competent clinical expert 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.

The clinical evidence must primarily demonstrate that the device complies with the EPs 1, 3, and 6[16] as outlined below.

Other EPs also should be considered in the context of the clinical evidence available for the device, for example, the period within which the manufacturer claims the device can be safely used must be supported by the relevant evidence,[17] the warnings and precautions stated on the labelling and instructions for use for the device must clearly reflect hazards and known side effects associated with the use of the device.[18]

Principle one: Use not to compromise health and safety

Key considerations from a clinical perspective here include the *context* of how the device is used, i.e. is it used by specialist medical practitioners only, or by the general public? This will impact on the safety assessment for many devices. How is the device used? In other words, what sort of treatment is *administered*, and is there any inherent danger in this? Is there an inherent danger in the proposed treatment *setting* rather than the treatment itself? The patient, user, and any other person in the vicinity of the device may need to be considered.

[14] MD Regulation 3.11(2) requires that the clinical evaluation procedures outlined in Schedule 3 Part 8 need to be applied to all medical devices, with narrow exceptions for some devices exempt from inclusion in the ARTG (such as devices imported for personal use) or those devices approved for special or experimental purposes (under Act s.41HB) or under authorised prescriber arrangements (s.41HC). <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407027946>, <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028058>

[15] <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028058>

[16] MD Regulation 3.11(1)

[17] Essential Principle 4

[18] Essential Principles 13.3 and 13.4

Principle three: Must perform the way the manufacturer intended

The purpose(s) for which the device is intended to be used (intended purpose) is ascertained from the labelling, instructions for use, any advertising material relating to the device and/or technical documentation describing the mechanism of action of the device.[19]

The assessor will examine whether there is sufficient clinical evidence to demonstrate that the device performs as intended. *Each* of the intended uses proposed must be substantiated by the clinical evidence submitted, and the evidence must be a true and complete account of available scientific knowledge.

Principle six: Benefits must outweigh undesirable side-effects

Under the regulatory framework medical devices must have clinical evidence which provides assurance of safety and performance. The level of 'assurance' required will vary with the risk of the device. Any likely benefits to health from the use of the device should be weighed against any risks of injury or illness from such use; essentially the greater the risk, the greater the benefit that needs to be demonstrated to balance the risk.[20] In developing the device all possible methods to minimise hazards identified in the risk assessment should have been incorporated into the device. The residual risk then needs to be demonstrated to be 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 argue for safety based upon data for a predicate or similar device which is already marketed.

Other EPs that manufacturers are expected to consider in the context of the clinical evidence available for the device include:

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

The clinical assessor will take note of the intended purpose of the device and therefore its likely lifespan. The clinical evidence must demonstrate that the device performs as intended for the length of time appropriate to the purpose without adversely affecting characteristics and performances mentioned in EP 1, 2 and 3. However, for many devices, this is difficult to demonstrate in pre-market clinical investigations (trials and studies). In this case surrogate markers and post-market data may be used to provide evidence of long-term safety.

Principle thirteen: Information to be provided with a medical device

The intended purpose is ascertained from all documentation provided with the device, and therefore 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 supported by the clinical evidence available for the device. During assessment of the clinical evidence clinical assessors review compliance of the device with some or all aspects (items) of EP 13.

The substantiation of each and every purpose put forward is required and the patient groups for whom the device has a positive benefit-risk balance need to be well defined. Manufacturers should bear these uppermost in their mind when deciding upon the wording of the intended purpose(s) of the medical device and the patient group(s) in which it can be used. Other information provided with the device must also be consistent and supported by the evidence.

[19] Paragraph 41BD(2) of the Act

[20] Further reading on balancing risk and benefit is included in FDA, *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications*, 2012 <http://www.fda.gov/RegulatoryInformation/Guidances/ucm267829.htm>

Information should explain how to use the device safely, and very clearly highlight any potential hazards, with appropriate contraindications, warnings or precautions indicating who may or who may not safely use the device and directions on how it may be inserted or used. For example, the following information must be provided on the labelling/packaging and/or instructions for use: device-related and/or procedure-related adverse events expected and/or reported;[21] for implantable devices - information about any risks associated with the implantation;[22] warnings, restrictions or precautions that may apply to the use of the device (including clinical or environmental),[23] requirements for handling or storage,[24] risks (if any) associated with the disposal of the device.[25] These are risk minimisation tools.

These principles have a significant impact on the clinical assessment and manufacturers should be mindful about this when compiling their clinical data.

Lastly, the clarity and comprehensiveness of the information provided with a medical device can significantly affect its safety. This has an impact on the risks and therefore the safety of the device. Unclear or ambiguous terms, poor grammar and spelling, foreign words or poor diagrams can all negatively impact on the ability of a patient or another person to safely use the device, and therefore negatively affect the benefit versus harms ratio of the device.

Standards

Compliance with recognised standards published by an Australian or International Standards Agency may be used to satisfy the clinical evidence requirements and the relevant EPs for devices based on technologies with well-established safety and performance characteristics. Conformity with such standards is not mandatory in Australia, but if they are not followed, adequate justification must be provided. If a manufacturer chooses to use other standards they must demonstrate that the application of the standard satisfies the requirements of the regulations. There are three main International Standards Organization (ISO) standards relevant to clinical evidence requirements for medical devices:

- ISO13485:2003[26] on Quality Management Systems (QMS)
- ISO14155:2011[27] on Good Clinical Practice.
- ISO 14971:2007[28] Application of risk management to medical devices

ISO 13485:2003 Quality Management Systems

The primary objective of this standard is to facilitate harmonised medical device regulatory requirements for QMS. The standard is based on ISO 9001,[29] and

[21] Items 3 and 4 of RP 13.4.(3)
[22] Item 19 of 13.4
[23] Items 5 of EP 13.3 and 13.4.(3)
[24] Items 4 of 13.3 and 7 of EP13.4(3)
[25] Item 26 of 13.4.(3)
[26] International Standards Association. ISO 13485:2003. Medical devices - Quality management systems - Requirements for regulatory purposes 2011. Available from: <http://www.iso.org/iso/catalogue_detail?csnumber=36786>
[27] International Standards Association. ISO 14155:2011. Clinical investigation of medical devices for human subjects - Good clinical practice 2011. Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=45557>
[28] International Standards Association. ISO 14971:2007. Application of risk management to medical devices. Available from: <http://www.iso.org/iso/catalogue_detail?csnumber=38193>
[29] ISO 9001 is a series of standards that define, establish, and maintain a quality assurance system for manufacturing and service industries. The emphasis of ISO13485 is different, i.e., focussed on meeting national regulations rather than promoting continuous improvement and customer satisfaction.

> ...specifies requirements for a QMS where an organisation needs to demonstrate its ability to provide medical devices and related services that consistently meet customer requirements and regulatory requirements applicable to medical devices and related services.[30]

Manufacturers are expected to continue to monitor the performance and safety of a device 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. The data generated from safety and adverse event reports, literature, any updated or new clinical investigations 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. As this information is incorporated into the ongoing risk analysis it may result in changes to the Instructions For Use (IFU) and other information supplied with the device.

Compliance with ISO 13485:2003 is not mandatory in Australia, however, under the Conformity Assessment Standards Order (Standard for Quality Management Systems and Quality Assurance Techniques) 2008,[31] compliance with ISO 13485:2003 is considered to satisfy the Quality Management System requirements specified in the legislation.

ISO 14155:2011 Good clinical practice

ISO 14155:2011 provides guidance on the design and conduct of clinical investigations on 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[32]), subjects' rights, a determination that benefits outweigh risks and oversight by an independent ethics committee.

As is common to all standards for devices, compliance with ISO14155 is not mandatory in Australia, and the manufacturer of a device is free to choose to demonstrate compliance to the EPs (including EP14) by other means (e.g. by using clinical evidence from literature, or using data from trials which are not compliant with ISO 14155). Any research not undertaken in compliance with this standard would be of less evidentiary weight, all other considerations notwithstanding, as the principle aims of this standard is to ensure protection of study subjects and the credibility of the data gathered.

The manufacturer must additionally ensure it takes account of any further standards that apply to the device.

ISO 14971:2007 Application of risk management to medical devices

ISO 14971:2007 specifies a process for a manufacturer to identify the hazards associated with medical devices, including IVD medical devices, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls. The requirements of ISO 14971:2007 are applicable to all stages of the life-cycle of a medical device.

Examples of two device types which have specific ISO standards outlining requirements for demonstrating clinical evidence are:

- ISO 11979-7:2006[33] on intraocular lenses

[30] International Standards Association, ISO 13485:2003 (abstract) <http://www.iso.org/iso/catalogue_detail?csnumber=36786>
[31] <https://www.comlaw.gov.au/Details/F2008L04337>
[32] World Medical Association, Declaration of Helsinki, 2013. Available at <http://www.wma.net/en/30publications/10policies/b3/>
[33] International Standards Association, ISO 11979-8:2006, Ophthalmic implants -- Intraocular lenses 2010. Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=36408>

· ISO 5840:2005[34] on cardiac valve prostheses

[34] International Standards Association, ISO 5840:2005, Cardiovascular implants -- Cardiac valve prostheses, 2005. Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=34164>

3. Clinical evidence

This chapter outlines the sources and types of clinical evidence and how these may be used to demonstrate compliance with the EPs to establish the safety and performance of the medical device for its intended purpose(s). This document is based on publically available GHTF documents.

Appendix 2: Constructing the clinical report provides a flowchart outlining the components which may comprise clinical evidence, and the process to compile a clinical evaluation report whether based on direct or indirect clinical evidence.

Key definitions and concepts

The following definitions used in this chapter are consistent with that provided in the GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007

> **Clinical investigation:** Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.
>
> This term is synonymous with 'clinical trial' or 'clinical study' (these terms are used interchangeably in this document).
>
> Clinical investigations include feasibility studies and those conducted for the purpose of gaining market approval, as well as investigations conducted following marketing approval.
>
> Routine post-market surveillance may not constitute a clinical investigation (e.g. investigation of complaints, individual vigilance reports, literature reviews).
>
> **Clinical data:** Safety and/or performance information that are generated from the use of a medical device in or on humans.
>
> **Clinical evaluation:** The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.
>
> **Clinical evidence:** The clinical data and the clinical evaluation report pertaining to a medical device.[35]

Definitions of additional terms used throughout this document:

> **Critical analysis:** the process of the careful and systematic examination, appraisal and evaluation of 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 sponsor is seeking to demonstrate substantial equivalence with that device.
>
> **Similar marketed device:** An existing marketed device with a similar structure and design and the same intended purpose as the device but not a predicate of the device in relation to which a sponsor is seeking to demonstrate substantial equivalence.
>
> **Substantial equivalence:** Substantial equivalence confirms that the new device is as good, as safe and performs as well as the predicate or similar marketed device. This

[35] These terms are further explained in GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf>)

determination is based on a review of the new device's intended purpose and clinical, technical and biological characteristics.

There are two types of clinical evidence, direct and indirect.

Direct clinical evidence is derived from an evaluation of clinical data pertaining to the device. The data can be generated by or sourced from clinical investigation(s), literature reviews and clinical experience (generally post-market) with the actual device. It is important to clarify the exact version of the device if any changes have been made to the device since the clinical data were gathered.

Indirect clinical evidence is derived from an evaluation of clinical data pertaining to a predicate or similar marketed device with which the sponsor seeks to establish substantial equivalence.

The requirement for clinical evidence drives the process of data generation and clinical evaluation, producing clinical data and clinical evidence, respectively. [36] Clinical evidence is needed to satisfy the EPs specifically that the device continues to be safe and to perform as intended and the benefits outweigh the undesirable effects while the device is included on the ARTG. Generating clinical evidence is therefore an ongoing process of monitoring for new data and the evaluation of this data by a competent clinical expert. This clinical evidence is used to compile the CER. The clinical evaluation report should be updated as new evidence is generated once the device is marketed. The data may be generated from clinical investigation(s), literature reviews and clinical experience (generally post market) for either the device or the predicate/similar marketed device.

Clinical data

Clinical data (meaning data relating to use of the device in or on humans) may be generated for either the device or the predicate/similar marketed device. It includes:

- Clinical investigations (synonymous with trials and/or studies)
- Literature reviews
- Clinical experience, usually post market data

Each is described below.

Clinical investigation data

Clinical investigation data as referred to in Schedule 3 Part 8 of the MD regulations includes:

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

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;

[36] GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf>)

This data should be critically evaluated by a competent clinical expert and the evidence must be documented in writing.[37]

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 device has been modified since the clinical data were gathered and, if so, to clarify the device version and the nature of the changes. It is acknowledged that in some circumstances clinical investigation data is not available for the device or is insufficient in quantity or quality. In this case, clinical investigation data from a 'substantially equivalent' device such as a predicate or similar marketed device may be used to support the safety and performance of the device under assessment. The substantial equivalence decision making process is described in ***Chapter 5: Demonstrating Substantial Equivalence.***

Literature review

A literature review may be presented in addition to clinical investigation data described above, or on its own.

According to the MD Regulations Schedule 3 Part 8, a literature review in relation to a kind of medical device includes:

a. a compilation, prepared using a documented methodology, of published 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[38]

This should be critically evaluated by a competent clinical expert and synthesised into a written report.

A literature review involves the systematic identification, synthesis and analysis of the literature on the device when used for its intended purpose. The highest standard of literature review is a systematic review with meta-analysis. Such a systematic review is usually required for assessment for both premarket and post-market reviews.[39] A literature review may or may not pertain directly to the device under evaluation as there may not always be publications which discuss the specific device. Where this is the case, 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 device under review. Similarities and differences in clinical, technical and biological characteristics must be compared and substantial equivalence demonstrated to make an argument as to why the data supports the device under review, as recommended in ***Chapter 5. Demonstrating substantial equivalence.***

[37] The manufacturer must ensure that the clinical data is evaluated by competent clinical experts under MD Regulations Schedule 3 Part 8 Clause 8.6 (1) and (2) <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148420>

[38] MD Regulations Schedule 3 Part 8 Clause 8.5 <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148420>

[39] Literature reviews are required under the MD Regulations Schedule 3 Part 8 Clause 8.3 and 8.5. <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148420>

It is critical that the methods used to conduct the literature review are comprehensive and transparent in order for the clinical assessor to evaluate the objectivity (lack of bias) and quality of the CER. If the clinical assessor is unable to understand how the literature review was conducted, the evaluator cannot have confidence that the CER is an objective synthesis of the current published literature.

A literature review consists of the following key 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 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 and objectively apply inclusion/exclusion criteria.

The search strategy should describe the method used to extract data from included studies and any processes for confirming data extracted by investigators. All variables for which data are extracted (e.g. funding sources) should be listed and defined. A recommended way to demonstrate the rigour of the search strategy is to present in the supporting documents the full electronic search strategy for at least one database searched.

Selection strategy

The search output (that is, the citations) should be assessed against clearly defined selection criteria. This should contain enough detail to enable the clinical assessor to understand exactly how the final list of studies included in the review was compiled.

When selecting papers to be included in the assessment of performance and safety, the quality of the literature, design of any clinical investigations reported in the paper, quality of the data reported and the clinical significance of the results of those trials should be considered.

The quality of the paper can be judged by assessing its scientific impartiality, the completeness of reporting, the clarity and logic of the argument and the validity of any conclusions drawn in the paper. Both favourable and unfavourable literature, published or unpublished, should be included when available.

A flow diagram detailing each step in the screening process, including total numbers of studies screened, assessed for eligibility, and included in the review, should be provided in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines referenced in ***Appendix 3: Guidelines for reporting full clinical study reports and systematic literature reviews***. The report should also summarise how each citation did or did not fit the selection criteria for inclusion in the review. This can be presented as an appendix of all excluded studies and justification for this decision.

Review and critical analysis

The overall body of evidence from the literature should be synthesised. Studies should not be discussed in isolation from one another. The study characteristics and results of individual studies may be summarised in table format. For all outcomes considered (including safety or performance) provide a simple summary table for each intervention group and an effect size estimate and confidence interval for each study. The method of synthesising the results of included studies, including methods of handling data and combining results of studies should be described.

A 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. Sponsors must understand the distinct relationship between the pre-planned search protocol and the subsequent critical analysis of the body of "selected" literature.

Literature report

A report must be provided, written by a competent clinical expert, containing a critical appraisal of this compilation, as per the legislative requirements. [40] It is recommended that reviews are prepared by researchers skilled in systematic review methods in conjunction with a clinical expert. This will increase the scientific rigour of the review.

Where the review relies in part or wholly on literature for a predicate or similar marketed device, the report should also clearly justify how the device described in the compiled literature is relevant to the safety and performance of the device under review. 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.

Post-market data

Data from clinical experience, generally post-market data, can support the substantiation of the safety and performance claims of the device and it should be provided for pre- and post-market reviews, particularly where there may be a paucity of data from clinical investigation(s) or literature reviews. It may consist of investigation of complaints and individual vigilance and literature reports. If the device is approved for use in another jurisdiction the sponsor 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 (such as MRI designation) in other jurisdictions should be provided.

Post-market data is useful for identifying less common but serious device-related adverse events and it provides long-term information about the safety and performance of a device. All post-market data should be reported where possible including:

- The number of units sold worldwide since launch (or for at least 5 years) stratified by year of supply and geographic region.
- The number and types of complaints to the manufacturer regarding the device stratified by year of supply and/or year of occurrence of complaint.
- The total number of adverse events reported to regulatory agencies, 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) and stratified by year of supply and/or year of occurrence of event.
- Any regulatory issues such as voluntary or mandatory recalls, removals, suspensions or withdrawals for IFU changes or other reasons and cancellations of the device anywhere in the world.

Together, this data should be compiled into an adverse event rate and a device complaint rate which will allow the clinical assessor to better evaluate the benefit-risk profile of the device. 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. If the sponsor chooses to use indirect clinical evidence to demonstrate compliance with the EPs, post-market data for the predicate or similar marketed device should be presented. As the time since approval lengthens, the relevance of predicate data diminishes and should be replaced by data for the

[40] MD Regulations Schedule 3 Part 8 Clause 8.5 <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148420>

device itself. The sponsor should clearly indicate whether the data reported is for the device or a predicate/similar marketed device.

Guidance on methods of sourcing appropriate post-market data is provided in ***Appendix 4: Identifying relevant post-market data***.

Data from pre-clinical assessment

This may include biocompatibility testing, bench testing, animal studies and computer simulation and/or modelling data that have been clinically validated. Any aspects of non-clinical testing results that inform the design of the clinical trial should be included in the supporting documents.

4. Clinical evaluation report and supporting documents

- Clinical evaluation is an ongoing process conducted throughout the lifecycle of a medical device. Sponsors and manufacturers must periodically review the performance, safety, and risk-benefit profile of the device, and update the clinical evidence accordingly.
- Over the life cycle of the device the clinical evaluation will change. For instance when the device is on the market for a long time, the meaning of comparisons to predicates is less significant, and post-market data is likely to be of greater relevance.

Clinical evaluation report

After the completion of the clinical evaluation process a report should be compiled outlining the scope and context of the evaluation; the clinical data, analysis and conclusions reached about performance, safety and presentation (that is labelling, patient information and IFU) of the medical device when used for the intended purpose. This chapter provides an overview of the recommended content and format of the clinical evaluation report. The clinical evaluation report may be requested by the TGA for pre- and post-market reviews. Standardising the content and format of these submissions will allow the TGA to assess applications and undertake post-market reviews of medical devices more effectively and efficiently. Sponsors should refer to the GHTF document *Clinical Evaluation* SG5/N2R8:2007[41]. This has been adapted for this chapter.

Appendix 5: Constructing the clinical evaluation report provides a flowchart outlining the components which may comprise clinical evidence, and the process to compile a clinical evaluation report whether based on direct or indirect clinical evidence.

The recommended structure of the components of the clinical evaluation report is provided in ***Appendix 6: Clinical evaluation report and supporting documents*** and includes the following sections:

1. Device description, lineage and version if applicable
2. Intended purpose/indications and claims
3. Regulatory status in other countries
4. Summary of any relevant pre-clinical data
5. Demonstration of substantial equivalence (if applicable)
6. Overview of clinical data
7. Critical evaluation of clinical data
8. Critical evaluation of post-market data (clinical experience)
9. Risk analysis and risk management

[41] GHTF document, *Clinical Evaluation* SG5/N2R8:2007 *Appendix E: A Possible Format for a Clinical Evaluation Report* (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-2007-clinical-evaluation-070501.pdf>)

10. Instructions for use, labelling and other documents supplied with the device
11. Risk-benefit analysis
12. Conclusions
13. The name, signature and *curriculum vitae* of the clinical expert and date of report

1. Device description and lineage

Identify the device by its proprietary name, and any code names assigned during its development. Provide a brief physical description of the device, including the materials used, whether it incorporates a medicine (new or existing), biological tissues and/or blood products, the device components (including software and accessories), the mechanical characteristics, how the device functions and other relevant information relating to the device such as sterility, radioactivity. Diagrams or photographs of the device, including steps for assembly and use, are helpful. This information should be cross-referenced and linked to the manufacturer's technical information. If the application is for a multi-component procedure pack, each component in the system must be itemised.

2. Intended purpose/indications and claims

Defining the indications for use, performance claims, contraindications and warnings relating to the device is a core requirement for medical device assessment. In this context, a description of the 'indications for use' should include the clinical condition being treated, intended patient population, the severity and stage of disease, the site and nature of interaction with the body and the intended application of the device; that is whether single use/reusable; invasive/non-invasive, implantable. In addition the magnetic resonance (MR) status of the device (MR unsafe, MR conditional, MR safe or 'safety in magnetic resonance imaging (MRI) not evaluated') should be provided. Consideration should be paid to the duration of use or contact with the body. Outline any safety or performance claims made for the device. Particular attention should be paid to whether the intended purpose claimed by the manufacturer is supported by the clinical data provided.

3. Regulatory status in other countries

The clinical evaluation report should clearly describe the regulatory history of the device, including a list of countries in which the device has been marketed, the dates of introduction into each country and information about the quantity of product distributed in each country. Any countries in which the device has been recalled, withdrawn, suspended, removed or cancelled should be listed and the reasons for this, if relevant. The exact wording of the intended purpose in other jurisdictions, including MR status should also be provided. Certificates of conformity in other regulatory jurisdictions (e.g. CE marking, FDA, Health Canada should be provided including the number and date of issue of international certificates as these provide a useful tool to verify data and to search databases for adverse events, e.g. FDA's Manufacturer and User Facility Device Experience (MAUDE)). The date of issue of certificates also gives a useful indication of whether post-market data should be expected. The trade name(s) of the device in other regulatory jurisdictions should also be clearly stated, if different from the name used in Australia. If the device has evolved from a predicate/s over time the number and dates of certificates for these may be useful in exploring the history of the device. Information concerning applications for registration in the other jurisdictions, particularly Europe, the USA and Canada, should also be provided when applicable.

4. Summary of relevant pre-clinical data

The clinical expert should comment on any potential safety and performance issues highlighted by pre-clinical testing and comment also on any potential risks for which testing has not been done.

5. Demonstration of substantial equivalence

In some circumstances, the safety and performance of the device may be substantiated by presenting evidence from a predicate or similar marketed device (indirect clinical evidence). Information to help sponsors determine whether clinical evidence from a predicate or similar marketed device may be suitable, and the steps involved in demonstrating substantial equivalence are provided in ***Chapter 5. Demonstrating Substantial Equivalence***. Where indirect evidence is presented, the clinical expert must carefully and comprehensively critically evaluate whether there is either no clinical impact or no detrimental impact attributable to the differences between the device and any chosen comparators. In order to demonstrate this, any differences between the clinical, technical and biological characteristics of the device should be clearly stated, including a comparison between the materials, design, function, energy source and any other device features that may alter the safety or performance of the device. This may be presented in a summary table clearly identifying and demonstrating the impact of any differences between the device and the predicate or similar marketed device (example format provided below).

Table 1. Example summary table

Evidence presented	The Device	Predicate or similar marketed device	Impact of difference on safety and performance
Clinical characteristics			
{when used for same clinical condition or purpose, same site in body, similar population including age, anatomy physiology and similar clinical performance of device}			
Technical characteristics			
{e.g. materials, design, function, energy source etc.}			
{e.g. deployment methods}			
Biological characteristics			
{e.g. biocompatibility}			

When claiming substantial equivalence with a predicate as a means of establishing the safety and performance of a new iteration of a device, the applicant must provide a detailed analysis of

the clinical data they have generated and undertake a literature search and review for the predicate. Overall this will establish that the safety and performance of the predicate is acceptable before any comparisons are made. An analogous process is required for comparisons with a similar marketed device although access to a detailed analysis of the clinical data may not always be available. Manufacturers should always consider the age of the initial data generated to support the product (i.e. do these data still present an accurate, current picture of medical knowledge for this product or treatment area?) The literature review should be up-to-date to identify any new safety issues that have been identified since the clinical data for a predicate or similar marketed device was generated.

Note: The clinical evaluation report should clearly specify whether the clinical data being reported relate to the device, or a predicate/similar marketed device that is claimed to be substantially equivalent to the device.

6. Overview of clinical data

What constitutes appropriate clinical data will vary depending on the type of device under assessment and its state of development, but this should include clinical investigation(s) data and/or a literature review and/or post-market data (clinical experience) with the device or predicate/similar marketed device with which the sponsor is claiming substantial equivalence. The CER should include a summary of all the clinical data with the full clinical investigation reports, literature search and selection strategy and post-market data provided in the supporting documents.

7. Evaluation of clinical data

A competent clinical expert should evaluate all the clinical data and provide a reasoned argument as to how the clinical data constitutes valid clinical evidence, demonstrates the safety and performance of the device and establishes a satisfactory benefit- risk profile for the device when used for the intended purpose(s). This evaluation seeks to explain and justify the clinical data and typically involves a discussion of the quality of the clinical data, the relative strengths and weaknesses of the investigations and/or literature presented, the appropriateness of the inclusion and exclusion criteria, the appropriateness of the outcome measures, efforts to minimise bias, presence of confounders, length of follow-up, sample size, generalisability etc. Particular emphasis should be placed on explaining in detail the links between the clinical data and the contraindications, warnings and precautions and actual and potential adverse effects of the device on health. This enables the clinical experience to be adequately conveyed to users of the device.

The applicant should objectively link the medical claim(s) for the device to the hypotheses tested and conclusions drawn from all the clinical data including those presented in the literature.There are many tools available to guide the evaluation of clinical data that are specific to different study methods. Guidance on the recommended reporting requirements for clinical studies and examples of validated tools that can be used to guide the quality appraisal of both clinical investigations and literature reviews are provided in ***Appendix 4: Evaluation of clinical data.***

- It cannot be over-emphasised that a clinical evaluation report 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 is commonplace, but does not represent an adequate clinical evaluation.
- Finally, it must be explicitly clear to the clinical assessor whether direct (pertaining to the device) or indirect (pertaining to a predicate or similar marketed device) data is being evaluated. 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.

8. Evaluation of post-market data (clinical experience)

The clinical evaluation report 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 data can be provided in the supporting documents. In assessing the post-market data, the clinical expert should objectively comment on adverse event 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 device or a predicate/similar marketed device.

9. Risk analysis and risk management

The clinical expert should comment on the risk analysis and risk management approach by the manufacturer. All ongoing safety concerns (risks) and 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 the risk mitigation and minimisation strategies. The clinical expert and the sponsor should ensure that risks identified in the clinical data are included in the risk assessment and properly mitigated. A discussion highlighting how this has been done should be included in the clinical evaluation report.

The sponsor should discuss the adequacy of the documentation of the risks and address the clinical significance of risks that remain after the implementation of risk mitigation strategies. The sponsor should then comment on whether the risk analysis has adequately identified the potential hazards related to the device for its intended purpose (including device failure, adverse effects and use-related hazards such as those identified from the clinical data evaluated in sections 7 and 8 of the CER), and then evaluate whether the risk management document adequately controls for these risks.

10. Instructions for use, labelling and documents supplied with the device

Comments on any issues relating to the IFU, labelling and other documents supplied with the device should be provided in the clinical evaluation report with an assessment of whether these are consistent with the clinical data. The IFU should include all identified hazards and other clinically relevant information that may impact on the use of the device. Foreseeable safety or performance concerns that may arise from the IFU or labelling should be flagged and incorporated into the overall benefit-risk analysis, taking 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 clinician.

11. Risk-benefit analysis

Following the evaluation of all the clinical data, the clinical evaluation report should provide a well-reasoned and documented analysis of the foreseeable risks that could occur with the use of the device, and compare these with an analysis of the benefits that may be provided to the end user. This analysis should be clearly supported by evidence, including appropriate references. In demonstrating whether the benefits of the device outweigh the potential risks, 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 (e.g. level 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.
- The probability of patients receiving the benefits of the device.
- The duration of the proposed benefits of the device.
- The safety issues identified in the clinical investigation data and/or literature review and post-market data (clinical experience) for the intended purpose, as well as theoretical risks 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 an adverse event from the device.
- The duration and severity of adverse events caused by the device.
- 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, generalizability of results to an Australian population.

