



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Clinical evidence guidelines

## Medical devices

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**TGA** Health Safety  
Regulation



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The purpose of this guidance is to help manufacturers understand how the TGA interprets regulations, and thus indicate how a manufacturer can comply.

This is a guide only, and manufacturers and sponsors 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 manufacturer or sponsor to understand and comply with these requirements.

This document will evolve over time and updates and clarifications will be included as required. Feedback on the guidance is always welcome.

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# Introduction

The Clinical Evidence Guidelines for medical devices are intended to provide guidance to manufacturers of medical devices (including In vitro diagnostic medical devices (IVDs)) on what constitutes clinical evidence and the process of clinical data generation and clinical evaluation to produce such clinical evidence. While this guideline refers to IVDs, it is acknowledged that the information provided at this point is incomplete.

Sections of this guidance 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
- Implantable pulse generators
- Heart valve prostheses
- Supportive devices - meshes, patches and tissue adhesives

There is also a specific section ([Section 10](#)) on implantable medical devices in the magnetic resonance environment.

## Why (and when) clinical evidence is required

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<sup>1</sup>).

Clinical evidence is not only required when a medical device is first included on the ARTG, 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. The clinical evidence requirements described in this guidance apply in all these instances.

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.

## Development of these guidelines

The TGA has developed these guidelines 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) <sup>2</sup>.

These guidelines have been developed taking into account requirements of the *Therapeutic Goods Act 1989* and the *Therapeutic Goods (Medical Devices) Regulations 2002*. They reference and align 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**

The literature search method used by ASERNIP-S to collect and collate the information referenced in this guidance is described in [Appendix 3](#). This is subject to the limitations of the method, and it should be read and relied upon with this in mind.

## Legislative basis

The relevant Australian legislation for regulation of medical devices:

- [Therapeutic Goods Act 1989](#) (the Act),<sup>3</sup> particularly Chapter 4<sup>4</sup> of the Act
- [Therapeutic Goods \(Medical Devices\) Regulations 2002](#) (the MD Regulations).<sup>5</sup>

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<sup>6</sup> 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)
- IVDs are classified under Schedule 2A<sup>7</sup> of the MD Regulations from lowest to highest risk Classes 1 to 4.

Section 4 of the [ARGMD](#) provides guidance on medical device classifications, and [Classification of IVD medical devices](#)<sup>8</sup> 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](#)<sup>9</sup> (EPs) 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 with the manufacturer 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.<sup>10</sup> This applies to all medical devices regardless of risk class.

The manufacturer and sponsor must (among other matters) provide clinical evidence to demonstrate compliance of the devices with the EPs if requested.<sup>11</sup>

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# Part 1 – General requirements

## 1. The 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 of the MD Regulations outlines the EPs which discuss safety and performance.

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.

### 1.1. Compliance with essential principles

Compliance with the EPs is required for all devices included on the ARTG; however the principles do not set out categorically how manufacturers should comply. They leave some room for flexibility according to the intended use and risk profile or class of the device.

The following EPs (1, 3, 4, 6, 13 and 14) are particularly relevant to the clinical evidence, with EP 14 being the overarching principle.

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## 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.<sup>12</sup>

These clinical evaluation procedures must be implemented in accordance with the requirements specified in Schedule 3 Part 8<sup>13</sup> 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)
- ensure that the clinical data held in relation to the device is critically evaluated by competent clinical experts in the relevant field, and that the clinical evidence demonstrating that the device complies with the applicable provisions of the EPs is documented in writing.

The clinical evidence must primarily demonstrate that the device complies with the EPs 1, 3, and 6<sup>14</sup> 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;<sup>15</sup> 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.<sup>16</sup>

## Principle one: Use not to compromise health and safety

Key considerations from a clinical perspective include the context of how the device is used, for example, whether it is used by specialist medical practitioners only, or by the general public. This will impact on the safety assessment for many devices. How the device is used, for example, the type of treatment administered, or procedure or testing undertaken and if there are any inherent dangers in this all have implications on the safety of the device. Any inherent dangers in the proposed treatment setting rather than the treatment itself should also be taken into account. The patient, user and any other person in the vicinity of the device may need to be considered.

## 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.<sup>17</sup>

The assessor will examine whether there is sufficient clinical evidence to demonstrate that the device performs as intended. Each of the intended uses proposed should be substantiated by the clinical evidence submitted, and the evidence must be a true and complete account of available scientific knowledge. When the range of indications is broad and diverse it may be reasonable to provide evidence of safety and performance for the higher risk and most common indications with a justification as to why these were selected as ‘worst case scenarios’ and/or common



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indications and an explanation provided as to how these results can be justifiably extrapolated to other indications.

#### **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.<sup>18</sup> In developing the device all possible methods to minimise hazards identified in the risk assessment should have been incorporated into the device design. 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 marketed device.

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 lifetime. The clinical evidence must demonstrate that the device performs as intended for the length of time appropriate to the intended 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. In this case surrogate markers and post-market data from jurisdiction(s) where the device is already in use 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 the intended purpose 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.

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 may not safely use the device with directions on how it is to be inserted, implanted 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;<sup>19</sup> for implantable devices - information about any risks associated with the implantation;<sup>20</sup> warnings, restrictions or precautions that may apply to the use of the device

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(including clinical or environmental),<sup>21</sup> requirements for handling or storage,<sup>22</sup> risks (if any) associated with the disposal of the device.<sup>23</sup> These are risk minimisation tools.

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

The clarity and comprehensiveness of the information provided with a medical device 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 person to safely use the device and therefore negatively affect the benefit versus harm ratio of the device.

## 1.2. 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) documents relevant to clinical evidence requirements for medical devices:

- ISO13485:2016 - Quality Management Systems (QMS)<sup>24</sup>
- ISO14155:2011 - Good Clinical Practice<sup>25</sup>
- ISO 14971:2007 - Application of risk management to medical devices<sup>26</sup>

### ISO 13485:2016 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,<sup>27</sup> and

*“...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.”<sup>24</sup>*

Manufacturers are expected to continue to monitor the performance and safety of devices, including IVDs, via a surveillance program as part of their QMS once the device is marketed. These programs should be appropriate to the use and risks of the device. The data generated from safety and adverse event reports and complaints, newly identified risks, literature, any updated or new clinical investigations, significant regulatory actions and formal surveillance activities such as registries should be used to review the performance, safety and benefit-risk assessment of the device. This data should be evaluated and the CER updated in line with this new information. As a minimum the CER should be updated every 1-5 years depending on the novelty of the device and risk, as per MEDDEV 2.7/1 revision 4<sup>28</sup> (page 12) . 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.

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Compliance with ISO 13485:2016 is not mandatory in Australia, however, under the [Conformity Assessment Standards Order \(Standard for Quality Management Systems and Quality Assurance Techniques\) 2008](#),<sup>29</sup> compliance with ISO 13485:2016 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 involving medical devices. It can also be used by regulatory bodies and ethics committees when reviewing clinical investigational plans. Thirteen principles are included such as adherence to ethical principles (as per the Declaration of Helsinki [30](#)), subjects' rights, a determination that benefits outweigh risks and oversight by an independent ethics committee.

Compliance with ISO14155 is not mandatory in Australia, however the *Therapeutic Goods (Medical Devices) Regulations 2002* state in 8.4 (5) that:

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

The manufacturer must additionally ensure that any further standards that apply to the device are taken into account.

### **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 IVDs, 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 device types which have specific ISO standards outlining requirements for demonstrating clinical evidence are the current editions of the series of standards:

- ISO 11979-7- Ophthalmic implants - intraocular lenses [31](#)
- ISO 5840-1; ISO 5840-2 and ISO 5840-3 - Cardiovascular implants- cardiac valve prostheses [32](#) and
- ISO 14708 - Implants for surgery - Active implantable medical devices
- ISO 14117 - Electromagnetic compatibility test protocols for active implantable medical devices

In addition, there is a technical specification ISO/TS 10974 entitled 'Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device' [33](#) which refers to non-clinical testing of AIMDs in an MR environment.