Following the analysis of the benefits and risks of the device, the clinical expert should exercise professional judgement as to whether the benefit-risk profile of the device is favourable, considering the totality of the clinical data on the device.

12. Conclusions

Essential Principle 14 states that the manufacturer must hold clinical evidence that demonstrates compliance with the other EPs. The conclusion of the clinical evaluation report should outline key supporting clinical data and evaluation findings supporting the safety and performance of the medical device. This should be based on the following:

- Clinical information on predicate/similar marketed device demonstrated to be substantially equivalent which is supportive of the safety and performance of the device
- Clinical evidence demonstrates benefit
- The device performs as intended
- Post-market data shows a low and acceptable level of adverse events.

- The residual risks have been mitigated with appropriate justification, for example, inclusion of relevant statements in the IFU documentation.
- The benefits outweigh the risks of the device.

Therefore the device is safe and performs as intended when used for its intended purpose.

13. Name, signature and *curriculum vitae* of clinical expert and date of report

As stated in Schedule 3 Part 8.6 of the MD regulations:[42]

> Evaluation of clinical data
>
> 1. The manufacturer of a kind of medical device must ensure that the clinical data is evaluated by competent clinical experts.
> 2. The manufacturer must ensure that clinical evidence demonstrating that the device complies with the applicable provisions of the essential principles is documented in writing.

The name and signature of the clinical expert should be provided in the clinical evaluation report with the date of the report. A 'competent clinical expert', usually someone with experience in the use of the device type in a clinical setting and relevant clinical qualifications, must evaluate all the clinical data and sign the clinical evaluation report. The selection of a clinical expert will therefore depend on the type of device under assessment, and its intended purpose(s). For example, for a coronary stent submission the clinical expert should be a practising interventional cardiologist. In order for the clinical assessor to determine whether an appropriate clinical expert has been chosen, the full *curriculum vitae* of the clinical expert who evaluates the clinical data and signs the clinical evaluation report should be included in the CER. Any convergence of interests or potential for conflict with the sponsor or manufacturer must be acknowledged and addressed.

Supporting documents

Supporting documentation should be provided for pre- and post-market reviews in addition to the CER. The recommended structure of the additional components of the CER is provided in ***Appendix 5: Clinical evaluation report and supporting documents*****,** and includes the following sections:

A. Preclinical data (if relevant)

B. Full clinical investigation reports

C. Literature search and selection strategy

D. Full text articles from literature review

E. Full technical and physical specifications of device

F. Risk analysis and management documents

G. Post-market data

[42] The manufacturer must ensure that the clinical data is evaluated by competent clinical experts under MD Regulations Schedule 3 Part 8 Clause 8.6 (1) and (2) <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148420>

Note: When available, the clinical assessment report from acceptable European notified bodies will aid in timely clinical review of the submission

A. Preclinical data (if relevant)

Medical devices may contain elements that cannot be assessed solely through clinical testing, but are critical to the safety or performance of the device. In such cases, a concise summary of the preclinical data may be required to establish the safety and performance profile for the device including any aspects of non-clinical testing results that inform the design of clinical trial(s). These should be included in the supporting documents and may include, but are not limited to:

- 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 testing

Where preclinical data is referenced, details on the type of preclinical testing performed on the device must be provided.

B. Full clinical investigation reports

Full reports for the pivotal investigation(s) on the device should include significantly more detail than peer-reviewed publications or journal articles that report results from investigations. The investigation reports should include the design, subject selection and inclusion/exclusion criteria, population demographics, duration, safety and effectiveness data, adverse reactions 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 from the clinical investigations, as appropriate.

C. 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 section of the supporting documents as a way to demonstrate the rigour of the search and selection strategy. Excluded studies should be provided in an appendix with a brief justification as to why they were excluded.

D. Full text articles from the literature review

The full text of pivotal articles in the literature review contributing to the clinical evidence should be provided.

E. Full technical and physical specifications of device

The manufacturer must be able to demonstrate that the materials, physical properties and technical specifications of the device comply with the EPs and are appropriate for the intended purpose of the device. A summary with cross-references and linkages to the manufacturer's technical information should be provided here outlining the technical performance specifications of the device, as well as other specifications related to chemical, physical, electrical, mechanical, biological, software, sterility, stability, storage, transport and packaging.

F. Risk analysis and 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. In reporting the risk analysis, all device-related and use-related hazards should be identified, analysed and appropriate risk mitigation activities applied (for example statements in the IFU documentation or physician training materials).

Device-related hazards include, but are not limited to, chemical, mechanical, thermal, electrical, radiation, and biological hazards. Use-related hazards refer to hazards that occur 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.

For each hazard, the analysis should list all potential causes and determine the probability and severity of their occurrence. This type of analysis can and should be performed 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) have been identified, the manufacturer is expected to implement a Quality Management System (QMS) to mitigate the potential risks to end users. Details of the QMS should be provided so that the clinical expert who reviews and endorses the CER can determine whether the potential hazards associated with the device are being minimised and mitigated adequately. Comprehensive documentation of the risk analysis and QMS is necessary to allow the clinical expert to comment on the overall benefit-risk profile of the device. ISO 14971:2007[43] can provide further guidance on this, but is not a mandatory standard.

G. Post-market data (clinical experience)

Post-market data from jurisdictions where the device is already in use (including Australia if applicable), should be provided for pre- and post-market reviews, particularly where there may be a paucity of other clinical data. Post-market data is useful for identifying less common, but serious, device-related adverse events, and it may provide long-term information about the safety and performance of the device. All post-market data should be reported where possible, as discussed in ***Chapter 5. Clinical Evidence***.

Together, this information should be compiled into an adverse event rate and a device complaint rate, which will allow the clinical assessor to better assess the benefit-risk profile of the device. If the sponsor chooses to use indirect clinical evidence to demonstrate compliance with the EPs, post-market data for the predicate or similar marketed device should be presented. As the time since approval lengthens, the relevance of predicate data diminishes and should be replaced by data for the device itself. Guidance on methods of sourcing appropriate post-market data is provided in ***Appendix 6: Identifying relevant post-market data***.

[43] <http://www.iso.org/iso/catalogue_detail?csnumber=38193>

Common errors in the clinical evaluation report

There are a number of common errors made in clinical submissions that can be avoided, which include (but are not limited to):

- Absence of the required components of the CER
- Intended purpose(s), indication and claims inconsistent between documents ie submission, 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 (e.g. approvals for MR conditional use for implantable devices; recalls, withdrawals, removals from market, suspensions and cancellations in any jurisdiction)
- Information on predicate or previous related devices not included and/or substantial equivalence not demonstrated (if relevant)
- Insufficient or incomplete clinical investigation(s) data and/or literature review and/or post-market data (clinical experience) with the device (or predicate/similar marketed device if relevant).
- In submissions where a literature review is provided there is:
  - No demonstrated comprehensive literature review with documented methodology
  - 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
- Little or no critical evaluation of the clinical investigation data and/or literature presented and inadequate synthesis of this data, i.e.
  - No discussion of relative strengths of the data (for example, randomised controlled trials, case control studies, case series) or
  - Substantial equivalence covering technical characteristics, biological characteristics and clinical use not established to validate the data for a different device (i.e. predicate or similar marketed device) to the device under review
  - Lack of discussion of the validity or otherwise of outcome measures used
- Inadequate critique and summary of the totality of evidence provided for the device
- No post-market data including adverse events, complaints, failures in cases where this information is available
- More than one CER
- Author of CER not included, totality of clinical data not evaluated by competent clinical expert, CER not endorsed/signed by clinical expert and/or CER not dated or outdated
- Inappropriate selection of clinical experts. The clinical expert who critically evaluates the clinical data and endorses/signs the CER is expected to have direct clinical experience in the relevant field using similar devices or performing similar procedures.
- CV of clinical expert(s) is not provided

It cannot be over-emphasised that a CER 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 is commonplace, but does not represent an adequate clinical evaluation.

Finally, it must be explicitly clear to the clinical assessor whether direct (pertaining to the device) or indirect (pertaining to a predicate or similar marketed device) data is being evaluated. 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.

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

5. Demonstrating substantial equivalence

Clinical evidence requirements

Essential Principle 14

From the Therapeutic Goods (Medical Devices) Regulations 2002 – Schedule 1, Part 2

All medical devices require clinical evidence, appropriate for the use and classification of the device, demonstrating that the device complies with the applicable provisions of the essential principles.

Many devices are developed or modified by incremental changes and therefore are not completely novel. In such cases it may be possible to draw on the clinical experience of safety and performance from predicates of the device or similar devices. This may reduce the need for clinical data for the device under review. [44] In some instances it may be difficult to collect clinical data for a device prior to inclusion on the ARTG due to very small numbers of eligible patients or particularly high risk procedures limiting use. If there are no clinical data for the specific device, depending upon the nature of the device, it may be possible to provide a full clinical justification for why direct clinical evidence is either not required or only partially required. This involves referencing the performance and safety of a predicate or similar marketed device (as described below) and critically examining each change or difference in terms of materials, design, clinical use, and their likely impact on safety and performance.

If it can be established via contention and/or additional data that the differences should not have any impact on safety and performance, then the predicate/similar marketed device may be considered 'substantially equivalent' to the device. In this case, a clinical justification in addition to the clinical evidence for the predicate/similar marketed device can, in some circumstances, suffice for clinical evidence for the device.

Intended purpose

The predicate or similar marketed device should have the same intended purpose as the device in question. The only reference to intended purpose is in the Dictionary of MD Regulations[45]:

> ***intended purpose*** of a kind of medical device means the purpose for which the manufacturer of the device intends it to be used, as stated in:
>
> a. the information provided with the device; or
>
> b. the instructions for use of the device; or
>
> c. any advertising material applying to the device

The GHTF makes the following references to intended use:

[44] GHTF document, *Clinical Evaluation* SG5/N2R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-2007-clinical-evaluation-070501.pdf>)

[45] <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148428>

> "The intended use of a device relates to the clinical condition being treated, the severity and stage of disease, the site of application to/into the body and the patient population." [46]

The GHTF also infers that the intended purpose of a device should be based on the condition being treated and, where relevant, the patient population in whom the device should be used.

European Medical Device Directive guidance[47] states that 'intended purpose' means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the IFU and/or in promotional materials.

Given the overlapping concepts across existing documentation, TGA has interpreted intended purpose as being interchangeable with intended use and expects that information defining the condition being treated and the patient population will be included in the IFU for medical devices where such instructions are required.

When is the use of clinical evidence for a predicate or similar marketed device considered inappropriate?

The GHTF identified certain situations where devices are likely to require direct clinical data as outlined below:

> "Clinical evaluation of medical devices that are based on existing, established technologies and intended for an established 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**."[44] (emphasis added)

Predicate and similar marketed devices

What is a predicate device?

A device will be regarded as a predicate device in relation to a device for the purposes of demonstrating substantial equivalence if it:

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

What is a similar marketed device?

A device will be regarded as a similar marketed device in relation to a device for the purposes of demonstrating substantial equivalence if it:

[46] GHTF document, *Clinical Evaluation* SG5/N2R8:2007, page 8 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-2007-clinical-evaluation-070501.pdf>)

[47] Medical Device Directive 2.4/1 Revision 9 (June 2010) Classification of Medical Devices Guidance Document, available at: <http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf>

- is an existing marketed device,
- has a similar structure and design as the device,
- has the same intended purpose as the device, and
- is not a previous iteration of the device by the same manufacturer.

The identification of an appropriate predicate or similar marketed device is contingent on the characteristics of the device and the requirement to substantiate their equivalence to those of the predicate or similar marketed device. A predicate/similar marketed device should have clinical evidence available to support its safety and performance.

Substantial equivalence

If a device can be demonstrated to be substantially equivalent to an existing device then the clinical evidence for the existing device demonstrating compliance with the EPs can be used to demonstrate compliance with the EPs for the device. A determination of substantial equivalence is based on a detailed review of the intended purpose, technological and biological characteristics of the device.

The GHTF identifies when a predicate or similar marketed device can be used to support the safety and performance of a device:

> "The devices should have the same intended use and will need to be compared with respect to their technical and biological characteristics. These characteristics should be similar **to such an extent that there would be no clinically significant difference in the performance and safety of the device**." [48] (emphasis added)

Steps to demonstrate substantial equivalence

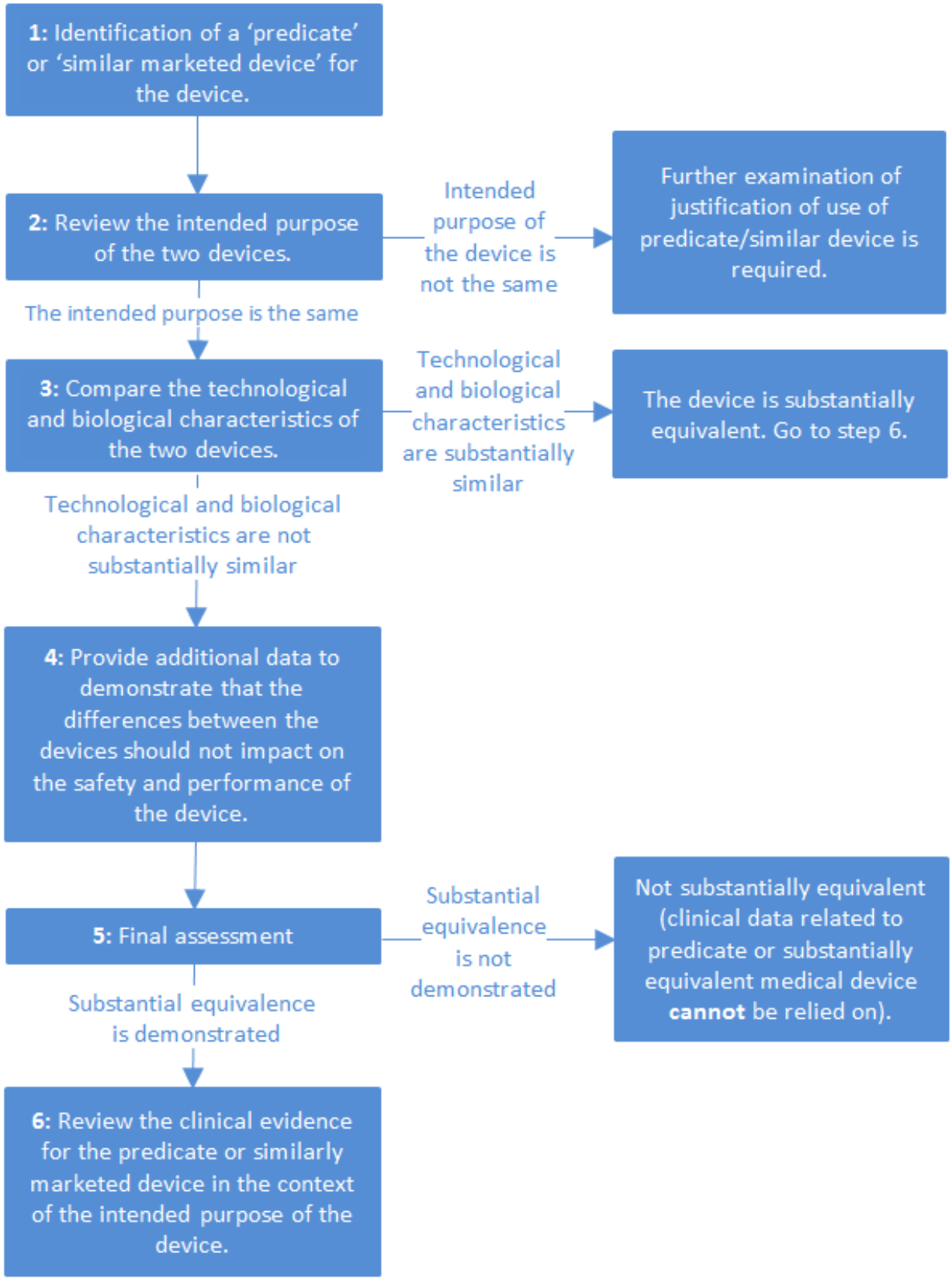
Each of the steps in the process is explained below. In each step a device that addresses each requirement may be found to be substantially equivalent to its predicate or similar marketed device. Devices that do not address these requirements may still be suitable for inclusion on the ARTG; however, this approval would need to be sought by providing direct clinical evidence on the device.

Any application that uses the substantial equivalence process should include a justification from a clinician with appropriate expertise relevant to the device under assessment to substantiate the proposal put forward by the sponsor at each step of the substantial equivalence process. A full *curriculum vitae* should be provided for the clinical expert to demonstrate appropriate clinical qualifications and experience to qualify as clinical expert in relation to the device.

The following flowchart provides guidance to sponsors on how to demonstrate substantial equivalence with a predicate device or similar marketed device.

[48] GHTF document, *Clinical Evidence* SG5/N2R8:2007, page 8 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-2007-clinical-evaluation-070501.pdf>)

Figure 1. Demonstrating substantial equivalence



Step 1: Identification of a predicate or similar marketed device

The sponsor should clearly identify if a predicate or similar marketed device is to be used to demonstrate substantial equivalence to the device under review. The predicate or similar

marketed device should meet the definition of these devices outlined earlier in the document including having the same intended purpose as the device under review.

Devices that had been approved for marketing but have been removed from the ARTG or from a recognised international market due to safety concerns are not suitable comparisons. It is incumbent upon sponsors to be aware of any safety concerns related to the predicate or similar marketed device. If the sponsor nominates a predicate or similar marketed device that has related safety issues, then it is unlikely that the application would be successful. There may be exceptions when the applicant claims that design flaws or superseded technology in the predicate or similar marketed device has been rectified or improved in the new device but evidence would be required to substantiate these claims.

Step 2: Review the intended purpose of the device

The intended purpose of the device should be clearly stated and provided in the sponsor's submission. If the device does not have an intended purpose that is the same as the predicate or similar marketed device it is generally not possible to establish that the devices are substantially equivalent, with the exception of the conditions below.

In some circumstances the clinical evidence for the predicate or similar marketed device *may* be used to demonstrate the device's compliance with EP 14 even if these other devices do not have the same intended purpose as the device, if the following criteria have been met:

- clinical evidence that demonstrates safety and performance is available for the predicate or similar marketed device for the intended purpose for which the sponsor of the device is applying and
- the other steps of the substantially equivalent process have been met.

Step 3: Compare the technological and biological characteristics

When comparing the technological characteristics of the device and predicate/similar marketed device, a **comprehensive** assessment of the characteristics should be provided. Technological characteristics include but are not limited to those outlined below by the GHTF:

> **"Technological characteristics** relate to the design, specifications, physicochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use and may include biological characteristics relating to biocompatibility of materials in contact with body fluids and tissues."[49]

This comprehensive comparison is best demonstrated in a table which provides a description of the characteristics for the two devices and notes **both** their similarities and differences. **All differences** between the devices should be clearly and explicitly stated.

The device in question is considered suitable for the substantial equivalence process if it has substantially similar technological and biological characteristics as the predicate or similar marketed device. A device that does not have substantially similar technological characteristics as the predicate or similar marketed device may only be considered suitable for the substantial equivalence process if the sponsor can demonstrate that the differences between the devices do not impact on the safety and performance of the device in question (see ***Step 4: Provision of additional data*** below).

The biological characteristics of the device under assessment should be compared with the biological characteristics of the predicate or similar marketed device. If there are differences the

[49] GHTF document, *Clinical Evidence* SG5/N2R8:2007, page 8-9 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-2007-clinical-evaluation-070501.pdf>)

sponsor is required to demonstrate that these would not impact on the safety and performance of the device.

What is considered substantially similar?

To be considered substantially similar, the differences in the technological and biological characteristics between the predicate/similar marketed device and the device should be minimal. Furthermore, these minimal differences should not be expected to impact safety and performance of the device.

Below are examples of changes to a predicate device. The clinical assessors would be likely to consider the device's technological characteristics to be substantially similar to the predicate in the case of a balloon angioplasty device if the changes consisted of:

- alterations to the radiopaque markings on an angioplasty balloon
- ergonomic changes to the handle of a delivery system for an angioplasty balloon or stent
- colour changes to an angioplasty balloon

If the sponsor considers the technological and biological characteristics of the device and predicate/similar marketed device to be substantially similar it is imperative that a justification from the clinical expert is provided which supports this claim.

Step 4: Provision of additional data

A device **may** be suitable for the substantial equivalence process if the technological characteristics are not substantially similar; **however,** in this circumstance additional evidence should be supplied that shows that the device is expected to be as safe and perform as well as the predicate/similar marketed device. This additional data may include clinical data and/or pre-clinical data (bench testing or *in vivo* studies) specifically designed to address the differences between the two devices.

Step 5: Final assessment

The onus is on the applicant to ensure that all information relating to the predicate/similar marketed device is provided for clinical assessment, in particular the clinical data which demonstrates safety and performance of the predicate/similar marketed device must be provided. The applicant may not have conducted the research, but they should ensure that the research method, clinical data and all information relevant to the assessment is included.

If the applicant is unable to demonstrate substantial equivalence, then direct clinical evidence will be required.

Step 6: Review clinical evidence

At this step in the substantial equivalence process, the device is considered substantially equivalent to the predicate/similar marketed device. Additionally, the clinical expert should provide a justification outlining why the clinical data for the predicate/similar marketed device support the safety and performance of the device.

The applicant should ensure there is robust clinical evidence to support equivalence where there are technological and/or biological characteristics of the device that differ materially from the predicate/similar marketed device. This should be summarised in the final component of the assessment.

Clinical evidence for the device must be updated by the sponsor/manufacturer on a regular basis. If a safety concern is identified by the sponsor/manufacturer for the predicate or similar marketed device which was used to demonstrate compliance with EP 14 for inclusion on the ARTG, the sponsor must investigate whether this safety concern also applies to their own device and if it does, report it to the TGA in accordance with the requirements of the Act s.41MP.[50]

[50] <https://www.comlaw.gov.au/Details/C2015C00086/Html/Text#_Toc414971381>

6. Requirements for specific high risk devices

Disclaimer: This chapter provides guidance to assist industry and clinical researchers to understand TGA's (current) requirements for clinical evidence for particular kinds of high risk medical device.

The requirements articulate the minimum evidentiary requirements that TGA considers will allow an adequate assessment of the benefit-risk profile of the device to be determined, taking into account the safety, performance and patient health outcomes. This assessment is part of the process by which TGA considers compliance of kinds of medical devices against the EPs set out in Schedule 1[51] of the MD Regulations.

Specific high risk devices currently covered in this section are:

- Total and partial joint prostheses
- Cardiovascular devices to promote patency or functional flow
- Electrical impulse generators
- Heart valve replacements using a prosthetic valve
- Supportive Devices - Meshes, Patches and Tissue Adhesives
- Demonstrating the safety of implantable medical devices (AIMDs)in the magnetic resonance environment.

Sponsors and applicants are advised to read this guidance in conjunction with earlier chapters outlining general clinical evidence requirements for all devices, including:

- Chapter 2. Legislative basis
- Chapter 3. Clinical evidence
- Chapter 4. Clinical evaluation report and supporting documents
- Chapter 5. Demonstrating Substantial Equivalence

[51] <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148401>

Total and partial joint prostheses

Joint prostheses include hip, knee and shoulder joint replacements. Joint replacement (also called arthroplasty) is a commonly performed orthopaedic operation with the objective of relieving pain and improving mobility.[52] [53] This section focuses on defining appropriate clinical evidence to demonstrate that a joint prosthesis is safe, and performs as intended through compliance with the applicable EPs of safety and performance outlined in Schedule 1[54] of the MD Regulations.

Summary recommendations

- Joint prostheses are complex medical devices that can be used in combination with other devices or components. Sponsors are advised to list the likely combinations and provide clinical data to support the safety and performance of the device for these nominated configurations.
- For clinical evidence based on an evaluation of predicate or similar marketed device data, sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between the device and the nominated predicate or similar marketed device.
- Sponsors should provide details of the clinical context within which the clinical data was obtained. The clinical context of the data should be congruent with the indications for use.
- Provision of clinical data:
  - sponsors 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 sponsor is advised to benchmark the device against devices of the same class as reported by an international joint registry
    - for patient performance data, sponsors 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 sponsor should consider using surrogate markers that are predictive of prosthesis failure - alternatively, sponsors may use post-market data if the device is approved and marketed in Australia or elsewhere
  - when submitting a comprehensive literature review, full details of the method used should be included in the CER with detail sufficient to enable the review process to be repeated by clinical assessors

[52] National Joint Registry UK. Patient introduction to the NJR. 2014 [cited 11 July 2014]; Available from: <http://www.njrcentre.org.uk/njrcentre/Patients/tabid/74/Default.aspx>
[53] Australian Orthopaedic Association. Hip and Knee Arthroplasty, Annual report 2013; 2013
[54] <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148401>

- risks identified in the clinical data should be appropriately mitigated and/or included in the IFU and other information supplied with the device

· For guidance on the conduct of comprehensive literature reviews and on the presentation of clinical evidence sponsors should review the relevant chapters in this document.

· Compilation of the CER:

- in compiling the clinical evidence for a supportive device the sponsor should ensure that a clinician who is an expert in the field and experienced in the use of the device compiles and critiques all the clinical data that informs on the safety and performance of the device
- the clinical expert must review and endorse the CER 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 joint prostheses

This guidance document describes joint prostheses as 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.

From the MD Regulations—Dictionary[55]

joint replacement medical device means an implantable medical device:

a. that is intended by the manufacturer to operate (either alone or together with one or more other implantable medical devices) as a replacement (in whole or in part) for the shoulder joint, hip joint or knee joint; and

b. that (either alone or together with one or more other implantable medical devices):

i. replaces or substitutes for the articulating surface of a shoulder joint, hip joint or knee joint (in whole or in part); or

ii. provides primary fixation to the bone for the replacement articulating surface; or

iii. connects directly or indirectly with an implantable medical device that has a function mentioned in subparagraph (i) or (ii) and operates as an intrinsic element of the joint replacement;

but does not include an ancillary medical device.

ancillary medical device means an implantable medical device that:

a. consists of screws, plates or wedges; or

b. is intended by the manufacturer to be used to:

i. provide stability for an implantable medical device that is intended to (either alone or together with one or more other implantable medical devices) replace the shoulder joint, hip joint or knee joint;

[55] 'Joint replacement medical device' is defined in the dictionary of the MD Regulations <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148428>

or

ii. provide bone substitution in relation to, or additional fixation for, any such device; or

iii. otherwise assist any such device;

where the individual requirements of a patient make it appropriate to do so.

Joint prostheses can consist of either a monoblock or modular design. 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 risk benefit profile that needs to be addressed by the sponsor.

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.

Further information on joint prostheses is included at ***Appendix 7: Joint prostheses***.

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.

Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data and/or a comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device and/or the predicate or similar marketed device.

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 predicate or similar marketed device may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in ***Chapter 5. Demonstrating Substantial Equivalence***.

Where the device and the predicate share a common design origin, particularly when the device is part of a modular system, 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.

Sponsors should refer to ***Chapter 3. Clinical Evidence*** 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. Sponsors are advised to justify the patient number recruited according to sound scientific reasoning through statistical power

calculation. Some examples of RCTs involving joints prostheses include the UK Knee Arthroplasty Trial (KAT)[56] and the A JOINTs Canada Project.[57]

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. Analysis of clinical events should be blinded and independently adjudicated wherever possible.

For clinical investigations of a joint prosthesis, the characteristics of the prosthesis and the intended purpose(s) are essential to the design of the investigation. Therefore, when investigations involve a predicate or similar marketed device, direct comparisons of the technical, physical, chemical and biological characteristics of the joint prosthesis and the comparator should be demonstrated through direct testing in order to establish substantial equivalence. Other 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. These characteristics will determine the criteria for a full and reasoned clinical justification for the selection of the comparator device.

Additional resources regarding the design and conduct of clinical investigation(s) are available on the TGA[58] and FDA[59] 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 ***Appendix 7: Joint prostheses***.

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 predicate/similar marketed device to which substantial equivalence has been established as described in ***Chapter 3. Clinical Evidence***.

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 the predicate or similar marketed device. The selection of a predicate or similar marketed device should be made prior to performing the literature selection, extraction of the clinical data and analysis of the pooled results.

Chapter 3. Clinical Evidence 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.

[56] 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

[57] 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.

[58] <https://www.tga.gov.au/clinical-trials>

[59] <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

- a review and critical analysis: the selected literature should be synthesised and critiqued by a competent clinical expert
- a literature report must be prepared, reviewed and endorsed by a competent clinical expert, containing a critical appraisal of this compilation.

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

Post-market data

Post-market data can be provided for the actual device or for the predicate or similar marketed device, see ***Chapter 3. Clinical Evidence***. It is particularly important to include the following:

- information about the regulatory status of the device (or predicate or similar marketed 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 any conditions such as MRI status in other jurisdictions
- any regulatory action including suspensions, withdrawals, removals or voluntary or mandatory recalls and cancellations (and the reason for these i.e. IFU changes)in any jurisdiction as reported to or required by regulatory bodies
- worldwide yearly distribution numbers[60] of the device(s) for every year since launch
- the number of years of use
- for every year since launch[61], the number of adverse events and complaints categorised by type and clinical outcome (e.g. death, serious harm, or revision due to loosening, fracture, implant breakage, etc.)
- the post-market surveillance data from national registries for jurisdictions where the device is approved for clinical use. National joint registries have been established in Canada, Denmark, England and Wales, Finland, New Zealand, Norway, Romania, Scotland, Slovakia and Sweden[62] as well as Australia.