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## 2. Clinical evidence

This section 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 publicly available GHTF and related MEDDEV documents in particular MEDDEV 2.7/1 revision 4.[28](#)

### 2.1. Key definitions and concepts

The following definitions used in this section are consistent with those provided in the GHTF document, Clinical Evidence - Key Definitions and Concepts, SG5/N1R8:2007 [34](#) and MEDDEV 2.7/1 revision 4 [28](#) (apart from addition of 'substantial').

**Clinical investigation:** systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device.

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

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

Clinical data are sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a device for which substantial equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which substantial equivalence to the device in question can be demonstrated.

**Clinical evaluation:** a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential principles (essential requirements in EU) for safety and performance when using the device according to the manufacturer's Instructions for Use.

Note: in exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.

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

**Clinical use:** use of a medical device in or on living human subjects. Note: Includes use of a medical device that does not have direct patient contact.

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Definitions of additional terms used throughout this document:

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

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

**Predicate:** A previous iteration of the device, within the same lineage of devices, with the same intended purpose and from the same manufacturer, in relation to which a manufacturer 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 manufacturer is seeking to demonstrate substantial equivalence. Such a device may not be manufactured by the same manufacturer.

**Substantial equivalence:** Substantial equivalence confirms that the new device is 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 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.
- **Indirect clinical evidence** is derived from an evaluation of clinical data pertaining to a predicate or similar marketed device with which the manufacturer 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. 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.<sup>35</sup> This clinical evidence is used to compile the clinical evaluation report (CER). The CER should be updated as new evidence is generated once the device is marketed.

## 2.2. Clinical data

Clinical data (meaning data relating to use of the device in or on living 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.

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### 2.2.1. 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; and
  - c) a written report by an expert in the relevant field, being a report that contains a critical evaluation of all the clinical investigation data held in relation to the device. [35](#)

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 are not available for the device or are insufficient in quantity or quality. In this situation 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 Section 4: [Demonstrating Substantial Equivalence](#).

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

The gap analysis should determine whether the existing data are sufficient to verify that the device is in conformity with all the EPs (corresponding to ERs in the EU) pertaining to clinical performance and clinical safety.

Special attention should be given to aspects such as:

- new design features, including new materials,
  - new intended purposes, including new medical indications, new target populations (age, gender, etc.),
  - new claims the manufacturer intends to use,
  - new types of users (e.g. lay persons),
  - seriousness of direct and/or indirect risks,
  - contact with mucosal membranes or invasiveness,
  - increasing duration of use or numbers of re-applications,
  - incorporation of medicinal substances,

- use of animal tissues (other than in contact with intact skin),
- issues raised when medical alternatives with lower risks or more extensive benefits to patients are available or have become newly available,
- issues raised when new risks are recognised (including due to progress in medicine, science and technology),
- whether the data of concern are amenable to evaluation through a clinical investigation,
- etc.

Data on the safety and performance of other devices and alternative therapies, including benchmark devices and equivalent devices, should be used to define the state of the art or identify hazards due to substances and technologies. This will allow the clinical data requirements to be established more precisely in relation to the intended purpose of a device. Precision in this analysis and the choice of selected medical indications and target populations may reduce the amount of clinical data needed from additional clinical investigations.<sup>28</sup>

### ***Conducting clinical trials***

Clinical investigations (synonymous with trials or studies) may be undertaken in Australia or outside of Australia.<sup>36</sup> 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](#).<sup>37</sup> Trials should comply with both the International Conference on Harmonisation's [Note for Guidance on Good Clinical Practice](#)<sup>38</sup> and ISO 14155:2011 regarding clinical investigation in human subjects.<sup>25</sup> When clinical investigations are undertaken outside of Australia, the investigation must have been conducted in accordance with the principles of the [Declaration of Helsinki](#),<sup>30</sup> as it is observed at the time and place the investigation is conducted.<sup>39</sup> The investigation report should note that the clinical investigation was carried out in accordance with such standards (and name the relevant regulatory authority or ethics committee/s giving approval) or indicate if it was not.

Since July 1, 2005, the International Committee of Medical Journal Editors (ICMJE) has required (and recommended that all medical journal editors require) registration of clinical trials in a public trials registry at or before the time of first patient enrolment as a condition of consideration for publication.<sup>40</sup> Registries include [clinicaltrials.gov](#) or any registry participating in the WHO International Clinical Trials Registry Platform,<sup>41</sup> such as the Australian New Zealand Clinical Trials Registry (ANZCTR).<sup>42</sup> Registration is currently not mandatory in Australia for regulatory purposes.

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.<sup>43</sup>

### ***Reporting standards for clinical trials***

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](#).<sup>25</sup> Annex D of this ISO provides useful information on what should go into a clinical trial report.



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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 \(CONSORT\)](#)<sup>44</sup> 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 \(STROBE\)](#)<sup>45</sup> 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 \(STARD\)](#)<sup>46</sup> statement is used for the reporting of *in vivo* diagnostic accuracy studies. The statement provides a 25-item checklist and flow diagram describing the design of the study and the flow of patients through the study. The focus of the statement is on identifying the quality of reporting.

#### *Reporting standards for systematic literature reviews*

Guidelines for reporting systematic literature reviews are outlined in the [Preferred Reporting Items for Systematic Reviews and Meta-Analyses](#) (PRISMA) statement.<sup>47</sup> It is recommended that the PRISMA be followed closely when compiling a literature review as part of a submission for pre- and post-market reviews. The statement includes a 27-item checklist and flow diagram describing the study selection process in systematic literature reviews. [Guidelines for Meta-analysis of Observational studies in Epidemiology](#) (MOOSE)<sup>48</sup> may also be used for meta-analyses of observational studies.

### **2.2.2. Literature review**

A literature review may be presented in addition to clinical investigation data described above, or on its own. If the literature review does not pertain directly to the device under evaluation, 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 Section 4: [Demonstrating substantial equivalence](#). A literature review relating to the specific device or a device demonstrated to be substantially equivalent provides direct or indirect clinical data for the device. A literature review may also be presented that does not relate to the specific device or device demonstrated to be substantially



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equivalent, but only to the same kind of device. In this case, it may be used to present the state of the art and to identify risks and adverse events associated with that kind of device, but not to provide clinical data for the device. The purpose of the literature review (i.e. to present clinical data or to present the state of the art for the kind of device) should be clearly identified, and literature reviews for different purposes should not be combined.

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

A written report must be prepared by an expert in the relevant field containing a critical evaluation of the compilation of the literature. The manufacturer of the medical device must ensure that the clinical data is evaluated by competent clinical experts and must ensure that clinical evidence demonstrating that the device complies with the applicable provisions of the essential principles is documented in writing.<sup>49</sup>

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 pre- and post-market TGA reviews.<sup>50</sup> It is critical that the methods used to conduct the literature review are comprehensive and transparent in order for the clinical assessor to evaluate objectivity (lack of bias) and quality.

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 the search, search limits applied (including language, study design, etc.) and inclusion and exclusion criteria. This must contain enough detail for a clinical assessor to reproduce the search. The search protocol should describe the method used to extract data from included studies and any processes for confirming data extracted by investigators.

### ***Selection strategy***

The selection criteria applied to the resulting list of studies should be clearly defined in 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, the study design, quality of the data reported, quality of analysis and the clinical significance of the results should be considered. Any weighting criteria applied to the included studies should be clearly detailed. Variables for which data are extracted should be listed and defined.