For further details see ***Appendix 46: Identifying relevant post-market data***. Publicly available post-market data such as adverse event reporting on the FDA Manufacturer and User Facility Device Experience (MAUDE) database and the TGA Incident Reporting and Investigation Scheme (IRIS) may be used for devices from other manufacturers. The sponsor should include post-market surveillance data from national jurisdictions where the device is approved for clinical use.

For reports of adverse events and revisions 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 evaluated and critiqued by a competent clinical expert to enable an understanding of the safety and performance profile of the device(s) in a 'real-world' setting.

[60] Providing yearly figures allows the estimation of cumulative percent incidence, or incidence as a fraction of observation years. It is good practice for the Manufacturer to perform these calculations on a regular basis. For implants such as orthopaedics, Kaplan Meyer analysis is preferred. This sort of analysis is often performed with revision surgery (ie % requiring revision at 1, 2, 3, .., n years from the time of primary surgery as an end point, but it can also be performed on many other endpoints.

[61] National Joint Registry UK. Patient introduction to the NJR. 2014 [cited 11 July 2014]; Available from: <http://www.njrcentre.org.uk/njrcentre/Patients/tabid/74/Default.aspx>

[62] Migliore A, Perrini MR, Romanini E et al. Comparison of the performance of hip implants with data from different arthroplasty registers. J Bone Joint Surg Br. 2009;91:1545-9

Supportive data and information

Additional information on the device should be provided in the clinical evaluation report or supporting documents as applicable (see ***Appendix 5: Clinical evaluation report and supporting documents***). This may include, but is not limited to:

- the full technical specification of the device(s)
- the materials from which the device is made including chemical composition
- other devices which may be used in conjunction with the prosthesis
- 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
- risk assessment and management document
- IFU and all other documents supplied with the device

Defining clinical success

Safety

For safety, the primary outcome measure is revision, with revision meaning the replacement of a prosthetic component, see ***Appendix 7: Joint prostheses,*** Table 7**.** Typically this 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)[63] provides annual reports on the performance of joint prostheses for hip, knee and shoulder and provides the CPR for joint prostheses.

The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) is a comprehensive database providing sponsors with detailed revision data for devices that are available and used in Australia.

Sponsors should demonstrate that CPRs for a device or the predicate or similar marketed device, if used to substantiate the safety and performance of the device, are as good as or better than published acceptable 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]).

If clinical trials or studies 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.[64] 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.[65] This supports the concept of the two year minimum patient follow-up in clinical trials. However, sponsors should be aware that this is the minimum and will not capture information relating to the late failure of a prosthesis. In this situation, sponsors can assist the

[63] <https://aoanjrr.dmac.adelaide.edu.au/>
[64] Goldberg VM, Buckwalter J, Halpin M et al. Recommendations of the OARSI FDA Osteoarthritis Devices Working Group. Osteoarthritis Cartilage. 2011;19:509-14.
[65] de Steiger RN, Miller LN, Davidson DC, Ryan P, Graves SE. Joint registry approach for identification of outlier prostheses. Acta Orthop. 2013;84:348-52.

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 sponsor should:

- identify the expected 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 predicate or a similar marketed 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[66] [67]
  - 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.[68]

Sponsors, 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 ***Appendix 7: Joint prostheses,*** Table 8.

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

[66] Pijls BG, Nieuwenhuijse MJ, Schoones JW, Middeldorp S, Valstar ER, Nelissen RG. RSA prediction of high failure rate for the uncoated Interax TKA confirmed by meta-analysis. Acta Orthop. 2012;83:142-7
[67] Pijls BG, Nieuwenhuijse MJ, Fiocco M et al. Early proximal migration of cups is associated with late revision in THA: a systematic review and meta-analysis of 26 RSA studies and 49 survivalstudies. Acta Orthop. 2012;83:583-91
[68] Hartmann A, Hannemann F, Lutzner J et al. Metal ion concentrations in body fluids after implantation of hip replacements with metal-on-metal bearing--systematic review of clinical and epidemiological studies. PLoS One. 2013;8:e70359

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.[69]

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

Ideally, sponsors should define both a Minimum Clinical 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, see ***Appendix 7: Joint prostheses*** Table 9. 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.

Compiling clinical evidence

In compiling the clinical evidence the sponsor should ensure that a competent clinical expert conducts a synthesis and critique of all the clinical data from clinical investigation(s) and/or literature review and/or post-market data (clinical experience) and reviews and endorses the written report, the CER, to allow the clinical assessor to determine if the clinical evidence is sufficient to demonstrate the requirements of the applicable EPs and that the device is safe and performs as intended.

Earlier chapters and appendices outline the process for collecting clinical data and evaluating the data to provide the clinical evidence and the recommended content and format of the clinical evaluation report. Guidance on defining a predicate or similar marketed device is provided in ***Chapter 5. Demonstrating Substantial Equivalence***. As time since approval lengthens predicate data becomes less relevant and should be replaced by data derived from clinical experience with the device.

The clinical expert should ensure that risks identified in the clinical data are included in the risk assessment documentation and properly mitigated. A discussion highlighting how this has been done should be included in the clinical evaluation report. Comments on any issues relating to the IFU, labelling and other documents supplied with the device should be included in the CER with an assessment of whether these are consistent with the clinical data. The IFU should include all identified hazards and other clinically relevant information that may impact on the safe use of the device.

[69] Ng CY, Ballantyne JA, Brenkel IJ. Quality of life and functional outcome after primary total hip replacement. A five-year follow-up. J Bone Joint Surg Br. 2007;89:868-73

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 (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. Sponsors are advised to list the likely combinations and provide clinical evidence to support the safety and performance of the new device for these nominated configurations.
- For submissions reliant on predicate or similar marketed device data, sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between a new device and the nominated predicate(s) or similar marketed device(s).
- Sponsors 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
  - Sponsors 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 or 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 total 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 sponsor is advised to benchmark the device against devices of the same class as reported for appropriate registers (if available) or provide direct comparative data comparing the device with similar marketed devices

§ For patient performance data, sponsors 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 sponsor 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 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 sponsor 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 sponsor should ensure that a clinician who is an expert in the field and experienced in the use of the device compiles and critiques all the clinical data that informs on the safety and performance of the device.

– the clinical expert must review and endorse the CER 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 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).[70] [71] [72]

Implants for Abdominal Aortic Aneurysm (AAA) repair

Open surgical excision of an aortic aneurysm with placement of a sutured implant is increasingly being replaced by endovascular surgery. 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

Non-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. [73] [74] 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.[75] [76]

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 mechanically traps fragmented clots in 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.[77]

Clinical evidence

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

[70] NICE. Interventional procedure overview of carotid artery stent placement for symptomatic extracranial carotid stenosis. 2010:IP 008_2.
[71] Canadian Agency of Drugs and Techologies in Health (CADTH). Carotid artery stenting verus carotid endoarterrectormy, a review of the clinical and cost-effectiveness. Health Technology Inquiry Service 2010 [cited December 2014]; Available from: <http://www.cadth.ca/media/pdf/L0130_CAS_vs._Endarterectomy_final.pdf>
[72] Raman G, Kitsios GD, Moorthy D et al. AHRQ Technology Assessments. Management of Asymptomatic Carotid Stenosis. Rockville (MD): Agency for Healthcare Research and Quality (US) 2012.
[73] Chen Z, Chen L, Wu L. Transcatheter amplatzer occlusion and surgical closure of patent ductus arteriosus: comparison of effectiveness and costs in a low-income country. Pediatr Cardiol. 2009;30(6):781-5.
[74] Wang K, Pan X, Tang Q, Pang Y. Catheterization therapy vs surgical closure in pediatric patients with patent ductus arteriosus: a meta-analysis. Clin Cardiol. 2014;37(3):188-94.
[75] Boehm W, Emmel M, Sreeram N. The Amplatzer duct occluder for PDA closure: indications, technique of implantation and clinical outcome. Images Paediatr Cardiol. 2007;9(2):16-26.
[76] Huang TC, Chien KJ, Hsieh KS, Lin CC, Lee CL. Comparison of 0.052-inch coils vs amplatzer duct occluder for transcatheter closure of moderate to large patent ductus arteriosus. Circ J. 2009;73(2):356-60.
[77] Young T, Tang H, Hughes R. Vena caval filters for the prevention of pulmonary embolism. Cochrane database of systematic reviews (Online). 2010(2):CD006212.

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 may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in ***Chapter 5. Demonstrating Substantial Equivalence.***

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. Sponsors should refer to ***Chapter 3. Clinical Evidence*** 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 predicate/similar marketed 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. Sponsors 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 time-frame 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, the predicate/similar marketed device to which substantial equivalence has been established as described in ***Chapter 5. Demonstrating Substantial Equivalence.***

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 the predicate or similar marketed device. The selection of a predicate or similar marketed device should be made prior to performing the literature selection, extraction of the clinical data and analysis of the pooled results.

Chapter 3. Clinical Evidence 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 must be provided, written by a competent clinical expert, containing a critical appraisal of this compilation.

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

Post-market data

Post-market data can be provided for the actual device or for the predicate or similar marketed device, see Chapter 3. It is particularly important to include the following:

- information about the regulatory status of the device (or predicate or similar marketed 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 any conditions such as MRI status in other jurisdictions
- any regulatory action including CE mark withdrawals, suspensions, removals, cancellations or voluntary recalls in any jurisdiction (and the reason for these ie IFU changes) as reported to or required by regulatory bodies
- worldwide yearly distribution numbers of the device(s) for every year since launch
- the number of years of use
- for every year since launch, the number of adverse events and complaints categorised by type and clinical outcome (e.g. death, serious harm)

For further details see ***Appendix 4: Identifying relevant post-market data***. Publicly available post-market data such as adverse event reporting on the FDA Manufacturer and User Facility Device Experience (MAUDE) database and the TGA Incident Reporting and Investigation Scheme (IRIS) may be used for devices from other manufacturers. The sponsor should include post-market surveillance data from national jurisdictions where the device is approved for clinical use.

For reports of adverse events and revisions 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 evaluated and critiqued by a competent clinical expert to enable an understanding of the safety and performance profile of the device(s) in a 'real-world' setting.

Supportive data and information

Additional information on the device should be provided in the CER or supporting documents, as applicable. In particular this should include (but is not limited to):

- the full technical specification 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.

- a well-documented and actionable risk analysis and quality management system
- IFU and all other documents supplied with the device. The clinical evidence must highlight these risks and ensure that they are appropriately communicated to user.

Defining clinical success

Clinical outcomes to define the safety and performance of the CV flow devices were identified from clinical studies published in the peer reviewed literature. The clinical studies relevant to CV flow implants were identified by using a modified rapid review method as described in ***Appendix 8: CV flow implants***. Details from the literature review are also in Appendix 8.

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 2 (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 2. 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	

Outcomes reported in studies	Carotid*	Coronary	Peripheral
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
Length of follow-up in included SRs	1 month to 4 years (one to 11 years) The CREST study†: 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=total 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[78] and Academic Research Consortium[79]

† Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)[80]

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. Sponsors are advised to use standardised definitions for clinical endpoints for coronary stents as defined by the Academic Research Consortium (ARC), in 2007.[79] The ARC nominated clinical outcomes

[78] European Commision - Directives on medical devices. Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies. 2008.
[79] Cutlip DE, Windecker S, Mehran R et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17):2344-51.
[80] Brott TG, Hobson RW, 2nd, Howard G et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11-23

have been adopted by the European Commission in their guidance MEDDEV 2.7.1.[78] These include, but are not limited to, outcomes listed in Table 2 (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.[79] [81]
- If MACE is the nominated clinical endpoint, sponsors are advised to provide a clear definition with clinical justification for the elements included in this composite measure.

Sponsors 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 is NO ischemia driven adverse events to a maximum of seven days post procedure.[78]

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.[79] This timeline is in line with reported patient follow-up times in the peer-reviewed literature (Table 2) and ***Appendix 8: CV flow implants***).

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

Note: Sponsors 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 is 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 may be considered clinically acceptable for a given patient cohort.[82]

Examples of indicative rates for death, stroke and MI events are reported for the CREST clinical trial.[83] These are reported as % ± SD:

- Peri-procedure (< 30days)

[81] Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. J Am Coll Cardiol. 2008;51(7):701-7.
[82] O'Brien M, Chandra A. Carotid revascularization: risks and benefits. Vasc Health Risk Manag. 2014;10:403-16.
[83] Brott TG, Hobson RW, 2nd, Howard G et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363(1):11-23.

- 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, sponsors 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.[84]

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 2 and ***Appendix 8: CV flow implants***).

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.[85] 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%[86]

· Given the physical dimensions of this class of stent, stent fracture may occur at rates in excess of 30% of treated legs[86]. Stent fracture significantly impacts primary patency rates and sponsors are advised to report these rates.

[84] NICE. Interventional procedure overview of carotid artery stent placement for symptomatic extracranial carotid stenosis. 2010:IP 008_2.
[85] Schillinger M, Minar E. Percutaneous treatment of peripheral artery disease: novel techniques. Circulation. 2012;126(20):2433-40.
[86] Kudagi VS, White CJ. Endovascular stents: a review of their use in peripheral arterial disease. Am J Cardiovasc Drugs. 2013;13(3):199-212.

- Patency at 1 and 3 years are reported to be 69 to 79% and 59 to 70% respectively.[87]

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 sponsors 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.[87]

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 2 and ***Appendix 8: CV flow implants.*** 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.[88] 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.
- Graft migration or failure of device to integrate.
- Type II endoleak with an aneurysm expansion.

Sponsors 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.

[87] Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007;45 Suppl S:S5-67.
[88] Chaikof EL, Blankensteijn JD, Harris PL et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg. 2002;35(5):1048-60.

Technical success is defined as the successful deployment and removal of delivery device without the need for surgical conversion or mortality. Chaikof *et al*[88] 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 endolumunal 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. These 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. Sponsors 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. Sponsors 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[89]
- Sponsors 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% CL 1.0 to 3.7).[90]

Follow-up in the studies included in the systematic review examined for this report was unclear but was possibly 6 months. However, sponsors 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. Sponsors are advised to provide details of target patient baseline risk for PE,

[89] Brunetti MA, Ringel R, Owada C et al. Percutaneous closure of patent ductus arteriosus: a multiinstitutional registry comparing multiple devices. Catheter Cardiovasc Interv. 2010;76(5):696-702.
[90] El-Said HG, Bratincsak A, Foerster SR et al. Safety of percutaneous patent ductus arteriosus closure: an unselected multicenter population experience. J Am Heart Assoc. 2013;2(6):e000424.

operator experience and technique, medical management goals and the primary study endpoints. These have been shown to be independently associated with adverse events.[91]

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

- Fatal PE is rarely reported and sponsors should use appropriate study designs with sufficient power to detect rare events. 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[91] more than 96% of filters were deployed as intended. However, sponsors should report the filter orientation on deployment (i.e. centralised, tilted or abutting the IVC wall).
- Sponsors should report the dwell time for the device and the impact on retrieval for temporary devices.
- Any structural failure should be reported.
- Sponsors are advised that DVT was reported to be lower than the 1% in BSIR registry data.[91] However, clinical profile of the patient cohort may affect this adverse event. Therefore, sponsors 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.[91]
- The BSIR IVC registry requires notification of filter migration of > 10mm. Sponsors 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. Sponsors are advised to provide a clear clinical context for the use of the IVC filter to assist the clinical assessor to determine the benefit-risk for the device.

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.

- Sponsors, 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 sponsors provide data with a minimum of one year follow-up post-surgery to reduce the risk of confounding due to procedure variables.

[91] Uberoi R, Tapping CR, Chalmers N, Allgar V. British Society of Interventional Radiology (BSIR) Inferior Vena Cava (IVC) Filter Registry. Cardiovasc Intervent Radiol. 2013;36(6):1548-61.

Compiling clinical evidence

In compiling the clinical evidence the sponsor should ensure that an expert in the relevant field conducts a synthesis and critique of all the clinical data from clinical investigation(s) and/or 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 the requirements of the applicable EPs and that the device is safe and performs as intended.

Previous chapters and related appendices outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a clinical evaluation report. These guidance documents apply whether the applicant is using direct clinical evidence or relying on indirect clinical devices for a predicate or similar marketed device. Guidance on defining a predicate or similar marketed device is provided in ***Chapter 5. Demonstrating Substantial Equivalence***.

The following should be included when relying on a predicate or similar marketed device for CV flow implants:

- A comparison of the technical and physical characteristics of the device and predicate or similar marketed 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.
  - 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 one predicate or similar marketed device is discouraged; however, these may be used if each predicate or similar marketed device is a valid predicate or similar marketed device and each is found to be substantially equivalent to the new device under consideration
  - a clinical justification should be presented for the selected predicate/similar marketed device as to why direct clinical data are either not required, or only partially required.
- The predicate/similar marketed device must have clinical data to support its safety and performance and all supporting data must be provided with the clinical evaluation report. As time since approval lengthens predicate data becomes less relevant and should be replaced by data derived from clinical experience with the device.

Electrical impulse generators

These are active medical devices that produce electrical discharges. This chapter specifically covers cardiac active implantable devices and implantable electrical nerve stimulation devices.

Summary recommendations

- Electrical impulse generators (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. Sponsors 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: Sponsors 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.
  - It is suggested that the patient follow-up for clinical trials for AIMDs should occur at 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 to determine performance and safety 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.[120]
- The clinical outcomes that determine safety and performance of electrical impulse generators vary significantly by device type:
  - The sponsor 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 sponsors are advised to define the anticipated improvement in patient scores post-surgery or post-treatment. Ideally, these should be internationally recognised assessment tool(s) used to measure clinical success e.g. pain assessment via a visual analogue scale.
  - The sponsor may use post-market data if the device is approved and marketed in another jurisdiction.
  - 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 repeated by others.
  - a well-documented and actionable risk analysis and quality management system should also be provided. 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, before assigning risk

reduction activities such as statements in the IFU and training materials to reduce residual risks.

- For guidance on the conduct of comprehensive literature reviews and presentation of clinical evidence sponsors are directed to the relevant chapters and appendices.
  - In compiling the clinical evidence for an electrical impulse generator, the sponsor should ensure that a clinician who is an expert in the field and experienced in the use of such devices conducts a synthesis and critique of all the clinical data that informs on 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 and that it is deemed to be safe and to perform as intended. The clinical expert should review and then endorse (by signing) the CER.
- A full *curriculum vitae* of the clinical expert should be included in the CER.

Defining electrical impulse generators

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 Medical Devices (AIMD) 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.

Further details on these devices are provided in ***Appendix 9: Electrical impulse generators***.

Implantable electrical impulse generators can pose a significant regulatory challenge as they must have long *in vivo* lives without exposing recipients to unduly high risks of adverse events.

Clinical evidence

Clinical investigation(s)

The clinical evidence can be derived from clinical investigation(s) data and/or a comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device (direct evidence) and/or the predicate or similar marketed device (indirect evidence). 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 may be used after substantial equivalence has been demonstrated (see ***Chapter 5. Demonstrating Substantial Equivalence).***

Where the device and the predicate share any common design origin, the lineage between the devices should be provided.

The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data. Sponsors should refer to ***Chapter 3. Clinical Evidence*** for further information.

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 in ***Chapter 3. Clinical Evidence***. The data can be generated from the use of the device or, if relying on indirect evidence, the predicate/similar marketed device to which substantial equivalence has been established. Data on the materials used to construct the electrical impulse generator, its design, dimensions and geometry and the intended purpose 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 predicate/similar marketed device. The selection should be made prior to performing the literature selection, extraction of the clinical evidence and analysis of the pooled results. A full description of the device used 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 predicate or similar marketed device. For implantable electrical impulse generators, the regulatory status of the device should include the MR conditional status in each jurisdiction where it is approved for use.

For reports of adverse events (AEs) and revisions 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 problems and AEs.

Examples of registry data for electrical impulse generators have been reported in peer reviewed studies from Spain,[92] Denmark,[93] Sweden,[94] France,[95] [96] Italy,[97] China,[98] Germany,[99] Poland,[100] the United States,[101] and Australia.[102]

[92] Coma Samartin R, Cano Perez O, Pombo Jimenez M. Spanish Pacemaker Registry. Eleventh official report of the Spanish Society of Cardiology Working Group on Cardiac Pacing (2013). Rev Esp Cardiol. 2014;67(12):1024-38.
[93] Moller M, Arnsbo P. [The Danish Pacemaker Registry. A database for quality assurance]. Ugeskr Laeger. 1996;158(23):3311-5.
[94] Gadler F, Valzania C, Linde C. Current use of implantable electrical devices in Sweden: data from the Swedish pacemaker and implantable cardioverter-defibrillator registry. Europace. 2015;17(1):69-77.
[95] Mouillet G, Lellouche N, Yamamoto M et al. Outcomes following pacemaker implantation after transcatheter aortic valve implantation with CoreValve devices: Results from the FRANCE 2 Registry. Catheter Cardiovasc Interv. 2015.
[96] Benkemoun H, Sacrez J, Lagrange P et al. Optimizing pacemaker longevity with pacing mode and settings programming: Results from a pacemaker multicenter registry. Pacing Clin Electrophysiol. 2012;35(4):403-8.
[97] Proclemer A, Zecchin M, D'Onofrio A et al. [The pacemaker and implantable cardioverter-defibrillator registry of the Italian Association Arrhythmology Cardiac Pacing and cardiac pacing - annual report 2013]. G Ital Cardiol (Rome). 2014;15(11):638-50.
[98] Chen KP, Dai Y, Hua W et al. Reduction of atrial fibrillation in remotely monitored pacemaker patients: results from a Chinese multicentre registry. Chin Med J. 2013;126(22):4216-21.
[99] Markewitz A. [Annual Report 2009 of the German Cardiac Pacemaker Registry: Federal Section pacemaker and AQUA - Institute for Applied Quality Improvement and Research in Health Ltd]. Herzschrittmacherther Elektrophysiol. 2011;22(4):259-80.
[100] Przybylski A, Derejko P, Kwasniewski W et al. Bleeding complications after pacemaker or cardioverter-defibrillator implantation in patients receiving dual antiplatelet therapy: Results of a prospective, two-centre registry. Neth Heart J. 2010;18(5):230-5.
[101] Poole JE, Gleva MJ, Mela T et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation. 2010;122(16):1553-61.

Supportive data and information

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

- the full technical specification 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
- risk assessment and management document
- IFU and all other documents supplied with the device

Defining clinical success[103]

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.[104] Given the long-term *in vivo* life of these implantable devices, sponsors are advised that long-term follow-up is required. From the peer reviewed literature typical follow-up periods are three plus years.

- Sponsors are advised that a clinical justification is required for the reported safety and performance outcomes, nominated reference values and associated follow-up periods. This should be provided by a clinical expert in the field with experience in the use of these devices.
- NOTE: as the baseline health status may influence the prevalence of functional states (e.g. atrial fibrillation), a detailed patient profile should be provided.

Sponsors 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

[102] Reid CM, Brennan AL, Dinh DT et al. Measuring safety and quality to improve clinical outcomes--current activities and future directions for the Australian Cardiac Procedures Registry. Med J Aust. 2010;193(8 Suppl):S107-10.

[103] Clinical studies published in the peer reviewed literature were used as the evidence base for this report in order to identify appropriate clinical outcomes to define the safety and performance of the specified types of electrical impulse generators. This evidence base was determined using a modified rapid review method and details from the evidence as described in ***Appendix 9: Electrical impulse GENERATORS***

[104] Nielsen JC, Thomsen PE, Hojberg S et al. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. Eur Heart J. 2011;32(6):686-96

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, medical impulse 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. Sponsors are advised to read the relevant section on ***Demonstrating the safety of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment*** (below) and ISO 14117:2012[105] (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.[106]

- Sponsors 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 documents.

[105] <http://www.iso.org/iso/catalogue_detail.htm?csnumber=54472>

[106] Crossley GH, Poole JE, Rozner MA et al. The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: Facilities and patient management: Executive summary this document was developed as a joint project with the American Society of Anesthesiologists (ASA), and in collaboration with the American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Heart Rhythm. 2011;8(7):e1-18.

Active implantable medical devices

Safety

Systematic reviews on dual-chamber and CRT pacemakers either with or without defibrillation capability[107] and ICDs included the following peri-procedure events and longer term outcomes that were tracked as safety measures: [108] [109] [110] [111] [112] [113]

- 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, vein 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[114] guidance report also listed 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

[107] Castelnuovo E, Stein K, Pitt M, Garside R, Payne E. The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: Systematic review and economic evaluation. Health Technol Assess. 2005;9(43):iii, xi-xiii, 1-246.
[108] Kong MH, Al-Khatib SM, Sanders GD, Hasselblad V, Peterson ED. Use of implantable cardioverter-defibrillators for primary prevention in older patients: A systematic literature review and meta-analysis. Cardiol J. 2011;18(5):503-14
[109] Colquitt JL, Mendes D, Clegg AJ et al. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: Systematic review and economic evaluation. Health Technol Assess. 2014;18(56):1-560
[110] Chen S, Ling Z, Kiuchi MG, Yin Y, Krucoff MW. The efficacy and safety of cardiac resynchronization therapy combined with implantable cardioverter defibrillator for heart failure: A meta-analysis of 5674 patients. Europace. 2013;15(7):992-1001
[111] Chen S, Yin Y, Krucoff MW. Effect of cardiac resynchronization therapy and implantable cardioverter defibrillator on quality of life in patients with heart failure: A meta-analysis. Europace. 2012;14(11):1602-7
[112] Pun PH, Al-Khatib SM, Han JY et al. Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: A meta-analysis of patient-level data from 3 randomized trials. American Journal of Kidney Disease. 2014;64(1):32-9
[113] Schinkel AF. Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications. Circulation: Arrhythmia and Electrophysiology. 2013;6(3):562-8
[114] Health Canada. Guidance Document: Medical Device Applications for Implantable Cardiac Leads. File No. 11-113340-236; 2011

- CRT and CRT-D: progression to pacemaker syndrome, atrial fibrillation, heart failure or stroke
- hazards related to use in the MRI environment (refer to the relevant section in ***Demonstrating the safety of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment***)
- explants should be accounted for with an explanation of device failures and corrective measures
- mortality (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 [115]
- post-market safety data including medical device vigilance reports

Performance

In guidance documents on pacemakers and their associated leads issued by Health Canada[114] and US FDA[115], and systematic reviews (SRs) [109] [116] related to CRT-D and ICD evidence, [108] [109] [110] [111] [112] [113] 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[117] 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 [115]
- 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 conditions

[115] US Food & Drug Administration (FDA). Guidance for the submission of research and marketing applications for permanent pacemaker leads and for pacemaker lead adaptor 510(k) submissions; 2000
[116] Castelnuovo E, Stein K, Pitt M, Garside R, Payne L, for the UK NHS R&D HTA Programme. The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation. 2004 [cited; Available from: <www.nice.org.uk/guidance/ta88>
[117] <http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp>

Implantable electrical nerve stimulation devices

Implantable electrical nerve stimulators (including such devices as deep brain and vagus 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, see ***Appendix 9: Electrical impulse generators***.

The different aetiologies of pain and other neurological symptoms can impact on the performance of neurostimulators. Therefore sponsors 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[118]) or extracranial (e.g. spinal cord, vagus nerve or peripheral nerve stimulators[119] [120]).

Safety: intracranial neurostimulators

Adverse events are variously reported[118] [121] and include:

- usual 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. shortened battery life, failed leads
- MRI environment safety concerns including heating (which has been reported to create the greatest concern for various neurostimulator devices)

Safety: extracranial neurostimulators

Adverse events are variously reported [119] [122] and include:

- device-related complications e.g. electrode migration, lead fracture
- distorted or loss of sensation (paraesthesia or numbness)

[118] Plow EB, Pascual-Leone A, Machado A. Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. The Journal of Pain. 2012;13(5):411-24
[119] Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: A systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. European Journal of Pain. 2006;10(2):91-101
[120] Coffey RJ, Lozano AM. Neurostimulation for chronic noncancer pain: An evaluation of the clinical evidence and recommendations for future trial designs. J Neurosurg. 2006;105(2):175-89
[121] Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: Critical review of the literature. J Neurosurg. 2009;110(2):251-6
[122] Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: Systematic review and economic evaluation. Health Technol Assess. 2009;13(17):iii, ix-x, 1-154

- 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[118 120 122] 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[120]
- 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
- analgesic consumption

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

Compiling clinical evidence

In compiling the clinical evidence the sponsor should ensure that an expert in the relevant field evaluates all the clinical data from clinical investigation(s) and/or literature review and/or post-market data (clinical experience). The clinical expert should review and then endorse (by signing) the CER 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.