A flow diagram should detail each step in the screening process, including total numbers of studies screened, assessed for eligibility and included in the review. Objective, non-biased, systematic search and review methods should be used such as PRISMA (Preferred Reporting

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Items for Systematic reviews and Meta-Analyses)<sup>47</sup> or Meta-analysis of Observational Studies in Epidemiology (MOOSE)<sup>48</sup> guidelines in accordance with the section: [Reporting standards for clinical trials](#). The report should also summarise how each citation did or did not fit the selection criteria for inclusion in the review. This may be presented as an appendix of excluded studies with justification for the decision.

### ***Review and critical analysis***

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

### ***Literature report***

A report must be provided, analysed and endorsed (evidenced by signature and date) by a competent clinical expert, containing a critical appraisal of this compilation, as per the legislative requirements.<sup>49</sup> It is recommended that reviews are prepared by researchers skilled in systematic review methods in conjunction with a clinical expert.

Where the review relies in part or wholly on literature for a 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.

For further guidance on performing a literature review see MEDDEV 2.7/1 revision 4 (section 9 and appendices 5 and 6).<sup>28</sup>

### **2.2.3. Post-market data**

Data from clinical experience, generally post-market data, can support the substantiation of the safety and performance claims of the device, help in identifying risks and guide risk assessment and risk management plans. Clinical experience data should be provided for pre- and post-market TGA reviews, and are particularly important where there may be a paucity of clinical data from other sources or when the data is not sufficiently robust to establish a favourable benefit-risk profile of the device. Post-market data may consist of investigation of complaints and individual vigilance reports, recalls or cancellations, registry data and literature reports or reviews.

### ***Adverse events and complaints***

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. In the case of a similar marketed device from a different manufacturer, publicly available data such as that from FDA's Manufacturer and User Facility Device Experience (MAUDE) database or TGA Incident Reporting and Investigation Scheme (IRIS) should be submitted. However, it is noted that one of the serious limitations of post-market adverse event and complaint reports is under-reporting by end-users. More information on reporting adverse events (and complaints) can be found on the [Database of Adverse Event Notifications - medical devices](#)<sup>50</sup> page on the TGA website.

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### ***Product recalls and cancellations***

Recall and cancellation information is also valuable. A recall takes place to resolve a problem with a device for which there are deficiencies or any other issues concerning safety, quality or performance. There are two key types of recall (a) correction, which may involve temporary removal from use for example, for changes to the IFU, and (b) permanent removal of deficient, defective or unsafe medical devices from use. More information about product recalls can be found on the [System for Australian Recall Actions](#) (SARA)<sup>51</sup> page on the TGA website. Suspensions, removals, withdrawals, cancellations or other corrective actions in any jurisdiction with the reasons for these should also be reported.

### ***Device registries***

Registries, systematic collections of data of medical outcomes, play a unique and important role in medical device surveillance. These can provide additional detailed information about patients, procedures, and devices not routinely collected by other means. Registries can provide valuable 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](#),<sup>52</sup> the Australian National Orthopaedic Association [National Joint Replacement Registry](#) (ANOANJRR)<sup>53</sup> and the [Victorian Cardiac Outcomes Registry](#).<sup>54</sup>

### ***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](#),<sup>55</sup> 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.

### ***Regulatory approval in other jurisdictions***

If the device is approved for use in another jurisdiction the manufacturer should provide regulatory status, including the certificate number, date of issue and name under which the device is marketed. The exact wording of the intended purpose and any specific conditions in other jurisdictions should be provided. If MRI designation in other jurisdictions is provided, this will improve the efficiency of the assessment.