Previous chapters and appendices outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a clinical evaluation report. These guidance documents apply whether the applicant is using direct clinical evidence or

relying on indirect clinical devices for a predicate or similar marketed device. Guidance on defining a predicate or similar marketed device is provided in ***Chapter 5. Demonstrating Substantial Equivalence.***

If the predicate or similar marketed device is approved for use in another jurisdiction, the sponsor should provide regulatory status, including the certificate number, date of issue and name under which the device is marketed, specific indications for use including MR status in key jurisdictions eg EU, US and Canada, as well as complaint and adverse event data and any recalls, suspensions, removals, withdrawals or cancellations of the device regardless of whether these were for specific indications or for the device itself.

Heart valve replacement 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. Sponsors are advised to provide clinical evidence to support the safety and performance of the particular device and any accessories used to deliver the device.
- For submissions reliant on predicate, or similar marketed device data, sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between a device and the nominated predicate or similar marketed device.
- 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.
- In addition, a well-documented and actionable risk analysis and quality management system should also 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, before assigning risk reduction activities such as statements in the IFU and training materials to reduce residual risks.
- Sponsors 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.
- Provision of clinical data:
  - sponsors 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 patients of 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[128]
  - for evaluating the performance of prosthetic heart valves it is recommended that the Objective Performance Criteria (OPC) as listed in ISO 5840-2005 (and updates) be reported including early (within 30 days post implantation), mid- term outcomes (after 30 days post implantation)[144] and at 1 year. The selection should be supported by a clinical justification;
  - typical safety and performance values are provided in Table 13, Table 14, Table 15, Table 16 and Table 17 and Table 18 in Appendix 10: Heart valve prostheses.
  - 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 repeated.

- Compilation of the clinical evidence
  - in compiling the clinical evidence for a prosthetic heart valve the sponsor should ensure that a competent clinical expert synthesizes and critiques all the clinical data that informs on the safety and performance of the device;
  - the competent clinical expert must then review and endorse the CER which demonstrate to the clinical assessor 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.

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 onto a catheter and are expanded at the time of implantation).[123] The guidance also applies to 'sutureless' (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.[124] Each type of valve has its own associated risk benefit profile that needs to be addressed by the sponsor.

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).[125]

Sponsors and applicants are advised to read this guidance in conjunction with earlier relevant chapters, appendices, ***Chapter 5. Demonstrating substantial equivalence*** and ISO documentation, ISO 5840:2005[126] and ISO 5840-3:2013.[127]

[123] Williams JW, Coeytaux R, Wang A, D.D. G. Percutaneous Heart Valve Replacement. Technical Brief No. 2. 2013 [cited 2014 20 October]; Available from: <http://effectivehealthcare.ahrq.gov/ehc/products/66/492/TechBrief_PercutaneousHeart_final.pdf>

[124] ASERNIPS. Sutureless aortic valve replacement in patients with severe aortic stenosis. 2012 [cited 2015 February 10th]; Available from: <http://www.health.qld.gov.au/healthpact/docs/briefs/WP121.pdf>

[125] Williams JW, Coeytaux R, Wang A, Glower DD. Percutaneous Heart Valve Replacment. Technical Brief No. 2. . Rockville, MD: Prepared by Duke Evidence-based Practice Center under Contract No. 290-02-0025. Agency for Healthcare Research and Quality; 2010.

[126] International Organisation for Standardisation. Cardiovascular implants - Cardiac valve prostheses (ISO 5840: 2005). 2005 [cited 2014 27 October]; Fourth Edition 2005-03-01:[Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=34164>

Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data and/or a comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device (direct) and/or the predicate or similar marketed 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 predicate or similar marketed device may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in ***Chapter 5. Demonstrating substantial equivalence.*** 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. Sponsors should refer to ***Chapter 3. Clinical Evidence*** 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 the sponsor refer to ISO documents (ISO 5840:2005, ISO 5840-3:2013) as guides to study design.[128] [129] At the time of writing a further three ISO documents on heart valve prostheses were under development (ISO/DIS 5840-1, ISO/DIS 5840-2 and ISO/NP 5840-3). Sponsors should consult these documents when available. 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. There must be at least 400 valve years of follow-up of each valve type. This is based on guidance in ISO 5840:2005.[128] The sponsor 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

[127] International Organisation for Standardisation. Cardiovascular implants - Cardiac valve prostheses - Part 3: Heart valve substitutes implanted by transcatheter techniques (ISO 5840-3: 2013). 2013 [cited 2014 27 October]; Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=51313>

[128] International Organisation for Standardisation. Cardiovascular implants - Cardiac valve prostheses (ISO 5840: 2005). 2005 [cited 2014 27 October]; Fourth Edition 2005-03-01:[Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=34164>

[129] International Organisation for Standardisation. Cardiovascular implants - Cardiac valve prostheses - Part 3: Heart valve substitutes implanted by transcatheter techniques (ISO 5840-3: 2013). 2013 [cited 2014 27 October]; Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=51313>

its intended purpose. The data can be generated from the use of the device or, if relying on indirect evidence, the predicate or similar marketed device to which substantial equivalence has been established. To demonstrate substantial equivalence the clinical, technical and biological characteristics must be compared.

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 predicate/similar marketed 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 in any given study must be extractable from the study report. If this is not possible, the study should be excluded from the review.The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data.

Post-market data

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

- information about the regulatory status of the device(s) (or predicate or similar marketed 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 any conditions such as MRI designation in other jurisdictions
- any regulatory action including CE mark withdrawals, removals, suspensions and cancellations or voluntary recalls (and the reason for these ie IFU changes) anywhere in the world and complaint or adverse event data, as reported to or required by regulatory bodies.

Publicly available post-market data such as adverse event reporting on the FDA Manufacturer and User Facility Device Experience (MAUDE) database and the TGA Incident Reporting and Investigation Scheme (IRIS) may be used for devices from other manufacturers. The sponsor 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). [130] [131] [132] [133] [134] [135] [136] [137] [138] [139] [140] [141]

[130] Avanzas P, Munoz-Garcia AJ, Segura J et al. Percutaneous implantation of the CoreValve self-expanding aortic valve prosthesis in patients with severe aortic stenosis: early experience in Spain. Rev Esp Cardiol. 2010;63(2):141-8

[131] Buellesfeld L, Gerckens U, Schuler G et al. 2-year follow-up of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. J Am Coll Cardiol. 2011;57(16):1650-7

[132] Eltchaninoff H, Prat A, Gilard M et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. Eur Heart J. 2011;32(2):191-7

[133] Godino C, Maisano F, Montorfano M et al. Outcomes after transcatheter aortic valve implantation with both Edwards-SAPIEN and CoreValve devices in a single center: the Milan experience. JACC Cardiovasc Interv. 2010;3(11):1110-21

[134] Haussig S, Schuler G, Linke A. Worldwide TAVI registries: What have we learned? Clin Res Cardiol. 2014;103(8):603-12

[135] Moat NE, Ludman P, de Belder MA et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol. 2011;58(20):2130-8

[136] Moynagh AM, Scott DJ, Baumbach A et al. CoreValve transcatheter aortic valve implantation via the subclavian artery: comparison with the transfemoral approach. J Am Coll Cardiol. 2011;57(5):634-5

[137] Tamburino C, Capodanno D, Ramondo A et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation. 2011;123(3):299-308

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 analysed and critiqued by a competent clinical expert to enable an understanding of the safety and performance profile of the device(s) in a 'real-world' setting.

Supportive data and information

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

- the full technical specification 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
- 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.
- risk assessment and management document
- IFU and all other documents supplied with the device

Defining clinical success

The evidence base for these guidelines used clinical studies published in the peer reviewed literature. This information was sourced using a modified rapid review method as described in ***Appendix 10: Heart valve prostheses.*** These studies identified appropriate clinical outcomes to establish the safety and performance of prosthetic heart valves.

The studies on prosthetic heart valves classified outcomes 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.

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[138] Thomas M, Schymik G, Walther T et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation. 2011;124(4):425-33

[139] Thomas M, Schymik G, Walther T et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation. 2010;122(1):62-9

[140] Walters DL, Sinhal A, Baron D et al. Initial experience with the balloon expandable Edwards-SAPIEN Transcatheter Heart Valve in Australia and New Zealand: the SOURCE ANZ registry: outcomes at 30 days and one year. Int J Cardiol. 2014;170(3):406-12

[141] Zahn R, Gerckens U, Grube E et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J. 2011;32(2):198-204

It is recommended that early outcomes, to be reported at 30 days post treatment, 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 renal replacement therapy)
- 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.[142]

The outcomes listed above are a recommended minimum based on a consensus report produced by the Valve Academic Research Consortium.[143] For appropriate definitions, diagnostic criteria and measurement of the above outcomes sponsors should consult the following documents:

- the Valve Academic Research Consortium Consensus Documents on standardised endpoint definitions for transcatheter aortic valve implantation[144] [145]
- guidelines by Akins et al (2008) for reporting mortality and morbidity after cardiac valve interventions[142]
- guidelines on the evaluation of prosthetic valves with echocardiography [146] [147]
- the update of objective performance criteria for clinical evaluation of new heart valve prostheses by ISO (Wu et al 2014)[148]

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[144] [146] [147] (Table 13, Table 14, Table 15, Table 16 and Table 17).

[142] Akins CW, Miller DC, Turina MI et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. Ann Thorac Surg. 2008;85(4):1490-5 Availoable at <http://aats.org/multimedia/files/Guidelines/AATS08-April-Guidelines-Manuscript.pdf>
[143] <http://ejcts.oxfordjournals.org/content/42/5/S45.full.pdf+html>
[144] Kappetein AP, Head SJ, Genereux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012;33(19):2403-18.
[145] Leon MB, Piazza N, Nikolsky E et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol. 2011;57(3):253-69
[146] Zamorano JL, Badano LP, Bruce C et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. J Am Soc Echocardiogr. 2011;24(9):937-65
[147] Zoghbi WA, Chambers JB, Dumesnil JG et al. Recommendations for Evaluation of Prosthetic Valves With Echocardiography and Doppler Ultrasound. A Report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, Developed in Conjunction With the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association. J Am Soc Echocardiogr. 2009;22(9):975-1014
[148] Wu Y, Butchart EG, Borer JS, Yoganathan A, Grunkemeier GL. Clinical Evaluation of New Heart Valve Prostheses: Update of Objective Performance Criteria. Ann Thorac Surg. 2014

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 18). A new valve should have complications rates lower than twice the OPC. [148] 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.

Sponsors should report early (within 30 days post implantation) and late valve outcomes (after 30 days post implantation) with a follow-up of 12 months or more and a minimum of 400 valve years of follow-up for each valve type.[128]

Outcomes are comprised of the most relevant patient endpoints as defined by the Valve Academic Research Consortium (VARC).[144]

For surgically implanted valves, sponsors 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.

Compiling clinical evidence

Previous chapters and appendices outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a clinical evaluation report. These guidance documents apply whether the applicant is using direct clinical evidence or relying on indirect clinical evidence for a predicate or similar marketed device. As time since approval lengthens predicate data becomes less relevant and should be replaced by data derived from clinical experience with the device.

In respect of the full technical specifications for heart valve prostheses refer to ***Appendix 10: Heart valve prostheses.*** The following should be included when relying on a predicate or similar marketed device for heart valve prostheses:

- A comparison of the technical and physical characteristics of the new and predicate or similar marketed 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 document 5840:2005 for a more comprehensive list[128]
  - 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 one predicate or similar marketed device is discouraged; however, these may be used if each predicate or similar marketed device is a valid predicate or similar marketed device and each is found to be substantially equivalent to the device under consideration
- a clinical justification should be presented when using a predicate or similar marketed device as to why direct clinical data are either not required, or are only partially required

· The predicate device(s) or similar marketed device(s) must have clinical data to support its safety and performance and a compilation and critique of all the clinical data must be provided in the CER.

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, CNS patches, and tissue adhesives but sheeting of various origins is also included.[149]

These devices can be made from biologic and non-biologic materials and be permanent or absorbable in various combinations. Each type of supportive devices has its own associated benefit-risk profile that needs to be addressed by the sponsor.

Summary recommendations

- For submissions reliant on predicate, or similar marketed device data, sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between a device and the nominated predicate(s) or similar marketed device(s).
- Sponsors are advised that preclinical 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.
- In addition, a well-documented and actionable risk analysis and quality management system should also be provided with the CER.
- Sponsors 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 sponsor seeks TGA approval.
- Provision of clinical data:
  - sponsors 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 meshes and patches and 15-17 months for tissue adhesives
  - across the surgical supports the main clinical outcomes that determine safety and performance are recurrence rate, clearance and metabolism times for absorbable devices, achievement of homeostasis, prevention of leakage and patient scores such as the Pelvic Organ Prolapse Quantification System (POP-Q)[150]
    - § for revision data, the sponsor is advised to benchmark the device against devices of the same class as reported by an international registry, if available
    - § for patient performance data, sponsors 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

[149] Food and Drug Administration. Surgical Mesh: FDA Safety Communication. 2012 [cited; Available from: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm142636.htm>

[150] Persu C, Chapple CR, Cauni V, Gutue S, Geavlete P. Pelvic Organ Prolapse Quantification system (POP–Q) – a new era in pelvic prolapse staging. Journal of Medicine and Life. 2011;4(1):75-81.

- when submitting a comprehensive literature review, full details of the methodology used should be included in the CER and to a standard whereby the review process can be repeated by others
- for guidance on the conduct of comprehensive literature reviews and presentation of clinical evidence sponsors are directed to relevant chapters and appendices in this document.

· Compilation of the clinical evidence report:

- in compiling the clinical evidence for a supportive device the sponsor should ensure that a clinician who is an expert in the field and experienced in the use of the device compiles and critiques all the clinical data that informs on the safety and performance of the device
- the clinical expert must review and endorse the CER containing the clinical evidence to demonstrate that the evidence meets the requirements of the applicable Essential Principles and the device is safe and performs as intended.

Defining supportive devices

The TGA describes supportive devices as devices in the following sub-groups.

· **Surgical mesh;** this is the most widely used type. It is used for hernia repair, pelvic organ prolapse (POP), stress urinary incontinence (SUI) and many other purposes. The two main classes of devices are biological and synthetic. Types of mesh include bio-mesh, polypropylene, expanded polytetrafluoroethylene (ePTFE), composite polypropylene-PTFE. More than one type can be used at once and they can be absorbable, semi-absorbable and non-absorbable. Configuration of mesh varies. Fixation methods include staples, sutures or glue.[151]

· **Patches**, specifically Central Nervous System (CNS) patches are impermeable adhesive membranes used in intradural neurosurgical procedures, as an alternative to using autologous grafts or cadaveric implants.

· **Tissue Adhesives**, such as Fibrin glue and cyanoacrylate adhesives, are used to control bleeding and as a sealant for closure, for example, of colostomies; in combination with, or as an alternative to, sutures in wound closure. Tissue adhesives can act as a barrier to microbial penetration as long as the adhesive film remains intact. They can also be used to fix mesh, patches and scaffolding in place.

· **Biocompatible coated materials** include devices coated with silver, titanium dioxide, hydroxyapatite, paclitaxel and many other components. Any of the supportive devices can include biocompatible coated materials.

Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data and/or a comprehensive literature review and/or post-market data (clinical experience) on the device (direct) and/or the predicate or similar marketed 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 predicate or similar marketed device may be used after substantial equivalence has been demonstrated through a comparison of the clinical,

[151] Furnee E, Hazebroek E. Mesh in laparoscopic large hiatal hernia repair: a systematic review of the literature. Surgical Endoscopy. 2013;27:3998–4008.

technical and biological characteristics as described in ***Chapter5. Demonstrating substantial equivalence.***

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. Sponsors should refer to ***Chapter 3. Clinical Evidence*** 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. Sponsors are advised to justify the patient number 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. 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 predicate/similar marketed device when used for its intended purpose.

The literature search protocol should be determined prior to implementing the search, detailing the aim, search terms, planned steps and inclusion and exclusion criteria. 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. The overall body of evidence from the literature should be compiled and critiqued 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 repeated.

Post-market data

Post-market data can be provided for the actual device or for the predicate or similar marketed device.

It is particularly important to include the following:

- information about the regulatory status of the device(s) (or predicate or similar marketed 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 any conditions in other jurisdictions
- any regulatory action including CE mark withdrawals, suspensions, removals, cancellations, or voluntary recalls (and the reason for these i.e. IFU changes) anywhere in the world in addition complaint and adverse event data as reported to or required by regulatory bodies

- worldwide yearly distribution numbers[152] of the device(s) since launch
- the number of years of use
- for every year since launch, the number of adverse events 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

Publicly available post-market data such as adverse event reporting on the FDA Manufacturer and User Facility Device Experience (MAUDE) database and the TGA Incident Reporting and Investigation Scheme (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 analysed and critiqued by an appropriately qualified clinical expert to enable an understanding of the safety and performance profile of the device(s) in a 'real-world' setting.

Supportive data and information

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

- the full technical specification 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
- 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.
- risk assessment and management document
- IFU and all other documents supplied with the device which form a key part of the risk reduction plan for known clinical risks. The clinical evidence must highlight these risks and they must be appropriately communicated to user.

[152] Providing yearly figures allows the estimation of cumulative percent incidence, or incidence as a fraction of observation years. It is good practise for manufacturers to perform these calculations for themselves on a regular basis. For implants such as surgical meshes, Kaplan - Meier analysis is preferred. This sort of analysis is often performed with revision surgery (i.e. % requiring revision at 1, 2, 3, etc. years from the time of primary surgery as an end point), but it can also be performed on many other endpoints.

Defining clinical success

Meshes

Surgical mesh is a loosely woven sheet which is used in surgery as either permanent or temporary support for organs or other tissues. The meshes can be made from both inorganic and biological materials, and are used for a variety of indications. Hernia repair surgery is the most common application, also reconstructive surgery for pelvic organ prolapse (POP) and stress urinary incontinence (SUI).[153]

Permanent (non-absorbable) meshes remain in the body, whereas absorbable meshes (short-term and long-term) are designed to be cleared from the body within a given time through a documented excretion pathway. There are also semi-dissolvable devices.[154] Some devices combine permanent and absorbable meshes (combination devices).

Commercial meshes are typically made of polypropylene, expanded polytetrafluoroethylene (ePTFE) or polyester in combination with materials such as titanium. Biologic meshes can consist of collagen matrix and absorbable meshes can consist of a synthetic material such as Vicryl (polyglactin 910).[155] Meshes can be used for either a primary or secondary repair and it is imperative that the clinical evidence reflects the indication for use of the mesh under review.

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.

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, extrusion and exposure. A summary of the safety data extracted from systematic reviews is provided in ***Appendix 11: Supportive devices,*** Table 24. Clinical experts have reported additional complications associated with the use of surgical mesh for POP and SIU which include inflammation, seroma, haematoma, infection, fistula, mesh extrusion, urinary tract infection, bowel dysfunction, nerve injury, chronic pain and de novo or worsening prolapse in a non-treated compartment.

The sponsor should report all post-surgical complications and serious adverse events or failure that have been found with the use of the mesh or predicate/similar marketed devices 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 was identified:

- Austrian Urogynecology Working Group registry for transvaginal mesh devices for POP repair[156]

[153] Food and Drug Administration. Surgical Mesh: FDA Safety Communication. 2012 [cited; Available from: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm142636.htmz>

[154] Dwyer P. Evolution of biological and synthetic grafts in reconstructive pelvic surgery. International Urogynecological Journal. 2006;17:S10-S5

[155] Brown CN, Finch JG. Which mesh for hernia repair? Annals of The Royal College of Surgeons of England. 2010;92(4):272-8

[156] Bjelic-Radisic V, Aigmueller T, Preyer O et al. Vaginal prolapse surgery with transvaginal mesh: results of the Austrian registry. International Urogynecology Journal. 2014;25(8):1047-52

In addition two registers for surgeries that involve meshes were identified:

- Swedish hernia register[157]
- Herniamed, a German internet-based registry for outcome research in hernia surgery[158]

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.[159] [160] However, sponsors should be aware that late adverse events of a device can occur 5 or more 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, function scores, quality of life scores and pain. For absorbable devices, clearance and metabolism times are also provided in ***Appendix 11: Supportive devices***Appendix 11: Supportive devices, 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.[161] Thus, rates within this range are considered acceptable. A satisfactory result of biologic mesh application is a recurrence rate of 18% or below and seroma formation of 12% or less.[162]

The rates of reoperation vary based on the indication, patient characteristics and surgical procedure undertaken. Importantly, patient follow-up periods must be comparable to accurately compare recurrence rates as a function of supportive devices.[161]

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

[157] Nilsson EK, Haapaniemi S. The Swedish hernia register: an eight year experience. Hernia. 2000;4:286-9
[158] Stechemesser B, Jacob DA, Schug-Pass C, Kockerling F. Herniamed: an internet-based registry for outcome research in hernia surgery. Hernia. 2012;16(3):269-76
[159] Jia X, Glazener C, Mowatt G et al. Systematic review of the efficacy and safety of using mesh in surgery for uterine or vaginal vault prolapse. Int Urogynecol J. 2010;21(11):1413-31
[160] Aslani N, Brown CJ. Does mesh offer an advantage over tissue in the open repair of umbilical hernias? A systematic review and meta-analysis. Hernia. 2010;14:455-62
[161] Hobart WH. Clinical Outcomes of Biologic Mesh. Surgical Clinical of North America. 2013;93(5):1217-25
[162] Bellows CF, Smith A, Malsbury J, Helton WS. Repair of incisional hernias with biological prosthesis: a systematic review of current evidence. American Journal of Surgery. 2013;205(1):85-101.

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.[163] The VHWG grading system is used to predict surgical site occurrences (SSO) not as measures of outcome.

Where validated measurement tools are not used, sponsors 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[164]
- For hiatal hernia, radiological or endoscopic absence of a recurrent hernia (defined as >2cm in size)[165]
- 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

Sponsors should, where possible, use validated measurement tools. When selecting and reporting surrogate markers of performance sponsors 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. [166] 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

[163] Bump RC, Mattiasson A, Bø K et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. American Journal of Obstetrics and Gynecology. 1996;175(1):10-7
[164] Lamb ADG, Robson AJ, Nixon SJ. Recurrence after totally extra-peritoneal laparoscopic repair: implications for operative technique and surgical training. Surgeon. 2006;4(5)
[165] Furnee E, Hazebroek E. Mesh in laparoscopic large hiatal hernia repair: a systematic review of the literature. Surgical Endoscopy. 2013;27:3998–4008
[166] Salamon CG, Culligan PJ. Subjective and objective outcomes one year after robotic-assisted laparoscopic sacrocolpopexy. Journal of Robotic Surgery. 2012;7(1):35-8

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.[167] [168]

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, see ***Appendix 11: Supportive devices***, Table 24. The sponsor should report all of the above and any other serious post-surgical events for the patch or predicate/similar marketed 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, sponsors 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. Sponsors 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 ***Appendix 11: Supportive devices,*** Table 25.

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. fluid leakage) 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. Sponsors 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

Tissue adhesives, an alternative to sutures and staples, are used for closure of wounds and fixation of devices such as surgical mesh, patches and scaffolding to the body tissue. 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. Fibrin sealants are the most commonly used adhesives. Other adhesives include cyanoacrylates, albumin-based compounds, collagen-based compounds, glutaraldehyde glues and hydrogels.[169]

Safety

Chronic pain, infection, inflammation, tissue damage, bleeding and leakage of bile and other fluids are primary outcome measures for tissue adhesive surgeries, see ***Appendix 11: Supportive devices,*** Table 24. Chronic pain can be measured with Visual Analogue Score (VAS) as mild, moderate or severe persisting from 3 months to 1 year. [170] Secondary outcomes

[167] Ferroli P, Acerbi F, Broggi M et al. A novel impermeable adhesive membrane to reinforce dural closure: a preliminary retrospective study on 119 consecutive high-risk patients. World Neurosurgery. 2013;79(3-4):551-7

[168] von der Brelie C, Soehle M, Clusmann HR. Intraoperative sealing of dura mater defects with a novel, synthetic, self adhesive patch: application experience in 25 patients. British Journal of Neurosurgery. 2012;26(2):231-5.

[169] Reece TB, Maxey TS, Kron IL. A prospectus on tissue adhesives. The American Journal of Surgery. 2001;182(2, Supplement 1):40S-4S.

[170] Kaul A, Hutfless S, Le H et al. Staple versus fibrin glue fixation in laparoscopic total extraperitoneal repair of inguinal hernia: a systematic review and meta-analysis. Surgical Endoscopy. 2012;26:1269–78.

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 sponsor should report any post-surgical complications and failure of the adhesive or predicate/similar marketed 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.[171] Another study found a recurrence rate of 2.3% at 15 months.[172] Thus a recurrence rate <2.3% in 15-17 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 function of supportive devices. [173] Sponsor-nominated recurrence rates need to have a rigorous clinical justification provided by a clinician expert with experience in the use of the device who considers the current research at the time of preparing, reviewing or updating the CER.

Performance

Recurrence is one performance related parameter reported in the peer reviewed literature for tissue adhesives, ***Appendix 11: Supportive devices,*** Table 25.

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 sponsor 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 sponsors provide data with a minimum of 15-17 months follow-up post-surgery. This is based on current literature.

As assessment tools of device performance may not be available, sponsors can assist the clinical assessors by providing data on direct markers. This may be the clinical evidence provided for tissue adhesives. The choice of surrogate markers and the validation of these to predict future device complications or failure should be clinically justified.

Examples of direct markers for performance of adhesives are:

achievement of homeostasis/ increased number of patients reaching homeostasis – measured as no evidence of bleeding from exposed surfaces[174]

· presence of haematoma/ seroma during study, visual perception of oedema 1-7 days post-operatively

[171] Topart P, Vandenbroucke F, Lozac'h P. Tisseel vs tack staples as mesh fixation in totally extraperitoneal laparoscopic repair of groin hernias. Surgical Endoscopy. 2005;19:724-7.
[172] Schwab R, Willms A, Kröger A, Becker HP. Less chronic pain following mesh fixation using a fibrin sealant in TEP inguinal hernia repair. Hernia. 2006;10(3):272-7.
[173] Hobart WH. Clinical Outcomes of Biologic Mesh. Surgical Clinical of North America. 2013;93(5):1217-25.
[174] Sanjay P, Watt DG, Wigmore SJ. Systematic review and meta-analysis of haemostatic and biliostatic efficacy of fibrin sealants in elective liver surgery. Journal of Gastrointestinal Surgery. 2013;17(4):829-36

- 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[175]
- reduction in drainage volume [175]
- 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 [174]

Sponsors should, where possible, use validated measurement tools. If selecting and reporting surrogate markers of performance sponsors should provide a clinical justification for the selection.

Compiling clinical evidence

Appendix 2: Constructing the clinical evaluation report outlines the components that may comprise clinical evidence for a medical device, and the process to compile a clinical evaluation report, whether the applicant is using direct clinical evidence or relying on indirect clinical devices for a predicate or similar marketed device.

The following headings in the clinical evaluation report are recommended:

1. Device Description, lineage and version if applicable
2. Intended Purpose, indications and claims
3. Regulatory Status in other countries
4. Summary of any relevant pre-clinical data
5. Demonstration of substantial equivalence (if applicable)
6. Overview of clinical data
7. Critical evaluation of clinical data
8. Critical evaluation of post-market data (clinical experience)
9. Risk analysis and risk management
10. Instructions for use, labelling and other documents provided with the device
11. Risk-benefit analysis
12. Conclusions
13. Name, signature and *curriculum vitae* (CV) of clinical expert and date of report

Supporting documents

Recommended supporting documents in addition to the clinical evaluation report include, but are not limited to:

[175] Therapeutic Goods Administration. AusPAR: Fibrin adhesive/sealant. Australian Public Assessment Report 2014 [cited 29 Oct 2014]; Available from: <https://www.tga.gov.au/auspar/auspar-fibrin-adhesivesealant>

1. Preclinical data
2. Full clinical investigation(s) reports
3. Literature search and selection strategy
4. Full text articles from literature review
5. Full technical and physical specifications of device. 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.
6. Risk analysis and management documents
7. Post-market data

If the predicate or similar marketed device is approved for use in another jurisdiction, the sponsor should provide regulatory status, including the certificate number, date of issue and name under which the device is marketed, specific indications for use including MR status in key jurisdictions e.g. EU, US and Canada, IFU used in other jurisdictions as well as complaint and adverse event data and recall, suspension, cancellation, removal and withdrawal actions, whether for removal of specific indications or of the device itself.

Demonstrating the safety of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment

Addressed in this section are the clinical and pre-clinical evidence requirements to demonstrate the safety and performance of IMDs in the 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)
  - implantable permanent pacemakers (PPM)
  - implantable cardioverter defibrillators (ICD)
  - cardiac resynchronisation therapy (CRT) devices
  - implantable loop recorders (ILR); and
  - their 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 sponsor.

Summary recommendations

- AIMDs and some PIMDs such as 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, sponsors are advised to provide appropriate clinical and/or non-clinical evidence to support the safety 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 other supporting documents with evidence supporting any reported thresholds.
- It is strongly recommended that sponsors follow international standards for testing AIMDs and PIMDs in the MR environment for safety.
- For AIMDs, sponsors are advised that the use of non-clinical data, including *in vitro* and *in vivo* (animal) studies and simulation/modelling, is a valuable addition to premarket applications for conformity assessment and application audit; however, non-clinical data alone do not meet the requirements for EP14. It is essential that any non-clinical data presented are also supported by clinical data. Non-clinical data may be used to support the clinical evidence only when the non-clinical data is linked to the clinical data generated for

the actual device or for a predicate device that has been demonstrated to be substantially equivalent.

- For PIMDs, the use of non-clinical data alone suffices to meet the requirements for the applicable EPs. Clinical data are not required.
- For submissions reliant on predicate, or similar marketed device data, sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between a device and the nominated predicate(s) or similar marketed device(s).
- A well-documented and actionable risk analysis and quality management system should also be provided with the clinical evaluation report (CER).
- For AIMDs, sponsors 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 sponsor seeks TGA approval and will inform the instructions for use documentation.
- Provision of clinical data for AIMDs:
  - sponsors who intend to conduct a clinical trial should design trials to the highest practical NHMRC Level of Evidence.[176] Trials 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 Appendix 12: Safety of active implantable medical devices in the MR environment.
  - when submitting a comprehensive literature review, full details of the methodology used should be included in the CER and described to a standard whereby the review process can be repeated.
  - for guidance on the presentation of clinical evidence and conduct of comprehensive literature reviews sponsors are directed to relevant chapters.
- Compilation of the CER for AIMDs:
  - in compiling the clinical evidence for an AIMD the sponsor should ensure that a clinician who is an expert in the field and skilled in the use of the device conducts a synthesis and critique of all the available clinical data and additional information that informs the safety and performance of the device in regard to MR conditional use.
  - the appropriately qualified clinical expert must review and endorse a CER that includes an evaluation as to whether the clinical evidence is sufficient to demonstrate the requirements of the applicable Essential Principles are met and the device is safe when used as intended in the MR environment.
  - a full *curriculum vitae* of the clinical expert should be included in the CER.

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*".[177] In this context, the term "MR

[176] <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2700132/?report=classic>
[177] ASTM F2503-13, Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment, ASTM International, West Conshohocken, PA, 2013

environment" refers to the physical space surrounding a MR magnet, which is affected by the static, gradient and radiofrequency (RF) electromagnetic fields.[177] [178] 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 the MR environment.[177] 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 that poses no known hazards resulting from exposure to the MR environment within specified conditions of use.[177] 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). [179]
- **MR unsafe:** An item that poses unacceptable risks to patients, medical staff or other persons in the MR environment.[177] Magnetic items, or items composed of ferrous metals, are considered to be MR unsafe under all conditions.

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.[179]

[178] Shellock FG, Woods TO, Crues JV, 3rd. MR labeling information for implants and devices: explanation of terminology. Radiology. 2009;253(1):26-30

[179] Gold MR, Kanal E, Schwitter J, Sommer T, Yoon H, Ellingson M, et al. Preclinical evaluation of implantable cardioverter-defibrillator developed for magnetic resonance imaging use. Heart Rhythm. 2014

Requirements for clinical and/or non-clinical evidence

Clinical and non-clinical 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. 'MR conditional' AIMD systems may meet the applicable EPs where there is sufficient clinical and non-clinical evidence, whilst for 'MR conditional' PIMD systems, the requirements may be satisfied with non-clinical data alone. In any case, the clinical and/or non-clinical data should be accompanied by appropriate warnings and specified conditions of use, outlined in the instructions for use (IFU) and other easily accessible documents.
- AIMD systems with inadequate clinical data in the MR environment, or non-clinical data that cannot be linked to adequate clinical data, are unlikely to satisfy EP14 and are required to be labelled as 'MR unsafe'. Likewise, PIMD systems with inadequate non-clinical data are required to be labelled as 'MR unsafe' as well. 'MR unsafe' device systems must include adequate warnings and precautions in the IFU and other easily accessible documents regarding the risks associated with using the device system in the MR environment.

Other information that should be provided for all IMDs includes:

- the full technical specification of the device(s)
- the components to which the device is paired when used clinically, including the pulse generator and lead
- the characteristics of the MRI scanner, including the manufacturer and model number, the imaging sequence(s) used, gradient slew rate, gradient field strength, static field strength, RF field strength etc.
- the clinical context of the trial, including inclusion and exclusion criteria and how these align with MR conditional labelling of device, for example, exclusion criteria are included as contraindications or warnings/precautions to MRI in IFU and other easily accessible documents as applicable
- descriptions of clinical outcomes
- scanning exclusion zones implemented
- a risk analysis and management document and
- a critical analysis of all of the clinical data by an appropriately qualified clinical expert.

Substantial equivalence

If the sponsor does not have direct clinical and/or non-clinical evidence for the IMD system under assessment, evidence from a predicate device or similar marketed device *may* be reported under certain conditions.

Data for a predicate device (for example, earlier version of the device made by the same manufacturer) may satisfy the requirements for evidence provided the devices have been demonstrated to be substantially equivalent in relation to their intended use, design, technical

specifications, engineering, materials and biocompatibility. If the comparable device is not manufactured by the same company as the device under assessment it is unlikely to satisfy the requirements for EP14. In such instances, a manufacturer would be required to collect direct evidence for the device under assessment, upon which future devices may be demonstrated to be substantially equivalent where appropriate.

Please note that the use of the term 'substantial equivalence' in the Australian context may differ from similar terminology used by overseas regulators. For example, similar marketed IMD systems produced by a different manufacturer are unlikely to be considered equivalent for the purpose of providing relevant clinical data for MRI safety. If the manufacturer does not have a direct predicate with the required clinical and/or non-clinical data and which is equivalent to a new IMD system, then there will be an expectation that direct data gained on the new IMD system, according to the method described below, would be required to provide assurance of safety in the MRI environment. Once the MR conditional safety of an IMD has been established via direct clinical evidence, then other devices developed by this manufacturer may leverage the clinical evidence for the predicate if equivalence can be demonstrated between the two devices.

Equivalence for a MR conditional device includes all the considerations normally needed, including clinical, technical and biological characteristics. In addition the manufacturer must provide justification and/or evidence that the device would behave or function in the same way as the predicate device when exposed to an MRI environment. The applicant would need to demonstrate that MRI exposure would not affect force and torque, heating, image artefact and the overall functioning of the new system such as auto-switching to different modes, pacing/sensing thresholds and amplitudes in a different manner or to a different degree than the predicate device. The device would be expected to be for the same intended use, including same clinical condition being treated, severity and stage of disease, site of application to/in the body and the patient population as the predicate device. In regards to legacy AIMD leads, if (substantial) equivalence with respect to MRI cannot be demonstrated, clinical data must be provided. For further information on demonstrating substantial equivalence in the Australian context, please refer to ***Chapter5. Demonstrating Substantial Equivalence.***

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.[180]

- 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

[180] U.S. FDA. Establishing safety and compatibility of passive implants in the magnetic resonance (MR) environment: Guidance for industry and Food and Drug Administration staff. RockvilleMD2014 [updated 2014]. Available from: <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm107708.pdf>

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).

Requirements for AIMDs

Non-clinical data (including modelling data)

- The non-clinical data should include adequate *in vitro* and *in vivo* (animal) data, and may include modelling or simulations in the MR environment.[179] [181] Compliance with relevant technical standards is expected where such standards exist.
- Simulations or modelled data may support the clinical data but are not considered to provide clinical evidence sufficient to demonstrate clinical safety on their own to satisfy EP 14 without clinical validation. Modelling data can be used to support the clinical evidence only if the specific modelling approach has been validated clinically.
- If validated clinically, the modelling data generated can then be used to demonstrate safety and performance to satisfy EP 14 for equivalent devices only within the same family or system (both leads and generator) produced by the same manufacturer.
- Modelling data may be accepted when assessing an increase in the strength of the magnetic field, e.g. from 1.5 to 3 Tesla or to move from restricted body scanning to whole body scanning with no change in the device. The modelling data must be derived from the same validated model.
- In regards to novel devices or any substantial changes to existing systems, there is an expectation that additional clinical data would be required, including to validate any modelling data.

Clinical data

When demonstrating the safety of an AIMD in the MR environment, direct clinical evidence for the device under assessment 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

[181] Wilkoff BL, Albert T, Lazebnik M, Park S-M, Edmonson J, Herberg B, et al. Safe magnetic resonance imaging scanning of patients with cardiac rhythm devices: A role for computer modeling. Heart Rhythm. 2013;10(12):1815-21.

to clarify the exact version of the device. It must be demonstrated that the quantity, quality and results of the clinical data presented are sufficient to support a 'MR conditional' claim.

If the sponsor does not have direct clinical evidence for the AIMD system under assessment, clinical evidence from a predicate device or similar marketed device *may* be reported under certain conditions.

For devices that are not reliant on predicate or similar marketed device data, the strong preference is for the sponsor to present clinical evidence from a clinical trial(s). Sponsors should aim for the highest achievable NHMRC Level of evidence when designing a clinical trial(s) to determine the safety and performance of a device.[182] The choice of study design should be sufficient to generate valid measures of clinically relevant outcomes. All trials should be conducted with demonstrable scientific rigour.

When presenting the clinical evidence, it is recommended that a full clinical study report documenting the conduct of the trial and presentation of clinical outcomes is included in the submission. Ideally, trial conditions should represent clinical practice in Australia. The submission should include an interpretation and analysis of the clinical data by an appropriately qualified clinical expert.

Compiling clinical evidence

Previous chapters and appendices outline the components that may comprise clinical evidence for a medical device, and the process to compile a clinical evaluation report, whether the applicant is using direct clinical evidence or replying on indirect clinical devices for a predicate or similar marketed device.

If the predicate or similar marketed device is approved for use in another jurisdiction, the sponsor should provide regulatory status, including the certificate number, date of issue and name under which the device is marketed, specific indications for use including MR status in key jurisdictions e.g. EU, US and Canada, IFU use in other jurisdictions as well as complaint and adverse event data and any recalls, suspensions, removals, cancellations and withdrawals in any jurisdiction, whether for withdrawal of specific indications or of the device itself.

Defining clinical safety for AIMDs[183]

Relevant clinical evidence is expected to investigate the exposure of AIMDs, or a suitable predicate device, to MR fields. The clinical evaluation report submitted for market authorisation and monitoring and compliance reviews should provide both non-clinical and clinical evidence.

Non-clinical evidence

For guidance on non-clinical evidence it is recommended that sponsors submitting an AIMD with an 'MR conditional' claim refer to ISO/TS 10974:2012 'Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device'.[184] The standard

[182] NHMRC. NHMRC levels of evidence and grades for recommendation for developers of guidelines [Internet]. Canberra2009 [updated 2009; cited 2013 07/02]. Available from: <http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/stage_2_consultation_levels_and_grades.pdf>

[183] Clinical studies published in the peer-reviewed literature were used to identify appropriate clinical safety outcomes for the use of AIMDs in the MR environment. This evidence base was determined using a modified rapid review method as described in ***Appendix 12: Safety of active implantable medical devices in the MR environment***. Additional detail on the evidence base identified in the preparation of this guidance document is contained in the same appendix under Selection of included studies. General guidance on appropriate test parameters that may be used to demonstrate the performance and safety of AIMDs (i.e. not solely MR safety) is provided in the same appendix under Conduct and reporting of clinical studies.

[184] ISO/TS 10974:2012, Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device, International Organization for Standardization, 2012.

describes specific methods for testing safety of active medical devices in the MR environment, in the non-clinical setting, in relation to:

- static-field-induced force
- static-field-induced torque
- image artefact
- RF-induced heating
- Gradient-induced heating
- Gradient-induced vibration
- Gradient-induced extrinsic electric potential
- RF rectification
- Static-field-induced malfunction
- RF-induced malfunction
- Gradient-induced malfunction
- Combined field tests

Other relevant standards for non-clinical testing include, but are not limited to:

- ASTM F2052-14, Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment[185]
- ASTM F2213-06 (Reapproved 2011), Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment[186]
- ASTM F2182-09, Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging[187]
- ASTM F2119-07, (Reapproved 2013) Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants[188]

Adhering to the test methods outlined in an international standard is not compulsory, but will increase the likelihood that the evidence presented will satisfy the requirements for EP14. Any outcomes reported from either clinical or non-clinical data must be justified.

[185] American Society for Testing and Materials International. Designation: ASTM F2052-14, standard test method for measurement of magnetically induced displacement force on medical devices in the magnetic resonance environment. West Conshohocken, Pa: American Society for Testing and Materials International, 2014.
[186] American Society for Testing and Materials International. Designation: ASTM F2213-06 (Reapproved 2011), standard test method for measurement of magnetically induced torque on medical devices in the magnetic resonance environment. West Conshohocken, Pa: American Society for Testing and Materials International, 2011.
[187] American Society for Testing and Materials International. Designation: ASTM F2182-09, standard test method for measurement of radio frequency induced heating near passive implants during magnetic resonance imaging. West Conshohocken, Pa: American Society for Testing and Materials International, 2009.
[188] American Society for Testing and Materials International. Designation: ASTM F2119-07 (Reapproved 2013), standard test method for evaluation of MR image artifacts from passive implants. West Conshohocken, Pa: American Society for Testing and Materials International, 2013.

Chosen thresholds in relation to the conditions for use should be clinically justified, and the method of testing by which these allowable limits were determined should also be stated and included in the pre-clinical evidence.

Examples of different types of non-clinical investigations for demonstrating device safety in relation to the potential hazards of the MR environment are outlined in Table 4.[179] Outcomes that have been assessed in pre-clinical, peer-reviewed literature include: [179] [181]

- Changes in pacing capture threshold (PCT)
- Effects of multiple MR exposures on PCT
- Changes in ventricular fibrillation (VF) detection time
- Effects of multiple MR exposures on VF detection
- Defibrillation coil heating
- MR-induced pulse stimulation thresholds
- Unintended cardiac stimulation

Table 4. Non-clinical methods for evaluating potential hazards in the MR environment

MR hazard	Bench/scanner testing	Model simulation	Animal studies
Force and torque	Ÿ		
Vibration	Ÿ		
Device interactions	Ÿ	Ÿ	
Device case heating	Ÿ	Ÿ	
Unintended cardiac stimulation	Ÿ	Ÿ	Ÿ
Lead electrode heating	Ÿ	Ÿ	Ÿ

MR = magnetic resonance. Table source: Gold et al 2014. [179]

The use of simulation or modelled data allows investigators to evaluate a wide range of potential scenarios beyond the scope of a clinical trial. [179] [181] For this reason, simulation and modelling data are likely to play an increasingly important role in demonstrating the safety of AIMDs in the MR environment.[189] These scenarios account for variable factors that may affect the safety of AIMDs in the MR environment, [179] including:

- lead length
- lead design
- lead path

[189] Gimbel JR. Computer modeling and MRI-device safety: modeling, myths, and magical thinking. Heart Rhythm. 2013;10(12):1822-3.

- scanner type
- field strength
- position within the bore
- imaging sequence
- patient anatomy and physiology

While simulation data may provide valuable evidence to support a premarket application for an AIMD, this type of evidence alone will not satisfy EP14 and should be accompanied by relevant clinical data. The TGA expects all non-clinical data presented in premarket applications to be linked to evidence from the clinical setting.

Clinical evidence

Clinical investigations are aimed at validation of non-clinical testing results in a study population representative of the Australian patient population targeted by the proposed indications for use (although the study does not have to be conducted within Australia), including subjects with co-morbidities that may affect clinical outcomes but that may not have been fully accounted for by the non-clinical testing, and other individual variations.

Existing review articles investigating the safety of AIMDs in the MR environment have identified over 40 primary studies in the peer-reviewed literature.[190] [191] [192] [193] [194] [195] [196] [197] The vast majority of available clinical evidence is low-level, single-arm case series investigations, however a minority of case-control and RCT level evidence exists. [190] [191] [192] [193] [194] [195] [196] [197]

Clinical investigations aimed at demonstrating the safety of an AIMD in the MR environment should aim to detect all potential hazards related to the static, gradient and radiofrequency fields, including:

- Force and torque
- Movement or dislodgement of devices
- Vibration
- Device interactions
- Device case heating
- Unintended cardiac stimulation

[190] Ahmed FZ, Morris GM, Allen S, Khattar R, Mamas M, Zaidi A. Not all pacemakers are created equal: MRI conditional pacemaker and lead technology. J Cardiovasc Electrophysiol. 2013;24(9):1059-65
[191] Ainslie M, Miller C, Brown B, Schmitt M. Cardiac MRI of patients with implanted electrical cardiac devices. Heart. 2014;100(5):363-9
[192] Beinart R, Nazarian S. Effects of external electrical and magnetic fields on pacemakers and defibrillators: from engineering principles to clinical practice. Circulation. 2013;128(25):2799-809
[193] Chow GV, Nazarian S. MRI for patients with cardiac implantable electrical devices. Cardiol Clin. 2014;32(2):299-304
[194] Ferreira AM, Costa F, Tralhao A, Marques H, Cardim N, Adragao P. MRIi-conditional pacemakers: Current perspectives. Medical Devices: Evidence and Research. 2014;7(1):115-24
[195] Nazarian S, Beinart R, Halperin HR. Magnetic resonance imaging and implantable devices. Circ Arrhythm Electrophysiol. 2013;6(2):419-28
[196] Shinbane JS, Colletti PM, Shellock FG. Magnetic resonance imaging in patients with cardiac pacemakers: era of "MR Conditional" designs. J Cardiovasc Magn Reson. 2011;13:63
[197] van der Graaf AWM, Bhagirath P, Gotte MJW. MRI and cardiac implantable electronic devices; current status and required safety conditions. Neth Heart J. 2014;22(6):269-76

- Lead electrode heating
- Image artifacts

A comprehensive list of relevant clinical outcomes and surrogate outcomes investigated in peer-reviewed literature are presented in ***Appendix 12: Safety of active implantable medical devices in the MR environment***. Outcome data that is presented in support of an 'MR conditional' claim must be justified, with justification also for the chosen threshold value upon which safety is benchmarked. Although AIMDs are broadly composed of the same design elements, they are sufficiently different in design and function that clinical evidence from one subtype of device, e.g. a PPM, cannot be used to substantiate the safety of a different device, e.g. an ICD.[179]

It is important to note details of all adverse events that occur during or after the MRI scan, including but not limited to serious adverse events and adverse events adjudicated to be likely related to the implanted device and the MRI scan.

It is also important to note the limitations in clinical trial data at detecting an adverse event, given the range of factors that affect device interactions within the MR environment. These include, implant placement, lead design, lead length, patient weight, patient position within bore, etc. The use of pre-clinical modelling data may be a useful supplement to *in vivo* clinical trial data, but does not meet the requirements to satisfy EP14 on its own.

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

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. This includes post-market experience for AIMDs and predicate or similar marketed devices (where applicable). If such information is available sponsors should provide:

- information about the regulatory status of the device(s), including the certificate number, date of issue, name under which the device is marketed, exact wording of the intended purpose including any specific conditions such as MR status in key jurisdictions, for example the US, EU, Japan and Canada, and the device combinations and MR conditions approved for MR conditional use
- worldwide distribution numbers of the device(s) for every year since launch
- the number of years of use
- the number of complaints and adverse events 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, for every year since launch
- the number of product recalls, suspensions, removals, cancellations and withdrawals, whether withdrawals of indications and/or devices, amendments to the IFU or other key documents such as product manuals
- the post-market surveillance data from national jurisdictions where the device is approved for clinical use
- discussion and critique of the clinical data by an appropriately qualified clinical expert, to enable an understanding of the safety of the device(s) in a 'real-world' setting. This should

include an analysis of any known complications of the MRI environment on the device, for example, device migration, electrical dysfunction, heating etc.

The MagnaSafe Registry specifically collects data on the risks of non-thoracic 1.5T MRI scanning in the presence of pacemakers and implantable cardioverter defibrillators, although the MR conditions specified in the registry study protocol may not coincide with the sponsor's intended MR conditions (for example, the specific combinations of leads and devices and enforcement of exclusion zones). Other existing registries for implantable medical devices are often designed to collect procedure-related adverse events and device failures, and may not accurately capture adverse events caused by interactions between AIMDs and the MR environment. Registry data have been reported in peer-reviewed studies from Spain,[198] Denmark,[199] Sweden,[200] France,[201] [202] Italy,[203] China,[204] Germany,[205] Poland,[206] the United States,[207] and Australia.[208] In lieu of available registry data, product experience from manufacturers is valuable data to support premarket applications.

Regardless of whether post-market data is available at the time of submission, sponsors and manufacturers must ensure that clinical evidence of MR conditional status is maintained post-approval. Clinical evidence is a key component of ensuring ongoing compliance with the EPs in the post-market space. Sponsors and manufacturers must demonstrate clear links between the analysis of new data (such as up to date clinical evidence, published literature, clinical trial data and post-market reports) informing changes to the risk assessment/risk management documentation including modelling approaches and assumptions and/or simulation data, leading to timely and targeted updates to risk reduction activities such as the IFU and other documentation. Where new risks are able to be identified, analysed and appropriately managed through risk reduction activities, the TGA can have confidence in the ongoing positive benefit/risk ratio of the device while on the market.

[198] Coma Samartin R, Cano Perez O, Pombo Jimenez M. Spanish Pacemaker Registry. Eleventh official report of the Spanish Society of Cardiology Working Group on Cardiac Pacing (2013). Rev Esp Cardiol (Engl Ed). 2014;67(12):1024-38

[199] Moller M, Arnsbo P. [The Danish Pacemaker Registry. A database for quality assurance]. Ugeskr Laeger. 1996;158(23):3311-5

[200] Gadler F, Valzania C, Linde C. Current use of implantable electrical devices in Sweden: data from the Swedish pacemaker and implantable cardioverter-defibrillator registry. Europace. 2015;17(1):69-77

[201] Mouillet G, Lellouche N, Yamamoto M, Oguri A, Dubois-Rande JL, Van Belle E, et al. Outcomes following pacemaker implantation after transcatheter aortic valve implantation with CoreValve devices: Results from the FRANCE 2 Registry. Catheter Cardiovasc Interv. 2015

[202] Benkemoun H, Sacrez J, Lagrange P, Amiel A, Prakash A, Himmrich E, et al. Optimizing pacemaker longevity with pacing mode and settings programming: results from a pacemaker multicenter registry. Pacing Clin Electrophysiol. 2012;35(4):403-8

[203] Proclemer A, Zecchin M, D'Onofrio A, Botto GL, Rebellato L, Ghidina M, et al. [The pacemaker and implantable cardioverter-defibrillator registry of the Italian Association Arrhythmology Cardiac Pacing and cardiac pacing - annual report 2013]. G Ital Cardiol (Rome). 2014;15(11):638-50

[204] Chen KP, Dai Y, Hua W, Yang JF, Li K, Liang ZG, et al. Reduction of atrial fibrillation in remotely monitored pacemaker patients: results from a Chinese multicentre registry. Chin Med J (Engl). 2013;126(22):4216-21

[205] Markewitz A. [Annual Report 2009 of the German Cardiac Pacemaker Registry: Federal Section pacemaker and AQUA - Institute for Applied Quality Improvement and Research in Health Ltd]. Herzschrittmacherther Elektrophysiol. 2011;22(4):259-80

[206] Przybylski A, Derejko P, Kwasniewski W, Urbanczyk-Swic D, Zakrzewska J, Orszulak W, et al. Bleeding complications after pacemaker or cardioverter-defibrillator implantation in patients receiving dual antiplatelet therapy: Results of a prospective, two-centre registry. Neth Heart J. 2010;18(5):230-5

[207] Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation. 2010;122(16):1553-61

[208] Reid CM, Brennan AL, Dinh DT, Billah B, Costolloe CB, Shardey GC, et al. Measuring safety and quality to improve clinical outcomes--current activities and future directions for the Australian Cardiac Procedures Registry. Med J Aust. 2010;193(8 Suppl):S107-10

Labelling and Instructions For Use (IFU) of devices used in the MR environment

Labelling

All devices that might be used in the MR environment should be assigned a label of 'MR safe', 'MR unsafe' or 'MR conditional', as demonstrated by appropriate clinical evidence. Detailed recommendations for labelling devices that might be used in the MR environment are outlined in ASTM Standard F2503–13. Examples of labelling graphics to be used on devices intended for use in the MR environment are shown in Figure 3.[177]

Figure 2. Labelling of medical devices intended to be used in the MR environment[177]

In certain circumstances, for devices that have historically not provided any information about MRI safety, the following labelling may be used to indicate that safety in MRI has not been evaluated. Manufacturers/Sponsors should provide a rationale as to why this labelling is appropriate for the device.

> The <*device name*> has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating, migration, or image artefact in the MR environment. The safety of <*device name*> in the MR environment is unknown. Scanning a patient who has this device may result in patient injury.

The above labelling option is NOT appropriate if:

- there are any known adverse effects or adverse events due to exposure to the MR environment for the device or device type, or
- the device or device type has typically been labelled as MR Conditional or MR Unsafe (for example, including but not limited to cardiovascular stents, intracranial aneurysm clips, endovascular grafts, and trans-prostatic tissue retractors), or
- this is a new device type, or
- the device contains ferromagnetic materials.

If sponsors/manufacturers are uncertain whether a device can be labelled "Safety in MRI Not Evaluated", it is recommended that manufacturers/sponsors submit a pre-submission meeting request to obtain feedback prior to a regulatory submission.

Instructions For Use

Devices labelled as 'MR conditional' have been demonstrated to pose no known hazards in the MR environment under specific conditions. Such a device should be accompanied by an IFU that outlines the conditions upon which the device is deemed to be safe when used in the MR environment. The Royal Australian and New Zealand College of Radiologists (RANZCR) provides

generic examples of conditions for use in the RANZCR MRI safety guidelines document.[209] Further examples of device-specific conditions are outlined in the peer reviewed literature by Nazarian et al.[210]

Kanal et al provide an example of proposed changes to standardised MR terminology and reporting currently being considered by professional organisations[211], with a response provided by the U.S. FDA.[212]

The following conditions should be included in the IFU:

- Static magnetic field strength (s) for which the device is safe (in T). All possible field options shall be mentioned and/or relevant radiofrequency applied.
- Maximum spatial field gradient for which the device is safe (in T/m or gauss/cm). This information may not be required for devices which are safe in any spatial field gradient.
- Maximum whole body averaged specific absorption rate (SAR):
  <2 W/kg (Normal Operating Mode) or <4 W/kg (First Level Controlled Operating Mode)
  or
  RF incident field $B1_{rms}$ (in µT)
- Maximum slew rate (in T/m/s) or Maximum gradient field (in T/s)
- MR-induced heating information (based on ASTM F2182). Suggested wording:
  Under the scan conditions defined above, the <device name> is expected to produce a maximum temperature rise of less than <specific value>°C after x (e.g. 15) minutes of continuous scanning.
  or
  When considering the Pacing Capture Threshold (PCT) approach for pacemaker lead heating, a particular temperature may not be required to be provided.
- Lack of quality imaging (image artefact) information (based on ASTM F2119). Suggested wording:
  In non-clinical testing, the image artefacts caused by the device extends approximately <specific value> mm from the <device name> when imaged with a <gradient echo or spin echo> pulse sequence and a <specific field strength> T MRI system.
  This information may not be required if there are scan exclusion zones defined.
- Any additional instructions or information essential to safe use in the MR environment that can be described briefly. Additional instructions may include:
  - Positional requirements (e.g. device must remain outside the scanner bore, implant at iso centre, legs, etc.)
  - Restrictions on RF coil type (e.g. head transmit/receive coil only, quadrature body coil only, whole body, no transmitting local coils, receiving local coils, multi transmitting coils, etc.)
  - Scan exclusion zones

[209] RANZCR. RANZCR MRI Safety Guidelines. Sydney, Australia: Royal Australia New Zealand College of Radiologists, 2007
[210] Nazarian S, Beinart R, Halperin HR. Magnetic resonance imaging and implantable devices. Circ Arrhythm Electrophysiol. 2013;6(2):419-28
[211] Kanal E, Froelich J, Barkovich AJ et al. (2015) Standardized MR terminology and reporting of implants and devices as recommended by the American College of Radiology Subcommittee on MR Safety. Radiology 274(3):866-870. doi: 10.1148/radiol.14141645
[212] Woods TO, Delfino JG, Shein MJ. Response to *Standardized MR Terminology and Reporting of Implants and Devices as Recommended by the American College of Radiology Subcommittee on MR Safety. Radiology*. 2016; 000:1-4. doi: 10.1148/radiol.2015151108

- Patients with fevers may be at higher risk from device-related heating and other effects. Clinicians should make a clinical assessment of the benefit and risks prior to scanning patients with a fever.

Additional conditions that may be outlined in the IFU include, but are not limited to:

- MRI scanner conditions:
  - Maximum head absorption rate
  - Scan duration restrictions (including lifetime cumulative duration of scanning);
- Patient conditions:
  - Minimum patient height
- Device conditions (where applicable):
  - Range of lead impedance
  - Battery status
  - MRI mode that the device needs to be programmed into before the MRI
  - The combinations of pulse generators and leads that are submitted for approval
  - Minimum timeframe since device implantation
  - Absence of other devices or leads (e.g. abandoned leads)
  - Location of device implantation
  - Post-MRI checks of device function
- Staff and monitoring conditions:
  - Availability of resuscitation equipment nearby for emergency use.
  - Patient parameters that require continuous monitoring, e.g. blood oxygen saturation, blood pressure, ECG.