### ***Post-market data to 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 (or unit demand) worldwide since launch stratified by country (particularly if numbers are small) or geographic region. Note: this may not always be appropriate for high use devices, those with several components or those on the market for many years.
- The number and types of complaints to the manufacturer regarding the device, both as reported and as confirmed on analysis and, in the case of new devices, stratified by year of occurrence of complaint.
- The total number of adverse events and vigilance data reported to regulatory agencies, both as reported and as confirmed on analysis and categorised by type (e.g. device malfunction, use error, inadequate design or manufacture) and clinical outcome (e.g. death, amputation,

surgical procedure required, no harm to patient). These should be stratified by year of supply and/or year of occurrence of event.

- Any regulatory actions such as voluntary or mandatory recalls, including recalls for product correction, removals, suspensions, withdrawals or other corrective actions occurring in the market for IFU changes or other reasons and cancellations of the device anywhere in the world.

Together this data should be compiled into an adverse event, vigilance report and a device complaint rates which will allow the clinical assessor to better evaluate the benefit-risk profile of the device. The CER should include an analysis and commentary on the profile, severity and frequency (rate) of events reported. Adverse event and complaint data and rates should be discussed and critiqued to enable an understanding of the safety profile of the device in a 'real-world' setting. If the manufacturer 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 first approval worldwide lengthens, the relevance of predicate data diminishes and should be replaced by data for the device itself. The manufacturers should clearly indicate whether the data reported is for the device or a predicate/similar marketed device.

## 2.3. Evaluation of the clinical data

The clinical data should be evaluated to identify potential sources of bias that may influence the results of the clinical investigations and 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:

**Table 1: Commonly used quality appraisal tools**

Tool	Applicable study designs	Source
Jadad Score	Randomised studies	<a href="https://www.ncbi.nlm.nih.gov/pubmed/8721797">https://www.ncbi.nlm.nih.gov/pubmed/8721797</a>
Downs & Black	Randomised & non-randomised studies	<a href="http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/">http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/</a>
QUADAS	Studies of diagnostic accuracy	<a href="http://www.bris.ac.uk/quadas/">http://www.bris.ac.uk/quadas/</a>
AMSTAR	Systematic reviews	<a href="http://amstar.ca/">http://amstar.ca/</a>

Additional guidance on critical appraisal tools is provided by the [Scottish Intercollegiate Guidelines Network \(SIGN\)](#),<sup>56</sup> the [Centre for Evidence-Based Medicine \(CEBM\)](#),<sup>57</sup> and the [Cochrane Collaboration's Handbook for Systematic Reviews of Interventions](#).<sup>58</sup> 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.

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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.<sup>59</sup> The levels of evidence rank different study designs into a hierarchy according to their potential to adequately answer a particular research question (e.g. diagnostic, intervention, screening etc.). The hierarchy is based on the level of bias inherent in the study design. Using this hierarchy, systematic reviews of randomised controlled trials represent the 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. Manufacturers should 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 CER. 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. The manufacturer should present data on risk of bias of each study and outcome level assessments. The results of any assessment of risk of bias across studies (e.g. publication bias, selective reporting within studies) should also be presented where such information is available. Funding sources should be included if it is one of variables for data extraction.

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

- a. Lack of information on elementary aspects**
- b. This includes reports and publications that omit disclosure of
  - the methods used
  - the identity of products used
  - numbers of patients exposed
  - what the clinical outcomes were
  - all the results the clinical study or investigation planned to investigate
  - undesirable side-effects that have been observed
  - confidence intervals/ calculation of statistical significance
  - if there are intent-to-treat and per protocol populations: definitions and results for the two populations
- c. Numbers too small for statistical significance**
- d. Includes publications and reports with inconclusive preliminary data, inconclusive data from feasibility studies, anecdotal experience, hypothesis papers and unsubstantiated opinions.
- e. Improper statistical Methods**
- f. This includes

- results obtained after multiple subgroup testing, when no corrections have been applied for multiple comparisons.
- calculations and tests based on a certain type of distribution of data (e.g. Gaussian distribution with its calculations of mean values, standard deviations, confidence intervals, t-tests, others tests), while the type of distribution is not tested, the type of distribution is not plausible, or the data have not been transformed. Data such as survival curves, e.g. implant survival, patient survival, symptom-free survival, are generally unlikely to follow a Gaussian distribution.