Examples of conditions for use for commercially available "MR conditional" AIMDs are presented in a narrative review by Shinbane et al.[213] Chosen thresholds in relation to the conditions for use should be clinically justified, and the method of testing by which these allowable limits were determined should also be included in the pre-clinical evidence.

Patient card

The manufacturer should provide a patient card to all patients with such implants. The content of the patient card shall at least contain the following information:

- Manufacturer
- Model number and article/serial number of all devices implanted
- MR condition per ASTM F2503-13 (symbol and/or text)[214]

[213] Shinbane JS, Colletti PM, Shellock FG. Magnetic resonance imaging in patients with cardiac pacemakers: era of "MR Conditional" designs. J Cardiovasc Magn Reson. 2011;13:63

[214] ASTM F2503-13, section 7, 'For implants, the MR marking should be included in the package labelling (including the instructions for use and package inserts) and on the patient information card'.

Appendices

Appendix 1: Glossary and abbreviations

Glossary

Adverse event: An incident in which harm resulted to a person receiving health care.

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.

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.

Clinical data: Safety and/or performance information that is generated from the use of a medical device in or on humans.[215]

Clinical evaluation: The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.[216]

Clinical evidence: The clinical data and the clinical evaluation report pertaining to a medical device.[217]

[215] The term "clinical data" is further explained in GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf>)

[216] The term "clinical evaluation" is further explained in GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf>)

Clinical expert: A clinician with appropriate qualifications who is experienced in the use of the device.

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 expert. [218]

Clinical investigation: Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.[219]

Clinical investigation data: Safety and/or performance information that are generated from the use of a medical device (based on definition above this information is generated in or on one or more human subjects).[220]

Clinical performance: The ability of a medical device to achieve its intended purpose as claimed by the manufacturer.

Clinical Safety: The absence of unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use.

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.[221]

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.

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[217] The term "clinical evidence" is further explained in GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf>)

[218] The term "clinical evaluation report" is further explained in GHTF document, *Clinical Evaluation*, SG5/N2R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-clinical> ***evaluation***)

[219] The term "clinical investigation" is further explained in GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf>)

[220] The term "clinical investigation data" is further explained in GHTF document, *Clinical Evidence - Key Definitions and Concepts*, SG5/N1R8:2007 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n1r8-clinical-evaluation-key-definitions-070501.pdf>)

[221] Adapted from GHTF document, *Principles of Conformity Assessment for Medical Devices*, SG1/N78:2012 (available at <http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n78-2012-conformity-assessment-medical-devices-121102.pdf>)

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.

Essential Principles: The Essential Principles provide the measures for safety and performance and are set out in Schedule 1[222] of the MD Regulations. For a medical device to be supplied in Australia, it must be demonstrated that the relevant Essential Principles have been met. The Essential Principles are:

- ***General principles that apply to all devices***
  - EP 1. Medical devices not to compromise health and safety
  - EP 2. Design and construction of medical devices to conform to safety principles
  - EP 3. Medical devices to be suitable for intended purpose
  - EP 4. Long term safety
  - EP 5. Medical devices not to be adversely affected by transport or storage
  - EP 6. Benefits of medical devices to outweigh any side effects
- ***Principles about design and construction that apply depending on the kind of device***
  - EP 7. Chemical, physical and biological properties
  - EP 8. Infection and microbial contamination
  - EP 9. Construction and environmental properties
  - EP 10. Medical devices with a measuring function
  - EP 11. Protection against radiation
  - EP 12. Medical devices connected to or equipped with an energy source
  - EP 13. Information to be provided with medical devices
  - EP 14. Clinical evidence
- ***Additional essential principle for IVDs only***
  - EP15. Principles applying to IVD medical devices only (this includes 7 principles relating specifically to the safety and performance of IVD medical devices).

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.[223]

[222] <http://www.comlaw.gov.au/Details/F2015C00373/Html/Text#_Toc418148401>
[223] US Food and Drug Administration . The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]: Guidance for Industry and Food and Drug Administration Staff. Federal Register. 2014:39

Intended purpose: Of a kind of medical device, means the purpose which the manufacturer of the device intends to be used, as stated in:

- the information provided with the device; or
- the instructions for use of the device; or
- any advertising material applying to the device

In-Vitro Diagnostic device (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: A manufacturer of a medical device is the person who is responsible for the design, production, packaging and labelling of the device before it is supplied under the person's name, whether or not it is the person, or another person acting on the person's behalf, who carries out those operations. Refer to section 41BG of the Act for remainder of definition.

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:
   - diagnosis, prevention, monitoring, treatment or alleviation of disease
   - diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability
   - investigation, replacement or modification of the anatomy or of a physiological process
   - control of conception
   - 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

aa. any instrument, apparatus, appliance, material or other article specified under subsection (2A)

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)

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 definition.

Medical device classifications: Medical devices are classified by the manufacturer according to the intended purpose of the medical device and the degree of risk involved for the patient and user. 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.

Medical devices (other than IVD medical devices):

Class	Risk	Examples
Class 1	Low risk	Surgical retractors, tongue depressors
Class I - supplied sterile	Low-medium risk	Sterile bandages, drainage bags
Class I - incorporating a measuring function		Hypodermic needles, suction unit
Class IIb	Medium-high risk	Lung ventilator, hip, knee and shoulder joint implants
Class III	**High risk**	Heart valves
Implantable Medical Devices)		Implantable defibrillator

IVD medical devices:

Class	Risk	Examples
Class 1 IVD	No public health risk or low personal risk	Enzyme immunoassay analyser. Ready to use microbiological culture media.
Class 2 IVD	Low public health risk or moderate personal risk	Pregnancy self-testing kit. Liver function tests.
Class 3 IVD	Moderate public health risk or high personal risk	Test to detect the presence or exposure to a sexually transmitted agent such as C. trachomatis or N. gonorrhoea. System for self-monitoring of blood glucose.

Class	Risk	Examples
Class 4 IVD	High public health risk	Assay intended for the clinical diagnosis of infection by HIV 1 & 2. Assay intended for screening blood donations for Hepatitis C virus.

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 sponsor is seeking to demonstrate substantial equivalence with that device.

Similar marketed device: An existing marketed device with a similar structure and design and the same intended purpose as the device but not a predicate of the device in relation to which a sponsor is seeking to demonstrate substantial equivalence.

Sponsor: Under Section 7 of the Act a Sponsor, in relation to therapeutic goods, means:

a. a person who exports, or arranges the exportation of, the goods from Australia; or

b. a person who imports, or arranges the importation of, the goods into Australia; or

c. a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere); but does not include a person who:

d. exports, imports or manufactures the goods; or

e. arranges the exportation, importation or manufacture of the goods on behalf of another person who, at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia.

Substantial equivalence: Substantial equivalence confirms that the new device is as good as, as safe as and performs as well as the predicate or similar marketed device. This determination is based on a review of the new device's intended purpose and technological and biological characteristics.

Technological characteristics: these relate to the design, specifications, physicochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use and may include biological characteristics relating to biocompatibility of materials in contact with body fluids and tissues."[224]

[224] GHTF document, *Clinical Evidence* SG5/N2R8:2007, page 8-9 (available at <http://www.imdrf.org/docs/ghtf/final/sg5/technical-docs/ghtf-sg5-n2r8-2007-clinical-evaluation-070501.pdf>)

Abbreviations

Abbreviation	Meaning
AAA	Abdominal aortic aneurysm
AE	Adverse event
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
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
CONSORT	Consolidated Standards of Reporting Trials
CPR	Cumulative Percent Revision
CRT	Cardiac Resynchronisation Therapy
CSR	Clinical Study Report
CTA	Computed tomography angiography
D&B	Downs & Black [quality assessment tool]
DES	Drug-eluting stent
DVT	Deep vein thrombosis

Abbreviation	Meaning
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
ISO	International Standards Organization
IVD	In vitro device
KAT	Knee Arthroplasty Trial
LOHS	Length of hospital stay
MA	Meta-analysis
MACE	Major adverse cardiac events

Abbreviation	Meaning
MAUDE	Manufacturer and User Facility Device Experience database
MCID	Minimum clinically important difference
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
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]
NICE	National Institute for Heath and Care Excellence
NOS	Newcastle-Ottawa scale [quality assessment tool]
NR	Not Reported
PAL	Pharmaceutical Affairs Law [Japan]
PCT	Pacing Capture Threshold
PDA	Patent Ductus Arteriosus
PE	Pulmonary Embolus
PMA	Pre-Market Approval [USA]
PMDA	Pharmaceuticals and Medical Devices Agency [Japan]

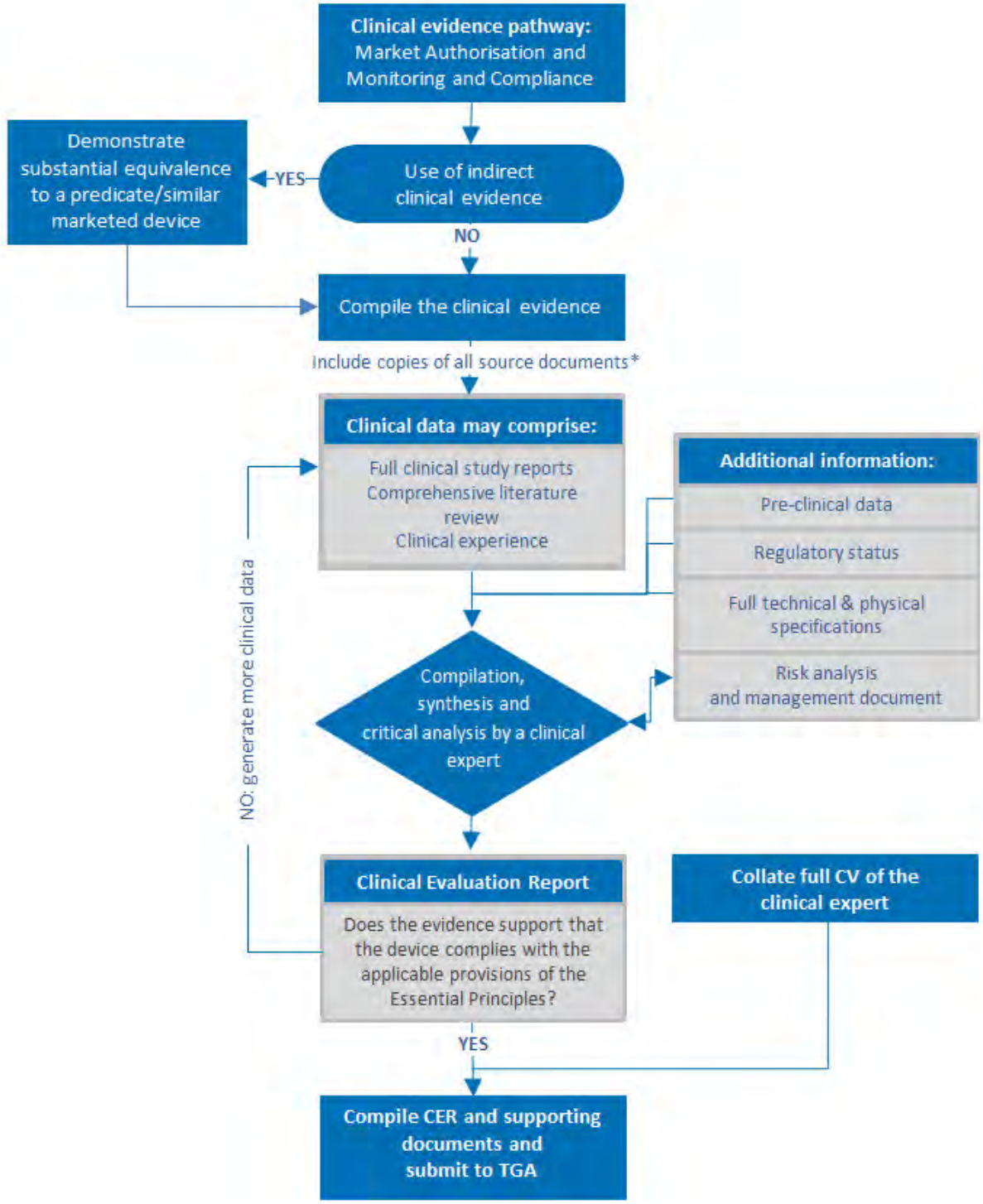
Abbreviation	Meaning
PPM	Permanent Pacemaker
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PS	Post-market Surveillance
QMS	Quality Management System
QOL	Quality Of Life
QUADAS	Quality Appraisal of Diagnostic Accuracy Studies
RANZCR	Royal Australian and New Zealand College of Radiologists
RCT	Randomized controlled trial
RF	Radiofrequency
RIND	Reversible Ischemic Neurological Deficit
RSA	Radiostereometric analysis
SAR	Specific Absorption Rate
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guidelines Network
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	Total Lesion Revascularisation
TVR	Total Vessel Revascularisation
UK	United Kingdom

Abbreviation	Meaning
USA	United States of America
VTE	Venous Thromboembolism
WHO	World Health Organisation

Appendix 2: Constructing the clinical evaluation report

The following flow-chart outlines the components that may comprise clinical evidence for a medical device, and the process to compile a clinical evaluation report.

Figure 3. Flow chart for constructing a clinical evaluation report



* Source documents for clinical data may not initially be required for an application audit clinical assessment, provided that the clinical evaluation report contains sufficient detail for the TGA assessor to appreciate how the clinical expert was able to conclude compliance with the Essential Principles.

Appendix 3: Guidelines for reporting full clinical study reports and systematic literature reviews

International guidance on reporting standards for clinical trials can be found in International Standard Order (ISO) 14155: 2011 - Clinical investigation of medical devices for human subjects – Good clinical practice.[225] 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, outlined below. ***Note***: 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)[226] 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)[227] 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)[228] 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) [229] statement. It is recommended that the PRISMA guidelines 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.

[225] <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=45557>
[226] <http://www.consort-statement.org/>
[227] <http://www.strobe-statement.org/>
[228] <http://www.stard-statement.org/>
[229] <http://www.prisma-statement.org/>

Appendix 4: Identifying relevant post-market data

Sponsors are encouraged to provide all available post-market data to support pre- and post-market reviews if possible. Post-market data may be sourced from another jurisdiction where the device is already supplied, or may include data from a predicate/similar marketed device once substantial equivalence has been demonstrated. Reporting post-market data in submissions is particularly important when there is a paucity of clinical data available, or when the data is not sufficient to establish the benefit-risk profile of the device. The clinical evaluation report should include an analysis and commentary on the profile, severity and frequency (rate) of events reported. Submissions for pre- and post-market reviews should attempt to include the following types of post-market data where possible:

Adverse events and complaints

Adverse events and complaints notifications are a source of information regarding the safety and performance of a medical device. Adverse events are required to be reported to the governing body in the country the device is in use when the event leads to or may lead to death or serious injury. Data from extractions of the Manufacturer's own internal complaint handling log should be provided where applicable. In the case of a similar marketed device from a different manufacturer, publicly available data such as that from MAUDE or IRIS should be submitted. **However, it is noted that one of the serious limitations of post-market adverse event and complaint reports is the risk of under-reporting by end-users.** More information on adverse events and complaints can be found on the TGA website.[230]

Product recalls and cancellations

Recall and cancellation information is also valuable. A recall takes place to resolve a problem with a device already in the market for which there are deficiencies or any other issues concerning safety, quality or performance. Most device recalls are made voluntarily by the sponsor. There are two key types of recall (a) correction, which may involve temporary removal from the market or from use, and (b) permanent removal of deficient medical devices from the market or from use. More information about product recalls can be found on the TGA website.[231] Suspensions, removals, withdrawals and cancellations in any jurisdiction should also be reported.

Device registries

Registries, systematic collections of data about medical outcomes, play a unique and prominent 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 comparative information on the performance in terms of functional outcomes and quality of life of patients. 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,[232] and the Australian National Orthopaedic Association National Joint Replacement Registry (ANOANJRR).[233]

[230] <https://www.tga.gov.au/DEVICES/daen-entry.aspx>
[231] <https://www.tga.gov.au/recall-actions>
[232] <http://www.med.monash.edu.au/sphpm/depts-centres-units/abdr/>
[233] <https://aoanjrr.dmac.adelaide.edu.au>

Published literature

To ascertain if any post-market data exists particularly if the above tools are not fruitful, a targeted literature search of biomedical databases, e.g. PubMed,[234] can be conducted to source post-market information. Keywords might include: brand name/ product name/ generic device description AND adverse events/ recall/ registry/ post-market surveillance.

[234] <http://www.ncbi.nlm.nih.gov/pubmed>

Appendix 5: Clinical evaluation report and supporting documents

The following checklist outlines the recommended heading structure for the **clinical evaluation report**. 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 clinical evaluation report.

1. Device Description, lineage and version if applicable

☐Yes ☐No ☐N/A Author(s): Located on page(s):

2. Intended Purpose/indications and claims

☐Yes ☐No ☐N/A Author(s): Located on page(s):

3. Regulatory Status in Other Countries

☐Yes ☐No ☐N/A Author(s): Located on page(s):

4. Summary of relevant pre-clinical data

☐Yes ☐No ☐N/A Author(s): Located on page(s):

5. Demonstration of substantial equivalence (if applicable)

☐Yes ☐No ☐N/A Author(s): Located on page(s):

6. Overview of clinical data

☐Yes ☐No ☐N/A Author(s): Located on page(s):

7. Evaluation of clinical data

☐Yes ☐No ☐N/A Author(s): Located on page(s):

8. Evaluation of post-market data (clinical experience)

☐Yes ☐No ☐N/A Author(s): Located on page(s):

9. Risk analysis and risk management

☐Yes ☐No ☐N/A Author(s): Located on page(s):

10. Instructions for use, labelling and other documents supplied with the device

☐Yes ☐No ☐N/A Author(s): Located on page(s):

11. Risk-benefit analysis

☐Yes ☐No ☐N/A Author(s): Located on page(s):

12. Conclusions

☐Yes ☐No ☐N/A Author(s): Located on page(s):

13. Name, signature and *curriculum vitae* of clinical expert and date of report

☐Yes ☐No ☐N/A Author(s): Located on page(s):

The following checklist outlines the recommended heading structure for the **supporting documents**. Indicate whether each of the recommended sections has been included, who authored each section, and which page(s) they can be located within the submission.

A Preclinical data (if relevant)

☐Yes ☐No ☐N/A Author(s): Located on page(s):

B Full clinical investigation reports

☐Yes ☐No ☐N/A Author(s): Located on page(s):

C Literature search and selection strategy

☐Yes ☐No ☐N/A Author(s): Located on page(s):

D Full text articles from the literature review

☐Yes ☐No ☐N/A Author(s): Located on page(s):

E Full technical and physical specifications of device

☐Yes ☐No ☐N/A Author(s): Located on page(s):

F Risk analysis and management documents

☐Yes ☐No ☐N/A Author(s): Located on page(s):

G Post-market data

☐Yes ☐No ☐N/A Author(s): Located on page(s):

Appendix 6: Collection and evaluation of clinical data

Clinical investigation data (synonymous with trials or studies) may be collected in Australia or outside of Australia.[235] When clinical trial data is collected in Australia, it is subject to the National Health and Medical Research Council's (NHMRC) National Statement of Ethical Conduct in Human Research. [236] Trials should comply with both the International Conference on Harmonisation's Note for Guidance on Good Clinical Practice[237] and the Australian Standards ISO 14155:2011 regarding clinical investigation in human subjects. [238] When clinical investigations are undertaken outside of Australia, the investigation must have been conducted in accordance with the principles of the Declaration of Helsinki,[239] as it is observed at the time and place the investigation is conducted.[240] The investigation report should note that the clinical investigation was carried out in accordance with such standards or indicate if it was not.

Since July 1, 2005, the International Committee of Medical Journal Editors (ICJME) 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.[241] Registries include clinicaltrials.gov or any registry participating in the WHO International Clinical Trials Registry Platform,[242] such as the Australian New Zealand Clinical Trials Registry (ANZCTR).[243] Registration is currently not mandatory in Australia for regulatory purposes, with the caveat that the TGA requires trials to be registered if they are on products that do not have an ARTG entry.

Clinical trials can be conducted within Australia under either the Clinical Trial Notification (CTN) or Clinical Trial exemption (CTX) schemes for devices not currently included on the ARTG, or to extend the use of a medical device beyond the conditions of current market approval.[244]

Evaluation of the clinical data provided for pre- and post-market reviews is necessary to identify potential sources of bias that may influence the results of the clinical investigations and/or information sourced from the literature review. It is important to describe the methods used for assessing risk of bias and to mention how this information will be used in data synthesis. Several quality appraisal tools are available for assessing trials reported in literature. A reviewer must pick a tool which is appropriate for the study design of every study in the literature sourced, some tools can be used for multiple study designs but more often than not, more than one tool will be used. Commonly used quality appraisal tools include:

[235] Therapeutic Goods (Medical Devices) Regulations 2002, Schedule 3, Part 8, Item 8.4 (4) and (5) <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028058>
[236] <https://www.nhmrc.gov.au/guidelines-publications/e72>
[237] <https://www.tga.gov.au/publication/note-guidance-good-clinical-practice>
[238] International Standards Association. ISO 14155:2011. Clinical investigation of medical devices for human subjects - Good clinical practice 2011. Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=45557>
[239] http://www.wma.net/en/30publications/10policies/b3/>
[240] Therapeutic Goods (Medical Devices) Regulations 2002, Schedule 3, Part 8, Item 8.4 (5) <http://www.comlaw.gov.au/Details/F2014C01375/Html/Text#_Toc407028058>
[241] For further details on ICJME clinical trial registration requirements see: <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration>
[242] For further details on the WHO International Clinical Trials Registry Platform see: <http://apps.who.int/trialsearch/Default.aspx>
[243] For further details on ANZCTR see: <http://www.anzctr.org.au/Support/AboutUs.aspx>
[244] For further details on clinical trials see: <https://www.tga.gov.au/clinical-trials#ctaust>

Table 5. Commonly used quality appraisal tools

Tool	Applicable study designs	Source
Jadad Score	Randomised studies	<http://fhswedge.csu.mcmaster.ca/cepftp/qasite/documents/jadadetal1996.pdf>
Downs & Black	Randomised & non-randomised studies	<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/>
QUADAS	Studies of diagnostic accuracy	<http://www.bris.ac.uk/quadas/>
AMSTAR	Systematic reviews	<http://amstar.ca/>

Additional guidance on critical appraisal tools is provided by Scottish Intercollegiate Guidelines Network (SIGN),[245] Centre for Evidence-Based Medicine (CEBM),[246] and the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions.[247] It is preferable to use a tool that has been validated. Indicate in the report which tool was used and present checklists and other information about the tool in Appendices.

An important part of 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.[248] 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.). Studies are ranked in the hierarchy based on the level of bias inherent in their design. Using this hierarchy, systematic reviews of randomised controlled trials represents the highest level of evidence, followed by individual randomised controlled trials, pseudo randomised controlled trials, non-randomised comparative trials, and case series. The level of evidence ultimately affects the confidence that can be placed in the study results. Where possible, sponsors should endeavour to source the highest level of evidence available that demonstrates the safety and performance of the device for the intended purpose(s).

A summary of the evaluation conducted should be reported in the clinical evaluation report. Results of an evaluation usually take the form of a table showing a quality assessment on different aspects of the study, for all studies appraised. The layout and presentation of this information will vary depending on the tool used for evaluation. Present data on risk of bias of each study and, if available, any outcome level assessment. The results of any assessment of risk of bias across studies (e.g. publication bias, selective reporting within studies) should also be presented.

[245] <http://www.sign.ac.uk/methodology/checklists.html>
[246] <http://www.cebm.net/critical-appraisal/>
[247] <http://handbook.cochrane.org/>
[248] <http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/stage_2_consultation_levels_and_grades.pdf>

Appendix 7: Joint prostheses

Search method: Identification and selection of clinical studies

The identification, retrieval and review of evidence which supports this guidance document used a pragmatic adaption of a rapid systematic review method.[249] 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.

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 sponsors were included. For regulatory documents, the scope of the search was confined to Australia and the comparator jurisdictions of Canada, the EU/UK, Japan and the USA.

In addition, Medline, Embase and the Cochrane library were searched using appropriate text words and subject headings. Searches were restricted to English language articles published between January 2009 and June 2014. All citations were retrieved and initial selection was based on title and abstract with potentially relevant articles retrieved in full text for final selection.

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 joint prostheses have also been presented. These include systematic reviews and meta-analyses, RCTs or comparative clinical trials and single arm trials. These examples also inform on what constitutes appropriate clinical evidence for a given type of partial or total joint prosthesis.

Reports were selected based on recency and relevance and included partial and total joint prostheses representative of those currently used in clinical practice in Australia.

Characteristics of clinical studies hip, knee and shoulder prostheses

Table 6. Summary of study characteristics extracted from systematic reviews and primary research reports on safety and performance of hip, knee or shoulder arthroplasty

Characteristic of included studies	Hip (3 systematic reviews [i] [ii] [iii])	Knee (5 systematic reviews [iv] [v] [vi] [vii] [viii], 1 RCT[ix] & 1 registry trial[x])	Shoulder (2 systematic reviews [xi] [xii] & 2 registry trials[xiii] [xiv])
Number of included studies per systematic review	4 to 236	5 to 34	7 to 29

[249] 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.

Characteristic of included studies	Hip (3 systematic reviews [i] [ii] [iii])	Knee (5 systematic reviews [iv] [v] [vi] [vii] [viii], 1 RCT[ix] & 1 registry trial[x])	Shoulder (2 systematic reviews [xi] [xii] & 2 registry trials[xiii] [xiv])
Sample size (range) for included studies	All clinical trials (12 to 5000) Identified RCTs (40 to 200)	All clinical trials (12 to 6500) Identified RCTs (23 to 566)	All clinical trials (20 to 690) Identified RCTs (20 to 47)
Dominant design of included studies	Level III /IV > 80% of included studies	Level II > 80% of included studies	Limited evidence-base Level IV ≈ 65% of included studies
Reported comparisons	Comparison of prostheses by component composition Clinical performance of prostheses Resurfacing vs. Total hip replacement.	Total knee arthroplasty ± patellar resurfacing Mobile vs. fixed bearings Metal backed vs. all polyethylene tibial components Cemented vs. uncemented fixation vs. hybrid	Total shoulder arthroplasty vs. Hemiarthroplasty
Quality of included evidence as reported	Low	Variable ranging from low to high	Low: No evidence on the comparison of Shoulder arthroplasty with other treatments
Patient Follow-up Comparative trials e.g. RCTs Registry trial	 3 – 10 years 10 years	I Immediately post-operative to 19 years. Most at 10 years 10 years (median 2.8 years)	 2 to years extending out to 19years 1 year extending out to 4 to 7 years

Possible study types

Based on the NHMRC levels of evidence[250] study designs used to evaluate the safety and performance of joint prostheses range from systematic reviews of RCTs down 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 for partial or total hip, knee and shoulder prostheses as documented in Table 6 (above) includes:

[250] <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2700132/?report=classic>

- systematic reviews of RCTs, comparative cohort trials and cases-series
  a. 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 total and partial hip, knee and shoulder replacements and included in the evidence base
- observational studies (Level III)
  - these are a valid alternative to RCTs[xv] provided appropriate matching of treatment groups is performed, e.g. through the application of propensity scores [xvi xvii]
- case series (Level IV)
  - these can inform on the safety and performance of joint prostheses and have a high sensitivity for adverse events
- post-market registries
  - these are established for hip, knee and shoulder prostheses and provide a valuable resource for post-market safety and performance data that can be used to support a pre- or post-market review of safety and performance of a joint prosthesis.

Reported clinical outcomes on hip, knee and shoulder prostheses

Table 7. Summary of safety data extracted from systematic reviews on safety and performance of hip, knee or shoulder arthroplasty

Safety parameter	Hip (3 systematic reviews [i ii iii])	Knee (5 systematic reviews [iv v vi vii viii])	Shoulder (2 systematic reviews [xi xii])
All cause revision/reoperation (time to first revision and revision rates)	a	a	a
Revision diagnosis			
Dislocation	a		a
Septic loosening	a	a	a
Aseptic loosening	a	a	a
Fracture	a		a
Postoperative alignment	a	a	

Safety parameter	Hip (3 systematic reviews [i ii iii])	Knee (5 systematic reviews [iv v vi vii viii])	Shoulder (2 systematic reviews [xi xii])
Wear/erosion			a
Surrogate markers for safety			
Radiostereometric analysis (RSA)		a	
Radiological findings (radiolucent lines)	a	a	

Table 8. 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 (3 systematic reviews [i ii iii])	Knee (5 systematic reviews, [iv v vi vii viii] 1 RCT [ix] & 1 registry trial [x])	Shoulder (2 systematic reviews [xi xii] & 2 registry trials [xiii xiv])
Revision/reoperation (time to first revision and revision rates)	a	a	a
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

Performance parameter	Hip (3 systematic reviews [i ii iii])	Knee (5 systematic reviews, [iv v vi vii viii] 1 RCT [ix] & 1 registry trial [x])	Shoulder (2 systematic reviews [xi xii] & 2 registry trials [xiii xiv])
Minimum Clinical Important Difference (MCID) identified in collating evidence for this guidance report.	a HHS[xviii] Oxford Hip Score (OHS) [xviii] WOMAC [xviii] EQ-5D [xviii] SF 12	a OKS [xix] SF 36 [xx xxi] SF 12 [xix] WOMAC[xxii]	a WOOS [xiii]

Table 9. Example Minimum Clinically Important Difference (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 [xviii]
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) [xxiii]	range: 5 to 7 [xviii]
Western Ontario and McMaster Osteoarthritis Index (WOMAC)			8 [xviii]

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) [xxiii]	5 [95% CI 4.4 to 5.5] [xix]
Western Ontario and McMaster Osteoarthritis index (WOMAC)			for TKR: ~15 [xiii]
Shoulder			
Western Ontario Osteoarthritis of the Shoulder Index (WOOS)			Primary Shoulder replacement: ~ 10% [xiii]
Constant Shoulder Score	Ratings; >30 poor 21 to 30 fair 11 to 20 good <11 excellent		
Quality of life			
EQ 5D			Hip: 0.074 [xviii]
SF12			4.5 [95% CI 3.9 to 5.2] [xix]
SF36			Multiple MCIDs for specific SF 36 domains [xx]

[i] Voleti PB, Baldwin KD, Lee GC. Metal-on-metal vs conventional total hip arthroplasty: a systematic review and meta-analysis of randomized controlled trials. J Arthroplasty. 2012;27:1844-9.
[ii] Kynaston-Pearson F, Ashmore AM, Malak TT et al. Primary hip replacement prostheses and their evidence base: systematic review of literature. BMJ (Clinical research ed). 2013;347:f6956.
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[v] Zeng Y, Shen B, Yang J, Zhou ZK, Kang PD, Pei FX. Is there reduced polyethylene wear and longer survival when using a mobile-bearing design in total knee replacement? A meta-analysis of randomised and non-randomised controlled trials. Bone Joint J. 2013;95-b(8):1057-63.
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[xii] Singh JA, Sperling J, Buchbinder R, McMaken K. Surgery for shoulder osteoarthritis. Cochrane Database Syst Rev. 2010(10).
[xiii] Rasmussen JV, Polk A, Sorensen AK, Olsen BS, Brorson S. Outcome, revision rate and indication for revision following resurfacing hemiarthroplasty for osteoarthritis of the shoulder: 837 operations reported to the Danish Shoulder Arthroplasty Registry. Bone Joint J. 2014;96-B(4):519-25.
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[xv] Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency medicine journal. 2003;20:54-60
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[xviii] NICE. Total hip replacement and resurfacing arthroplasty for end-stage arthritis of the hip; 2014.
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[xxii] Escobar A, Quintana JM, Bilbao A, Arostegui I, Lafuente I, Vidaurreta I. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. Osteoarthritis Cartilage. 2007;15:273-80

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Conduct and reporting clinical trials

The TGA provides extensive guidance on the regulations that govern the conduct of clinical trials in Australia. The TGA also provides guidance on the processes for conduct and reporting of clinical studies (Good Clinical Practice). Additional information can be accessed at the National Health and Medical Research Council website.

The Sponsor is advised to adopt the ISO standard 14155; 2011 when planning and conducting a clinical study. For partial or total joint prostheses, clinical studies must be appropriately designed to provide an unbiased assessment of the benefit risk profile of the device when used for its intended purpose as defined by the 'Instructions for Use' document supplied by the sponsor/manufacturer.

An example of a route map defining the necessary steps in the conduct of a clinical trial is provided by the National Institute for Health Research (UK). This map includes key control points designed to ensure internal validity of a clinical trial and to provide appropriate documentation for submission to the TGA.

When designing and reporting on results of trials it is recommended that sponsors:

- ensure that combinations of components that are to be included in the IFU are tested e.g. when an acetabular cup is examined the trial should include femoral components from a range of manufacturers and for modular devices the sponsor should test the most common combinations of components
- ensure that clinical trials are independently audited at key stages to document that the integrity of the trial was maintained
- report the clinical trial data using an internationally recognised standard for a given study design e.g. the CONSORT reporting standards for RCTs

For devices based on predicate/similar marketed devices the sponsor should:

- demonstrate substantial equivalence of the technical and biological characteristics and intended purpose of the predicate/similar marketed device
- demonstrate that clinical data is derived from clinical studies using sound methods
- ensure an internationally recognised method is followed when conducting a comprehensive literature review and demonstrate that all included studies on the predicate/similar marketed device have been be appraised for reporting quality and the risk of bias
- critique the evidence identified during a comprehensive literature review and when appropriate provide a meta-analysis of the pooled results

Defining the clinical context

To assist a TGA evaluator to differentiate between device and procedural related safety and performance issues a comprehensive documentation of the clinical context of trials is essential. Also, this information will be used to review the clinical outcomes reported in the studies and to determine the applicability to the Australian healthcare system. In addition, data on the clinical

context is essential for the construction of database search strategies and study selection when conducting a literature review of a device that is deemed to be substantially equivalent (predicate or similar marketed devices) to the one under review. For literature review based submissions, detail of the clinical context should be extractable from study reports. If this is not possible for any given study, that study should be excluded from the review.

For joint prostheses, information on the clinical context related to arthroplasty may include but is not limited to the following elements:

- surgeons and treatment teams
  - the experience level and volume for surgeons and treatment facility as defined by the number of procedures performed annually
- description of appropriate staff training if the use of the device in question requires a change in clinical practice
- patient data
  - the age and sex of the included patients
  - an assessment of clinical status e.g. patients ASA grade
  - the indication that escalated the arthroplasty
  - comorbidities that may influence the clinical outcomes

Use of Minimum Clinically Important Differences

If validated MCIDs are available, sponsors 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. [39] In this case, the sponsor must 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 good as a currently available device(s).

Appendix 8: CV flow implants

Search Method: Identification and selection of clinical studies

The identification, retrieval and review of evidence that supports this guidance report used a pragmatic adaption of a rapid systematic review method.[251] 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.

A focused internet search was conducted to identify recent and relevant legislation, current guidance documents and other standards/documentation to assist in the compilation and presentation of clinical evidence. Only documents that are publicly available to sponsors were included. For regulatory documents, the scope of the search was confined to Australia and the comparator jurisdictions of Canada, the EU/UK, Japan and the USA.

Medline, Embase and the Cochrane library were searched using appropriate text words and subject headings. 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.

Evidence from the peer reviewed literature identified in the internet searches focused on study designs that are based on scientific principles which generate clinical evidence of safety and device performance. 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 selected CV flow implants have also been presented. These include systematic reviews and meta-analyses, RCTs or comparative clinical trials and single arm trials. These examples also inform on what constitutes appropriate clinical evidence for a given type of CV flow implant.

Reports were selected based on recency and relevance and included selected CV flow implants of the following types:

- Arterial stents (carotid, coronary and peripheral)
- Implants for AAA repair
- Implants for PDA repair
- IVC filters to prevent PE

[251] 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(2):133-9.

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) [xxiv xxv xxvi xxvii xxviii xxix] Coronary(6 SRs) [xxx xxxi xxxv] Peripheral (5 SRs) [xl]			Implants for AAA repair (4 SRs) [xxxviii xli, xlii xliii] & (1 retrospective comparative cohort) [xliv]	Implants for PDA repair (1 SR) [xlv] & (1 retrospective cohort study) [xlvi]	IVC filters (2 SRs) [xlvii xlviii] & (1 RCT) [xlix]
	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
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:[23] All Level IV Primary study:[22] Level IV	SRs: Levels II-IV RCT=Level II

Characteristics of included studies	Arterial stents: Carotid (6 SRs) [xxiv xxv xxvi xxvii xxviii xxix] Coronary(6 SRs) [xxx xxxi xxxv] Peripheral (5 SRs) [xl]			Implants for AAA repair (4 SRs) [xxxviii xli, xlii xliii] & (1 retrospective comparative cohort) [xliv]	Implants for PDA repair (1 SR) [xlv] & (1 retrospective cohort study) [xlvi]	IVC filters (2 SRs) [xlvii xlviii] & (1 RCT) [xlix]
	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:[xlv] n=259 patients in device group; n=551 in control group Primary study:[xlvi] Level III-2 retrospective cohort with concurrent controls; n=51 in device group; n=130 in control group	SR 2010:[xlvii] 2 RCTs of 129 and 400 patients (division between arms NR) SR 2014:[xlviii] n=432 in filter groups; n=4160 in historical control groups RCT 2012:[xlix] 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) [xxiv xxv xxvi xxvii xxviii xxix] Coronary(6 SRs) [xxx xxxi xxxv] Peripheral (5 SRs) [xl]			Implants for AAA repair (4 SRs) [xxxviii xli, xlii xliii] & (1 retrospective comparative cohort) [xliv]	Implants for PDA repair (1 SR) [xlv] & (1 retrospective cohort study) [xlvi]	IVC filters (2 SRs) [xlvii xlviii] & (1 RCT) [xlix]
	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:[xlvii] With D&B, assessed studies as low quality SR 2014:[xlviii] 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:[xlvii] NR SR 2014:[xlviii] 34 days to 8 years RCT 2012: 15 (± SD 2) months

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

[xxiv] NICE. Interventional procedure overview of carotid artery stent placement for symptomatic extracranial carotid stenosis. 2010:IP 008_2.
[xxv] Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. BMJ. 2010;340:c467.
[xxvi] Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev. 2012;9:Cd000515.
[xxvii] Liu ZJ, Fu WG, Guo ZY, Shen LG, Shi ZY, Li JH. Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. Ann Vasc Surg. 2012;26(4):576-90.
[xxviii] Al-Damluji MS, Nagpal S, Stilp E, Remetz M, Mena C. Carotid revascularization: a systematic review of the evidence. J Interv Cardiol. 2013;26(4):399-410.
[xxix] Gahremanpour A, Perin EC, Silva G. Carotid artery stenting versus endarterectomy: a systematic review. Tex Heart Inst J. 2012;39(4):474-87
[xxx] Piccolo R, Cassese S, Galasso G, De Rosa R, D'Anna C, Piscione F. Long-term safety and efficacy of drug-eluting stents in patients with acute myocardial infarction: a meta-analysis of randomized trials. Atherosclerosis. 2011;217(1):149-57.
[xxxi] De Luca G, Dirksen MT, Spaulding C et al. Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Arch Intern Med. 2012;172(8):611-21; discussion 21-2.
[xxxii] Wallace EL, Abdel-Latif A, Charnigo R et al. Meta-analysis of long-term outcomes for drug-eluting stents versus bare-metal stents in primary percutaneous coronary interventions for ST-segment elevation myocardial infarction. Am J Cardiol. 2012;109(7):932-40.
[xxxiii] Bangalore S, Amoroso N, Fusaro M, Kumar S, Feit F. Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. Circ Cardiovasc Interv. 2013;6(4):378-90.
[xxxiv] Palmerini T, Biondi-Zoccai G, Della Riva D et al. Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol. 2013;62(6):496-504.
[xxxv] Kalesan B, Pilgrim T, Heinimann K et al. Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. Eur Heart J. 2012;33(8):977-87.
[xxxvi] Medical Advisory Secretariat. Stenting for peripheral artery disease of the lower extremities: an evidencebased analysis. Ont Health Technol Assess Ser [Internet]. 10(18)
[xxxvii] Acin F, de Haro J, Bleda S, Varela C, Esparza L. Primary nitinol stenting in femoropopliteal occlusive disease: a meta-analysis of randomized controlled trials. J Endovasc Ther. 2012;19(5):585-95
[xxxviii] Chambers D, Epstein D, Walker S et al. Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model. Health Technol Assess. 2009;13(48):1-189, 215-318, iii.
[xxxix] Simpson EL, Kearns B, Stevenson MD, Cantrell AJ, Littlewood C, Michaels JA. Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis. Health Technol Assess. 2014;18(10):1-252.
[xl] Chowdhury MM, McLain AD, Twine CP. Angioplasty versus bare metal stenting for superficial femoral artery lesions. Cochrane Database Syst Rev. 2014;6:Cd006767.
[xli] Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg. 2013;100(7):863-72.

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[xliii] van Beek SC, Conijn AP, Koelemay MJ, Balm R. Editor's Choice - Endovascular aneurysm repair versus open repair for patients with a ruptured abdominal aortic aneurysm: a systematic review and meta-analysis of short-term survival. Eur J Vasc Endovasc Surg. 2014;47(6):593-602.
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[xlv] Wang K, Pan X, Tang Q, Pang Y. Catheterization therapy vs surgical closure in pediatric patients with patent ductus arteriosus: a meta-analysis. Clin Cardiol. 2014;37(3):188-94.
[xlvi] Chen Z, Chen L, Wu L. Transcatheter amplatzer occlusion and surgical closure of patent ductus arteriosus: comparison of effectiveness and costs in a low-income country. Pediatr Cardiol. 2009;30(6):781-5.
[xlvii] Young T, Tang H, Hughes R. Vena caval filters for the prevention of pulmonary embolism. Cochrane database of systematic reviews (Online). 2010(2):CD006212.
[xlviii] Haut ER, Garcia LJ, Shihab HM et al. The effectiveness of prophylactic inferior vena cava filters in trauma patients: a systematic review and meta-analysis. JAMA Surg. 2014;149(2):194-202.
[xlix] Sharifi M, Bay C, Skrocki L, Lawson D, Mazdeh S. Role of IVC filters in endovenous therapy for deep venous thrombosis: the FILTER-PEVI (filter implantation to lower thromboembolic risk in percutaneous endovenous intervention) trial. Cardiovasc Intervent Radiol. 2012;35(6):1408-13.
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[xlix] International Organisation for Standardisation. Cardiovascular implants - Cardiac valve prostheses - Part 3: Heart valve substitutes implanted by transcatheter techniques (ISO 5840-3: 2013). 2013 [cited 2014 27 October]; Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=51313>

Possible study types

Based on the NHMRC levels of evidence [252] study designs used to evaluate the safety and performance of CV flow implants range from systematic reviews of RCTs down to case series reports (Level IV). Irrespective of level of evidence the quality of reporting in the reviewed literature varied from low to high as assessed by validated quality tools (see ***Appendix 4: Collection and evaluation of clinical data***). In summary, the clinical evidence for CV flow implants as documented in Table 10 (above) 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 for CV flow devices were found in the evidence base
- observational studies (Level III)
  - these are a valid alternative to RCTs, providing appropriate matching of treatment groups is performed, e.g. through the application of propensity scores
- case series (Level IV)
  - These can inform on the safety and performance of CV flow implants and have a high sensitivity for adverse events.
- post-market registries,
  - when available registries can provide a valuable resource for post-market safety and performance data that can be used to support marketing authorisations and monitoring and compliance reviews for a CV flow implant

[252] <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2700132/?report=classic>

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) [l] [li] [lii] [liii] [liv] [lv] – **Coronary** (6 SRs) [lvi] [lvii] [lviii] [lix] [lx] [lxi] – **Peripheral(**5 SRs) [lxii] [lxiii] [lxiv] [lxv] [lxvi]	· 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) [lxiv] [lxvii] [lxviii] [lxix] & (1 retrospective comparative cohort) [lxx]	· 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
Implants for PDA repair (1 SR) [lxxi] & (1 retrospective cohort study [lxxii])	· AEs · Primary success · Residual shunt

Type of CV flow implant	Outcomes reported in included research
	· Blood transfusion · LOHS
IVC filters (2 SRs) [lxxiii] [lxxiv] & (1 RCT)[lxxv]	· 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=total lesion revascularisation; TVR=total vessel revascularisation; VTE=Venous thromboembolism

[l] NICE. Interventional procedure overview of carotid artery stent placement for symptomatic extracranial carotid stenosis. 2010:IP 008_2.
[li] Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. BMJ. 2010;340:c467.
[lii] Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev. 2012;9:Cd000515.
[liii] Liu ZJ, Fu WG, Guo ZY, Shen LG, Shi ZY, Li JH. Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. Ann Vasc Surg. 2012;26(4):576-90.
[liv] Al-Damluji MS, Nagpal S, Stilp E, Remetz M, Mena C. Carotid revascularization: a systematic review of the evidence. J Interv Cardiol. 2013;26(4):399-410.
[lv] Gahremanpour A, Perin EC, Silva G. Carotid artery stenting versus endarterectomy: a systematic review. Tex Heart Inst J. 2012;39(4):474-87.
[lvi] Piccolo R, Cassese S, Galasso G, De Rosa R, D'Anna C, Piscione F. Long-term safety and efficacy of drug-eluting stents in patients with acute myocardial infarction: a meta-analysis of randomized trials. Atherosclerosis. 2011;217(1):149-57.
[lvii] De Luca G, Dirksen MT, Spaulding C et al. Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Arch Intern Med. 2012;172(8):611-21; discussion 21-2.
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[lxi] Kalesan B, Pilgrim T, Heinimann K et al. Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. Eur Heart J. 2012;33(8):977-87.
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[lxv] Simpson EL, Kearns B, Stevenson MD, Cantrell AJ, Littlewood C, Michaels JA. Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis. Health Technol Assess. 2014;18(10):1-252.
[lxvi] Chowdhury MM, McLain AD, Twine CP. Angioplasty versus bare metal stenting for superficial femoral artery lesions. Cochrane Database Syst Rev. 2014;6:Cd006767.
[lxvii] Stather PW, Sidloff D, Dattani N, Choke E, Bown MJ, Sayers RD. Systematic review and meta-analysis of the early and late outcomes of open and endovascular repair of abdominal aortic aneurysm. Br J Surg. 2013;100(7):863-72.
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[lxx] Edwards ST, Schermerhorn ML, O'Malley AJ et al. Comparative effectiveness of endovascular versus open repair of ruptured abdominal aortic aneurysm in the Medicare population. J Vasc Surg. 2014;59(3):575-82
[lxxi] Wang K, Pan X, Tang Q, Pang Y. Catheterization therapy vs surgical closure in pediatric patients with patent ductus arteriosus: a meta-analysis. Clin Cardiol. 2014;37(3):188-94
[lxxii] Chen Z, Chen L, Wu L. Transcatheter amplatzer occlusion and surgical closure of patent ductus arteriosus: comparison of effectiveness and costs in a low-income country. Pediatr Cardiol. 2009;30(6):781-5.
[lxxiii] Young T, Tang H, Hughes R. Vena caval filters for the prevention of pulmonary embolism. Cochrane database of systematic reviews (Online). 2010(2):CD006212
[lxxiv] Haut ER, Garcia LJ, Shihab HM et al. The effectiveness of prophylactic inferior vena cava filters in trauma patients: a systematic review and meta-analysis. JAMA Surg. 2014;149(2):194-202
[lxxv] Sharifi M, Bay C, Skrocki L, Lawson D, Mazdeh S. Role of IVC filters in endovenous therapy for deep venous thrombosis: the FILTER-PEVI (filter implantation to lower thromboembolic risk in percutaneous endovenous intervention) trial. Cardiovasc Intervent Radiol. 2012;35(6):1408-13

Conduct and reporting of clinical studies

The TGA provides extensive guidance on the regulations that govern the conduct of clinical trials in Australia. The TGA also provides guidance on the processes for conducting and reporting of clinical studies (Good Clinical Practice [253]). Additional information can be accessed at the National Health and Medical Research Council website.[254]

The sponsor is advised to adopt the ISO standard 14155; 2011 [255] when planning and conducting a clinical study. For CV flow implants, clinical studies must be appropriately designed to provide an unbiased assessment of the benefit risk profile when the device is used for its intended purpose as defined by the 'Instructions of Use' document supplied by the sponsor/manufacturer.

An example of a route map defining the necessary steps in the conduct of a clinical trial is provided by the National Institute for Health Research (UK).[256] This map includes key control points designed to ensure internal validity of a clinical trial and to provide appropriate documentation for submission to the TGA.

When designing and reporting on results of trials it is recommended that sponsors:

- ensure that combinations of components that are to be included in the instructions for use are tested
- ensure that clinical trials are independently audited at key stages throughout their conduct to document that the integrity of the trial was maintained
- report the clinical trial data using an internationally recognised standard for a given study design e.g. the CONSORT reporting standards for RCTs

For devices based on predicate/similar marketed device data the sponsor should:

- demonstrate substantial equivalence of the technical characteristics and intended purpose of the predicate/similar marketed device
- demonstrate that clinical data is derived from clinical studies using sound methods
- ensure an internationally recognised method is followed when conducting a comprehensive literature review and demonstrate that all included studies on the predicate/similar marketed device have been be evaluated for reporting quality and the risk of bias
- critique the evidence identified during a comprehensive literature review and when appropriate provide a meta-analysis of the pooled results

Defining the clinical context

To assist the clinical assessor to differentiate between device and procedural-related safety and performance issues, a comprehensive documentation of the clinical context of trials is essential. This information will be used to review the clinical outcomes reported in the studies and determine the applicability to the Australian healthcare system. Data on the clinical context is essential for the construction of database search strategies and study selection when conducting a literature review of a device that is deemed to be substantially equivalent to the one under review. For literature review based submissions, detail of the clinical context should be extractable from study reports. If this is not possible for any given study, that study should be excluded from the review. For CV flow implants, information on the clinical context may include but is not limited to the following elements:

253 <https://www.tga.gov.au/industry/clinical-trials.htm#guidance>
254 <http://www.australianclinicaltrials.gov.au/node/36>
255 <http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=45557>
256 <http://www.ct-toolkit.ac.uk/routemap>

- Surgeons and treatment teams: the experience level and volume for surgeons and treatment facility as defined by the number of procedures performed annually.
- Description of appropriate staff training if the use of a new device requires a change in clinical practice.
- Patient data:
  - Age and sex of the included patients
  - An assessment of clinical status
  - The indication that escalated the surgery
  - Comorbidities that may influence the clinical outcomes

Appendix 9: Electrical Impulse Generators

Search Method: Identification and selection of clinical studies

The identification, retrieval and review of evidence that supports this guidance report used a pragmatic adaption of a rapid SR methodology. [257] Selection criteria were established *a priori* and include publication type, type of medical device under review, intended purpose of the medical device, AEs (safety), and clinical outcomes related to device performance.

A focused internet search was conducted to identify recent and relevant legislation, current guidance documents and other standards/documentation to assist in the compilation and presentation of clinical evidence. Only documents that were publicly available to sponsors were included. For regulatory documents, the scope of the search was confined to Australia and the comparator jurisdictions of Canada, the EU/UK, Japan and the USA.

Medline, Embase and the Cochrane library were searched using appropriate text words and subject headings. Searches were restricted to English language articles published between January 2009 and June 2014 with updates to October 2014. All citations were retrieved and initial selection was based on title and abstract with potentially relevant articles retrieved in full text for final selection.

Evidence from the peer reviewed literature identified in the internet searches focused on study designs that are based on solid scientific principles which generate clinical evidence of safety and device performance. The emphasis was on rigorously conducted SRs, where available.

Brief summaries of information from SRs documenting clinical research on the safety and performance of selected electrical impulse generators have been presented. These examples inform what constitutes appropriate clinical evidence for a given type of electrical impulse generator.

Reports were selected based on recency and relevance and included selected electrical impulse generators of the following types:

- Active Implantable Medical Devices (AIMD) 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

[257] 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(2):133-9.

Characteristics of studies from the peer reviewed literature

Table 12 Study characteristics extracted from SRs on the safety and performance of selected electrical impulse generators

Characteristics of included studies	Pacemakers (including CRT) (2 SR)[lxxvi] [lxxvii]	ICDs (5 SRs)[lxxviii] [lxxix] [lxxx] [lxxxi] [lxxxii]	Pain management devices (5 SRs or narrative reviews)[lxxxiii] [lxxxiv] [lxxxv]
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

[lxxvi] Colquitt JL, Mendes D, Clegg AJ et al. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: Systematic review and economic evaluation. Health Technol Assess. 2014;18(56):1-560.
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[lxxviii] Kong MH, Al-Khatib SM, Sanders GD, Hasselblad V, Peterson ED. Use of implantable cardioverter-defibrillators for primary prevention in older patients: A systematic literature review and meta-analysis. Cardiol J. 2011;18(5):503-14.
[lxxix] Chen S, Ling Z, Kiuchi MG, Yin Y, Krucoff MW. The efficacy and safety of cardiac resynchronization therapy combined with implantable cardioverter defibrillator for heart failure: A meta-analysis of 5674 patients. Europace. 2013;15(7):992-1001.
[lxxx] Chen S, Yin Y, Krucoff MW. Effect of cardiac resynchronization therapy and implantable cardioverter defibrillator on quality of life in patients with heart failure: A meta-analysis. Europace. 2012;14(11):1602-7.
[lxxxi] Pun PH, Al-Khatib SM, Han JY et al. Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: A meta-analysis of patient-level data from 3 randomized trials. American Journal of Kidney Disease. 2014;64(1):32-9.
[lxxxii] Schinkel AF. Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications. Circulation: Arrhythmia and Electrophysiology. 2013;6(3):562-8.
[lxxxiii] Plow EB, Pascual-Leone A, Machado A. Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. The Journal of Pain. 2012;13(5):411-24.
[lxxxiv] Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: A systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. European Journal of Pain. 2006;10(2):91-101.
[lxxxv] Coffey RJ, Lozano AM. Neurostimulation for chronic noncancer pain: An evaluation of the clinical evidence and recommendations for future trial designs. J Neurosurg. 2006;105(2):175-89.
[lxxxvi] Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: Critical review of the literature. J Neurosurg. 2009;110(2):251-6.
[lxxxvii] Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: Systematic review and economic evaluation. Health Technol Assess. 2009;13(17):iii, ix-x, 1-154.

Regardless of design, clinical studies should provide unbiased results that allow an objective comparison of electrical impulse generators with respect to their safety and performance. To achieve this for new device applications based on direct clinical data the sponsor should:

- Ensure that clinical trials are conducted according to internationally recognised standards for a given trial design, e.g., follow the ISO standard 14155; 2011.
- 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.
- Ensure that combinations of components that are to be included in the IFU are tested.
- Ensure that clinical trials are independently audited at key stages throughout their conduct to document that the integrity of the trial(s) was maintained.
- Report clinical trial data using an internationally recognised standard for a given study design, e.g., the CONSORT reporting standards for RCTs.

For applications based on clinical data from a predicate or similar marketed device, the sponsor should:

- Provide a full clinical justification for the use of predicate/ similar marketed device clinical data based on demonstrating the substantial equivalence of the technical and biological characteristics and intended purpose of the predicate(s).
- Demonstrate that clinical data are derived from methodologically sound clinical studies.
- Ensure that a direct relationship between the predicate/ similar marketed device and new device exists with respect to the clinical data.
- Ensure that internationally recognised methodology is followed when conducting a systematic literature review and demonstrate that all included studies on the predicate or similar marketed device(s) have been appraised for reporting quality and risk of bias.
- Critique the evidence identified during a systematic literature review and, when appropriate, provide a meta-analysis of the pooled results.

Table 13. Reported clinical outcomes in the peer reviewed literature on selected electrical impulse generators

Type of pulse generator	Outcomes reported in the included research or resources
Pacemakers (including CRT) (2 SR)[17, 24]	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

Type of pulse generator	Outcomes reported in the included research or resources
ICDs (5 SRs)[16, 18-22, 34]	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, vein 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) [25-29]	· Safety intracranial (AEs / postop complications): usual 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 · 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 · 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

Conduct and reporting of clinical trials

The TGA provides extensive guidance on the regulations that govern the conduct of clinical trials in Australia. The TGA also provides guidance on the processes for conduct and reporting of clinical studies (Good Clinical Practice). Additional information can be accessed at the National Health and Medical Research Council website.

The sponsor is advised to adopt the ISO standard 14155; 2011 when planning and conducting a clinical study. For electrical pulse generators, clinical studies must be appropriately designed to provide an assessment of the risk/benefit profile when the device is used for its intended purpose as defined by the 'Instructions for Use' documentation supplied by the sponsor/manufacturer.

An example of a route map defining the necessary steps in the conduct of a clinical trial is provided by the National Institute for Health Research (UK). This map includes key control points designed to ensure internal validity of a clinical trial. The process also ensures the necessary documentation that constitutes the full clinical study report to be included in submission to the TGA.

Guidance regarding appropriate reporting standards and presentation of results are provided in ***Appendix 5: Guidelines for reporting full clinical study reports and systematic literature reviews and Chapter 4. Clinical evaluation report and supporting documents***.

Defining the clinical context

To assist a TGA evaluator in differentiating between device-related and procedure-related safety and performance issues, a comprehensive documentation of the clinical context of trials is essential. Also, this information will be used to review the clinical outcomes reported in the clinical studies and determine the applicability to the Australian health care system. For literature-review-based submissions, detail of the clinical context should be extractable from study reports. If this is not possible for any given study, that study should be excluded from the review.

For electrical impulse generators, information on the clinical context may include but is not limited to the following elements:

- surgeons and treatment teams: the experience level and volume for surgeons and treatment facility as defined by the number of procedures performed annually;
- description of appropriate staff training if the use of a new device requires a change in clinical practice;
- patient data:
- age and sex of the included patients
- an assessment of clinical status e.g. patients ASA grade
- the indication that escalated the surgery
- comorbidities that may influence the clinical outcomes

In addition, data on the clinical context is essential for the construction of database search strategies and study selection when conducting a literature review of devices that are deemed to be substantially equivalent (predicate or similar marketed device) to the one that is the subject of the submission.

Appendix 10: Heart valve prostheses

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 sponsors of heart valve prostheses refer to ISO documents (5840: 2005) and (5840-3: 2013) for guidance on the type of information that should be provided with respect to the characteristics of the device.[lxxxviii] [lxxxix]

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

Note: At the time of writing this guidance document a further three ISO documents (ISO/DIS 5840-1, ISO/DIS 5840-2 and ISO/NP 5840-3) were under development. These should also be consulted when available as they may outline further characteristics that should be reported. 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 that have no equivalent predicate/similar marketed device(s) (see ***Chapter5. Demonstrating substantial equivalence***).

If a predicate/similar marketed 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 predicate/similar marketed device selection. Furthermore, when providing a literature review based submission, a full description of the device used in any given study must be extractable from the study report. If this is not possible, the study should be excluded from the review.

In addition, data on the materials used to construct the prosthesis/similar marketed device, its dimensions and geometry and the intended purpose will define the construction of search strategies as well as study selection when conducting a comprehensive literature review. This ensures that the searches are comprehensive and the included studies are related to the new device and the predicate/similar marketed device. The selection of predicates/similar marketed device should be made prior to performing the literature selection, extraction of the clinical evidence and analysis of the pooled results.

Search Method: Identification and selection of clinical studies

The identification, retrieval and review of evidence which supports this guidance report used a pragmatic adaption of a rapid systematic review methodology. [28] 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.

A focused internet search was conducted to identify recent and relevant legislation, current guidance documents and other standards/documentation to assist in the compilation and presentation of clinical evidence. Only documents that are publicly available to Sponsors were included. For regulatory documents, the scope of the search was confined to Australia and the comparator jurisdictions of Canada, the EU/UK, Japan and the USA.

In addition, Medline, Embase and the Cochrane library were searched using appropriate text words and subject headings. Searches were restricted to English language articles published between January 2009 and June 2014. All citations were retrieved and initial selection was based on title and abstract with potentially relevant articles retrieved in full text for final selection.

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 of device safety and performance. 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 heart valve prostheses have also been presented. These include health technology assessments, systematic reviews, RCTs or comparative clinical trials and single arm trials. These examples also inform on what constitutes appropriate clinical evidence for a given type of heart valve prosthesis.

Reports were selected based on recency and relevance.

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	

Safety parameter	Surgical Aortic Valve Replacement	Transcatheter Aortic Valve Implantation	Sutureless valve replacement
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
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		

Safety parameter	Surgical Aortic Valve Replacement	Transcatheter Aortic Valve Implantation	Sutureless valve replacement
Reintervention/reoperation or freedom from reoperation	a		a
Aortic regurgitation/paravalvular regurgitation		a	a
Atrioventricular block			a
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[xc]

	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
	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
	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‡			
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 m^2 (note: dependent on the size of the valve and the size of the native annulus).

‖Use in setting of BSA <1.6 m^2, ¶ Use in setting of BMI <30 kg/m^2, # Use in setting of BMI ≥30 kg/m^2

**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) [xci]

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) [xci]

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‡

Parameter	Mild	Moderate	Severe
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) [xci]

	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
VTI_{PrMv}/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) [xci]

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

Parameter	Mild	Moderate	Severe
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; cutoffs 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) [xcii] *

	Mechanical Valve		Bioprosthetic Valve	
Adverse event	**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[xcii]

[lxxxviii] International Organisation for Standardisation. Cardiovascular implants - Cardiac valve prostheses (ISO 5840: 2005). 2005 [cited 2014 27 October]; Fourth Edition 2005-03-01:[Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=34164>

[lxxxix] International Organisation for Standardisation. Cardiovascular implants - Cardiac valve prostheses - Part 3: Heart valve substitutes implanted by transcatheter techniques (ISO 5840-3: 2013). 2013 [cited 2014 27 October]; Available from: <http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=51313>

[xc] Kappetein AP, Head SJ, Genereux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J. 2012;33(19):2403-18

[xci] Zoghbi WA, Chambers JB, Dumesnil JG et al. Recommendations for Evaluation of Prosthetic Valves With Echocardiography and Doppler Ultrasound. A Report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, Developed in Conjunction With the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association. J Am Soc Echocardiogr. 2009;22(9):975-1014

[xcii] Wu Y, Butchart EG, Borer JS, Yoganathan A, Grunkemeier GL. Clinical Evaluation of New Heart Valve Prostheses: Update of Objective Performance Criteria. Ann Thorac Surg. 2014

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[xciii]

Review	Design of included studies	Numbers of studies and patients	Follow-up	Comparison
Kassai et al 2000[xciv]	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[xcv]	RCTs	11 studies 919 patients	NR	Aortic: Stented vs. non-stented bioprosthetic
Lund and Bland, 2006[xcvi]	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[xcvii] Puvimanasinghe et al 2003[xcviii]	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[xcix]	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[c]	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[xciii]

Total number of patients	**12, 379**	
Valve types studied	Aortic (n=43) Aortic and mitral (n=11) Mitral alone (n=3)	
Valve comparisons	Aortic studies	Most common comparison was bioprosthetic stented vs. bioprosthetic unstented (n=15)
	Aortic and mitral studies	Homograft vs. mechanical (n=1) Mechanical vs. mechanical (n=7) Mechanical vs. bioprosthetic (n=2) Bioprosthetic vs. bioprosthetic (n=1)
	Mitral studies	All compared mechanical valves
Average follow-up time	Aortic studies	1 year or sooner (69% of studies) >1 to 5 years (24% of studies) > 5 to 10 years (7% of studies
	Aortic and mitral studies	>1 to 5 years (36% of studies) > 5 to 10 years (45% of studies) >10 years (18% of studies)
	Mitral studies	Mean of 5 years

*Note: Sixteen of the 57 trials were included in the systematic reviews in Table 19

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)[ci]	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)[cii]	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)[ci]

‡ 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)[ciii]	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)[civ]	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)[cv]	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[ciii]

Possible study types

Based on the NHMRC levels of evidence[cvi] study designs used to evaluate the safety and performance of heart valve prostheses range from systematic reviews of RCTs down 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 for heart valve prostheses as documented in Table 19, Table 20, Table 21 and Table 22.

Table 19 to Table 22 include:

- systematic reviews, RCTs, comparative cohort trials and cases-series
- RCTs (Level II)
  - when practical, this should be the preferred study design
  - within the evidence-based clinical trials of a RCT design are reported for transcatheter aortic valve implantation
- observational studies (Level III)
  - these are a valid alternative to RCTs[cvii] provided appropriate matching of treatment groups is performed, e.g. through the application of propensity scores [cviii] [cix]
- case series (Level IV)
  - these can inform on the safety and performance of heart valve prostheses and have a high sensitivity for adverse events
- post-market registries

– these are established for heart valve prostheses and provide a valuable resource for post-market safety and performance data that can be used to support a premarket application for the inclusion of a heart valve prosthesis on the ARTG

Irrespective of the level of evidence, each study should be considered within a quality framework.

It is recommended that clinical trials on heart valve prostheses are designed to the highest NHMRC Level of Evidence [cvi] that is practical and fit-for-purpose to inform on safety and performance.

In summary, regardless of design, clinical studies should provide unbiased results that allow an objective comparison of heart valve prostheses with respect to their safety and performance. To achieve this for device applications based on direct clinical data the Sponsor should;

· conduct clinical trials that are designed to demonstrate safety and performance that is appropriate for regulatory purposes with safety being a primary outcome

· design and document clinical trials to be appropriate, practical and ethical for the clinical setting

· ensure that clinical trials are conducted according to internationally recognised standards for a given trial design e.g. follow the ISO standard 14155; 2011[258]

· ensure that clinical trials are independently audited at key stages throughout their conduct to document that the integrity of the trial was maintained

· report the clinical trial data using an internationally recognised standard for a given study design e.g. the CONSORT reporting standards for RCTs

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.

For applications based on indirect clinical data (see ***Chapter5. Demonstrating substantial equivalence***) the sponsor should:

· provide a full clinical justification for the use of indirect clinical data. This should be based on demonstrating the substantial equivalence of the technical and biological characteristics and intended purpose of the predicate or similar market device

· demonstrate that clinical data is derived from methodologically sound clinical studies

· ensure that a direct relationship between the predicate or the similar marketed device and the device under review exists with respect to the clinical data

· ensure an internationally recognised method is followed when conducting a systematic literature review and demonstrate that all included studies have been be appraised for reporting quality and the risk of bias

· critique the evidence identified during a systematic literature review and when appropriate provide a meta-analysis of the pooled results.

[258] <http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=45557>

[xciii] Williams JW, Coeytaux R, Wang A, Glower DD. Percutaneous Heart Valve Replacment. Technical Brief No. 2. . Rockville, MD: Prepared by Duke Evidence-based Practice Center under Contract No. 290-02-0025. Agency for Healthcare Research and Quality; 2010
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[xcv] Kunadian B, Vijayalakshmi K, Thornley AR et al. Meta-analysis of valve hemodynamics and left ventricular mass regression for stentless versus stented aortic valves. Ann Thorac Surg. 2007;84(1):73-8
[xcvi] Lund O, Bland M. Risk-corrected impact of mechanical versus bioprosthetic valves on long-term mortality after aortic valve replacement. J Thorac Cardiovasc Surg. 2006;132(1):20-6.e3
[xcvii] Puvimanasinghe JP, Takkenberg JJ, Edwards MB et al. Comparison of outcomes after aortic valve replacement with a mechanical valve or a bioprosthesis using microsimulation. Heart. 2004;90(10):1172-8
[xcviii] Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ et al. Choice of a mechanical valve or a bioprosthesis for AVR: does CABG matter? Eur J Cardiothorac Surg. 2003;23(5):688-95; discussion 95
[xcix] Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ et al. Comparison of Carpentier-Edwards pericardial and supraannular bioprostheses in aortic valve replacement. Eur J Cardiothorac Surg. 2006;29(3):374-9
[c] Rizzoli G, Vendramin I, Nesseris G, Bottio T, Guglielmi C, Schiavon L. Biological or mechanical prostheses in tricuspid position? A meta-analysis of intra-institutional results. Ann Thorac Surg. 2004;77(5):1607-14
[ci] National Institute for Health and Clinical Excellence. Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis.: National Institute for Health and Clinical Excellence; 2011
[cii] Tice JA, Sellke FW, Schaff HV. Transcatheter aortic valve replacement in patients with severe aortic stenosis who are at high risk for surgical complications: Summary assessment of the California Technology Assessment Forum. J Thorac Cardiovasc Surg. 2014;148(2):482-91.e6
[ciii] National Institute for Health and Clinical Excellence. Interventional procedure overview of sutureless aortic valve replacement for aortic stenosis. ; 2012. Report No.: IPG456
[civ] Sinclair A, Xie X, McGregor M. Surgical aortic valve replacement with the ATS Enable sutureless aortic valve for aortic stenosis. Montreal, Canada: Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2013
[cv] Englberger L, Carrel TP, Doss M et al. Clinical performance of a sutureless aortic bioprosthesis: Five-year results of the 3f Enable long-term follow-up study. J Thorac Cardiovasc Surg. 2014;148(4):1681-7
[cvi] NHMRC. NHMRC levels of evidence and grades for recommendation for developers of guidelines. [Internet] 2009 2009 [cited 2013 07/02]; Available from: <http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/stage_2_consultation_levels_and_grades.pdf>
[cvii] Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54-60
[cviii] 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):1-13; discussion 5-7, 9-21, 3-7 passim
[cix] Yue LQ. Regulatory considerations in the design of comparative observational studies using propensity scores. J Biopharm Stat. 2012;22(6):1272-9
[cix] Furnee E, Hazebroek E. Mesh in laparoscopic large hiatal hernia repair: a systematic review of the literature. Surgical Endoscopy. 2013;27:3998–4008.

Conduct and reporting of clinical studies

The TGA provides extensive guidance on the regulations that govern the conduct of clinical trials in Australia. The TGA also provides guidance on the processes for conduct and reporting of clinical studies (Good Clinical Practice). Additional information can be accessed at the National Health and Medical Research Council website.

The sponsor is advised to adopt the ISO standard 14155; 2011 when planning and conducting a clinical study. For heart valve prostheses, clinical studies must be appropriately designed to provide an assessment of the risk/benefit profile when the device is used for its intended purpose as defined by the 'Instructions of Use' documentation supplied by the sponsor/manufacturer.

An example of a route map defining the necessary steps in the conduct of a clinical trial is provided by the National Institute for Health Research (UK). This map includes key control points designed to ensure internal validity of a clinical trial. The process also ensures the necessary documentation that constitutes the full clinical study report to be included in submission to the TGA.

When conducting clinical trials it is recommended sponsors adopt the ISO standard 14155; 2011

Defining the clinical context

To assist a TGA evaluator to differentiate between device and procedural related safety and performance issues a comprehensive documentation of the clinical context of trials is essential. Also, this information will be used to review the clinical outcomes reported in the clinical studies and determine the applicability to the Australian healthcare system. For literature review based submissions, detail of the clinical context should be extractable from study reports. If this is not possible for any given study, that study should be excluded from the review.

For heart valve prostheses, information on the clinical context may include, but is not limited to, the following elements:

- surgeons and treatment teams
  - the experience level and volume for surgeons and treatment facility as defined by the number of procedures performed annually
  - specifically for transcatheter aortic valve implantation procedures, details of expertise in the following should be reported for the interventional cardiologist:
    - coronary diagnostic procedures
    - coronary interventions
    - peripheral vascular diagnostic procedures
  - peripheral vascular interventions
    - balloon aortic, mitral and pulmonary valve dilatation
    - intra-aortic balloon pump, other cardiac support
    - large vessel access and closure

- details of expertise in the following should be reported for the cardiac surgeon:
  - aortic valve replacements (including the number of high risk replacements)
  - experience with, and management of, peripherally inserted cardiopulmonary bypass
  - experience with open retroperitoneal exposure of, and surgical intervention on, the iliac arteries

· description of appropriate staff training if the use of a the device requires a change in clinical practise

· patient data
  - the age and sex of the included patients
  - an assessment of clinical status e.g. echocardiographic measures of valve performance (valve flow velocities, valve area and valve pressure gradients), mortality risk prediction scores (e.g. the Society of Thoracic Surgeons score or the EuroSCORE) and risk factors not captured by traditional risk scores.[21]
  - comorbidities that may influence the clinical outcomes

Data on the clinical context provide essential detail for the IFU documentation.

Appendix 11: Supportive devices

The TGA describes supportive devices as devices in the following sub-groups.

- **Surgical mesh:** this is the most widely used type. It is used for hernia, pelvic organ prolapse (POP), stress urinary incontinence (SUI) and many other purposes. The two classes of devices are biological and synthetic. Types of mesh include bio-mesh, polypropylene, expanded polytetrafluoroethylene (ePTFE), composite polypropylene-PTFE. More than one type can be used at once (absorbable and non-absorbable). Configuration of mesh varies. Fixation methods include staples, sutures or glue.[cx]

- **Patches,** specifically Central Nervous System (CNS) patches, are impermeable adhesive membranes used in intradural neurosurgical procedures, as an alternative to using autologous grafts or cadaveric implants.

- **Tissue Adhesives** such as Fibrin glue and cyanoacrylate adhesives, are used to control bleeding and as a sealant for closure, for example, of colostomies; in combination with, or as an alternative to, sutures in wound closure. Tissue adhesives can act as a barrier to microbial penetration as long as the adhesive film remains intact. They can also be used to fix mesh, patches and scaffolding in place.

- **Biocompatible coated materials** include devices coated with silver, titanium dioxide, hydroxyapatite, paclitaxel and many other components. Any of the supportive devices can include biocompatible coated materials.

The design of clinical studies to demonstrate the clinical safety and performance of devices that have no equivalent predicate(s) or similar marketed device must include all device characteristics and all intended uses. If a predicate or similar marketed 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 predicate selection. Furthermore, when providing a literature based submission, a full description of the device used in any given study must be extractable from the study report. If this is NOT possible, the study should be excluded from the review.

In addition, 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 when conducting a comprehensive literature review. This ensures that the searches are comprehensive and the included studies are related to the device in question and/or predicate or similar marketed device(s). The selection of predicate or similar marketed device should be made prior to performing the literature selection, extraction of the clinical evidence and analysis of the pooled results.

Search Method: Identification and selection of clinical studies

The identification, retrieval and review of evidence which supports this guidance report used a pragmatic adaption of a rapid systematic review methodology.[cxi] 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.

A focused internet search was conducted to identify recent and relevant legislation, current guidance documents and other standards/documentation to assist in the compilation and presentation of clinical evidence. Only documents that are publicly available to sponsors were included. For regulatory documents, the scope of the search was confined to Australia and the comparator jurisdictions of Canada, the EU/UK, Japan and the USA.

In addition, Medline, Embase and the Cochrane library were searched using appropriate text words and subject headings. Searches were restricted to English language articles published between January 2009 and June 2014. All citations were retrieved and initial selection was based on title and abstract with potentially relevant articles retrieved in full text for final selection.

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 of safety and device performance. 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 supportive devices have also been presented. These include systematic reviews and meta-analyses, RCTs or comparative clinical trials and single arm trials. These examples also inform on what constitutes appropriate clinical evidence for a given type of supportive device. Reports were selected based on recency and relevancy.

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

Possible study types

Based on the NHMRC levels of evidence[cxii] study designs used to evaluate the safety and performance of supportive devices range from systematic reviews of RCTs down 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 (see ***Appendix 4: Collection and evaluation of clinical data***). In summary, the clinical evidence for supportive devices such as meshes, patches and tissue adhesives as documented in Table 23 (above), includes:

- systematic reviews of RCTs, comparative cohort trials and cases-series
- RCTs (Level II)
  - when practical, this should be the preferred study design

  - clinical trials of a RCT design are reported for meshes, patches and tissue adhesives

- observational studies (Level III)
  - these are a valid alternative to RCTs[cxiii] provided appropriate matching of treatment groups is performed, e.g. through the application of propensity scores [cxiv] [cxv]

- case series (Level IV)
  - these can inform on the safety and performance of supportive devices and have a high sensitivity for adverse events

- post-market registries

- these are established for some meshes, patches and tissue adhesives and provide a valuable resource for post-market safety and performance data that can be used to support a premarket application for the inclusion of a supportive devices on the ARTG

Irrespective of the Level of evidence, each study should be considered within a quality framework. Details of quality appraisal tools are provided in ***Appendix 4: Collection and evaluation of clinical data.***

It is recommended that clinical trials on supportive devices are designed to the highest NHMRC level of evidence that is practical and fit-for-purpose to inform on safety and performance.

In summary, regardless of design, clinical studies should provide unbiased results that allow an objective comparison of supportive devices with respect to their safety and performance. To achieve this for device applications based on direct clinical data the sponsor should:

- conduct clinical trials that are designed to demonstrate safety and performance that is appropriate for regulatory purposes with safety being a primary outcome

- design and document clinical trials to be appropriate, practical and ethical for the clinical setting

- ensure that clinical trials are conducted according to internationally recognised standards for a given trial design e.g. follow the ISO standard 14155; 2011[cxvi]

- ensure that clinical trials are independently audited at key stages throughout their conduct to document that the integrity of the trial was maintained

- report the clinical trial data using an internationally recognised standard for a given study design e.g. the CONSORT reporting standards for RCTs

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.

For applications based on predicate or similar marketed device clinical data, the sponsor should:

- provide a full clinical justification for the use of predicate or similar marketed device clinical data. This should be based on demonstrating the substantial equivalence of the technical characteristics and intended purpose of the predicate or similar marketed device(s)

- demonstrate that clinical data is derived from methodologically sound clinical studies

- ensure that a direct relationship exists between the predicate or similar marketed device and device under question with respect to the clinical data

- ensure an internationally recognised methodology is followed when conducting a systematic literature review and demonstrate that all included studies on the predicate or similar marketed device(s) have been be appraised for reporting quality and the risk of bias
- critique the evidence identified during a systematic literature review and when appropriate provide a meta-analysis of the pooled results

Reported clinical outcomes in the peer reviewed literature

Table 26. Summary of safety data extracted from systematic reviews on supportive devices

Safety parameter	Death	Urinary issues	Pain	Chronic pain	Infection	Bleeding	Organ perforation	Dyspareunia	Material exposure	Visceral injury	Mesh erosion	Haematoma	Seroma	Bile leak	Cytotoxicity	CSF leakage	Adhesions	Fistula	Bowel obstruction	Hydrocephalus
Vaginal Surgical Mesh		ü	ü			ü	ü	ü	ü	ü	ü				ü					
Hernia Surgical Mesh			ü	ü	ü	ü					ü	ü	ü				ü	ü	ü	
Patches	ü				ü											ü				ü
Tissue Adhesives	ü			ü	ü	ü						ü	ü	ü	ü	ü				

Greyed cells 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 supportive devices

Performance parameter	Surgical Mesh - Gynaecological	Surgical Mesh - Hernia	Absorbable devices	Patches	Tissue Adhesives
Revision/ reoperation (recurrence rates)	ü	ü	ü	ü	ü

Performance parameter	Surgical Mesh - Gynaecological	Surgical Mesh - Hernia	Absorbable devices	Patches	Tissue Adhesives
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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[cxi] 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. International Journal of Technology Assessment in Health Care. 2008;24(2):133-9
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[cxiv] Yue LQ. Statistical and regulatory issues with the application of propensity score analysis to nonrandomized medical device clinical studies. Journal of Biopharmaceutical Statistics. 2007;17(1):1-13
[cxv] Yue LQ. Regulatory considerations in the design of comparative observational studies using propensity scores. Journal of Biopharmaceutical Statistics. 2012;22(6):1272-9
[cxvi] <http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=45557>

Conduct and reporting of clinical studies

The TGA provides extensive guidance on the regulations that govern the conduct of clinical trials in Australia. The TGA also provides guidance on the processes for conduct and reporting of clinical studies (Good Clinical Practice). Additional information can be accessed at the National Health and Medical Research Council website.

The sponsor is advised to adopt the ISO standard 14155; 2011 when planning and conducting a clinical study. For supportive devices, clinical studies must be appropriately designed to provide an assessment of the risk/benefit profile when the device is used for its intended purpose as defined by the 'Instructions for Use' documentation supplied by the sponsor/manufacturer.

An example of a route map defining the necessary steps in the conduct of a clinical trial is provided by the National Institute for Health Research (UK). This map includes key control points designed to ensure internal validity of a clinical trial. The process also ensures the necessary documentation that constitutes the full clinical study report to be included in submission to the TGA.

Guidance regarding appropriate reporting standards and presentation of results are provided in ***Chapter 4. Clinical evaluation report and supporting documents***.

When conducting clinical trials it is recommended sponsor adopted the ISO standard 14155; 2011

Defining the clinical context

To assist the clinical assessor to differentiate between device and procedural related safety and performance issues, a comprehensive documentation of the clinical context of trials is essential. Also, this information will be used to review the clinical outcomes reported in the clinical studies and to determine the applicability to the Australian healthcare system. For literature based submissions, detail of the clinical context should be extractable from study reports. If this is NOT possible for any given study, that study should be excluded from the review.

For supportive devices, information on the clinical context related to supporting organs or adhesion may include but is not limited to the following elements:

- surgeons and treatment teams
  - the experience level and volume for surgeons and treatment facility as defined by the number of procedures performed annually
- description of appropriate staff training if the use of a device requires a change in clinical practice
- patient data
  - the age and sex of the included patients
  - an assessment of clinical status e.g. patients ASA grade
  - comorbidities that may influence the clinical outcomes

Data on the clinical context provide essential detail for the IFU documentation.

Appendix 12: Safety of active implantable medical devices in the MR environment

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.

Active implantable cardiac devices 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 different active implantable 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 non-life threatening arrhythmias, including abnormally fast heartbeat (tachycardia) and abnormally slow heartbeat (bradycardia).[cxvii] They may include one pacing lead for single-chamber pacing, or two pacing leads for right ventricular and/or right atrial pacing.[cxviii] [cxix]

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

Cardiac resynchronisation therapy (CRT) devices are pacing devices used to regulate abnormal heart rhythms due to delayed contractions in both the left and right ventricles. [cxxiii] 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, and/or right atrial pacing. CRT devices may also deliver high-energy impulses to correct life-threatening arrhythmias.[cxxiii]

Implantable loop recorders (ILR) are single-lead cardiac monitoring devices. They can be used to 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.[cxxiv] 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 sponsors 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.

Device characteristics and intended purposes are essential to determine the clinical safety of devices that have no substantially equivalent predicate. If data from a predicate device exists and is used to support a submission, the use of this evidence will need to be justified with reference to the characteristics and intended purposes of both the device and the predicate device. For literature review based submissions, a full description of the device must be reported for all included studies. If this is NOT possible, the study should be excluded from the review. Data on the materials used to construct the device, its dimensions and geometry, and the intended purpose will define the construction of search strategies and study selection when conducting a comprehensive literature review. This ensures that the searches are comprehensive and the included studies are related to the device and the predicate(s).

[cxvii] Castelnuovo E, Stein K, Pitt M, Garside R, Payne L, Programme. ftUNRDH. The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation 2004. Available from: <www.nice.org.uk/guidance/ta88>

[cxviii] Castelnuovo E, Stein K, Pitt M, Garside R, Payne L, Programme. ftUNRDH. The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation 2004. Available from: <www.nice.org.uk/guidance/ta88>

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[cxxiv] Krahn AD, Klein GJ, Yee R, Skanes AC. The use of monitoring strategies in patients with unexplained syncope--role of the external and implantable loop recorder. Clin Auton Res. 2004;14 Suppl 1:55-61

Search Method: Identification and selection of relevant literature

The identification, retrieval and review of evidence to support this guidance report were conducted using a pragmatic adaption of rapid systematic review methodology.[249] Selection criteria were established *a priori* and included publication type, publication year, type of medical device under review (i.e. AIMDs), and adverse events related to device interactions with the MR environment.

A focused internet search was conducted to identify recent and relevant legislation, current guidance documents and other standards/documentation to assist in the compilation and presentation of clinical evidence. For regulatory documents, the scope of the search was confined to Australia and the comparator jurisdictions of Canada, the EU/UK, Japan and the USA.

Clinical studies were identified through a systematic search of Medline, Embase, the Cochrane Library and the York Centre for Reviews and Dissemination databases. The search strategy was designed using relevant text words and medical subject headings. Searches were restricted to English language articles published between January 2005 and December 2014. All citations were imported into bibliographic management software (Endnote X7) and initial selection was based on title and abstract. Potentially relevant articles were retrieved in full-text for final selection.

Reports were selected preferentially for inclusion based on recency and relevancy. Evidence from both the targeted internet searches and peer-reviewed literature focused on study designs that are based on solid scientific principles. Such evidence sources include, but are not limited to, controlled clinical trials, case-control studies, case series, post-market registry data or systematic reviews of these study designs. Summaries of exemplar articles documenting clinical research on the safety of AIMDs in the MR environment have also been presented. These examples also inform on what constitutes appropriate clinical evidence for a given type of AIMD.

Selection of included studies

Table 28. Summary of primary studies report in narrative reviews on the safety of AIMDs in the MR environment[cxxv cxxvi cxxvii cxxviii cxxix cxxx cxxxi cxxxii]

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)

Characteristics of included studies	Evidence reported in narrative reviews
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** · 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 · Decrease in ventricular sensing amplitude ≥ 50%, or amplitude lower than 5.0 mV[cxxxiii] [cxxxiv] · Change in pacing lead impedance (≥ 50 Ω) **Unintended cardiac stimulation** · Inappropriate pacing · Induction of arrhythmia · Heart palpitations

[cxxv] Ahmed FZ, Morris GM, Allen S, Khattar R, Mamas M, Zaidi A. Not all pacemakers are created equal: MRI conditional pacemaker and lead technology. J Cardiovasc Electrophysiol. 2013;24(9):1059-65
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[cxxxi] Shinbane JS, Colletti PM, Shellock FG. Magnetic resonance imaging in patients with cardiac pacemakers: era of "MR Conditional" designs. J Cardiovasc Magn Reson. 2011;13:63
[cxxxii] van der Graaf AWM, Bhagirath P, Gotte MJW. MRI and cardiac implantable electronic devices; current status and required safety conditions. Neth Heart J. 2014;22(6):269-76
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[cxxxiv] Cohen JD, Costa HS, Russo RJ. Determining the risks of magnetic resonance imaging at 1.5 tesla for patients with pacemakers and implantable cardioverter defibrillators. Am J Cardiol. 2012;110(11):1631-6

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Version history

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