**g. Lack of adequate controls**

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

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

- i. In the situations described above, it is generally not adequate to draw conclusions based on direct comparisons with external or historic data (such as drawing conclusions by comparing data from a clinical investigation with device registry data or with data from published literature).
- j. Different study designs may allow direct comparisons and conclusions to be drawn in these situations, such as randomised controlled design, cross-over design, or split-body design.

**k. Improper collection of mortality and serious adverse events data**

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

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retrieval of medical information should be obtained during recruitment; when subjects can no longer be found, outcomes should be investigated with the reference persons/ institutions;

- the consequences of missing data on the results should be analysed (e.g. with a sensitivity analysis); alternatively, when patients can no longer be found and their outcomes cannot be identified, they should be considered to meet the SAE endpoint under investigation (e.g. the mortality endpoint of a study).
- m. In mortality studies (and other studies addressing serious outcomes) procedures for investigating serious patient outcomes, numbers of subjects lost to follow-up, reasons why subjects leave the study, and the results of sensitivity analysis should be fully disclosed in reports and publications.

**n. Misinterpretation by the authors**

- o. Includes conclusions that are not in line with the results section of the report or publication, such as
  - reports and publications not correctly addressing lack of statistical significance/ confidence intervals that encompass the null hypothesis.
  - effects too small for clinical relevance.

**p. Illegal activities**

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



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## 3. Clinical evaluation report and supporting documents



- Clinical evaluation is an ongoing process conducted throughout the lifecycle of a medical device. 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 has been on the market for a number of years, the relevance of comparisons to predicates or similar marketed devices is less significant, and post-market data is likely to be of greater relevance.

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 (including labelling, patient information and IFU) of the medical device when used for the intended purpose(s). This section provides an overview of the recommended content and format of the clinical evaluation report (CER) which may be requested by the TGA for pre- and post-market reviews. The CER should be updated as needed through the lifecycle of the device to incorporate new evidence including post-market data and updated risk/benefit analyses. A record of reviews and amendments should be kept, and the CER submitted with the device application or for post market review must be up to date (usually within at least two years).

### 3.1. Content and format of the report

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. Manufacturers should refer to the GHTF document Clinical Evaluation SG5/N2R8:2007<sup>60</sup> and MEDDEV 2.7/1 revision 4<sup>28</sup>. These have been adapted for this section.

The recommended structure of the CER is provided below, and checklists for these are in Appendix 1:

1. [Device description, lineage and version if applicable](#)
2. [Intended purpose/indications and claims](#)
3. [Regulatory status in other countries](#)
4. [Summary of relevant pre-clinical data](#)
5. [Demonstration of substantial equivalence \(if applicable\)](#)
6. [Overview and appraisal of clinical data](#)
7. [Critical evaluation of clinical data including post market data](#)
8. [Risk-benefit analysis](#)
9. [Conclusions](#)
10. [The name, signature and curriculum vitae of the clinical expert and date of report](#)



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## **Device description, lineage and version (if applicable)**

Manufacturers should identify the device by its proprietary name, and any code names assigned during its development and provide a description of the device including the models, sizes and device group to which the device belongs (e.g. biological artificial aortic valve). The description should also include 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 and 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. The description should be detailed enough to allow for a valid evaluation of compliance with EPs, retrieval of meaningful literature and, if applicable, assessment of equivalence to other devices described in the literature, or alternatively, the novelty of the design, features or mechanism of the device. If the application is for a multi-component procedure pack, each component in the system must be adequately described.

## **Intended 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 managed, 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 environment not evaluated') should be provided for all implantable devices (and components of these devices which may be taken into the MR scanner room). Consideration should be given 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.

## **Regulatory status in other countries**

The CER 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, including for product correction, withdrawn, suspended, removed or cancelled should be listed including the reasons for the action.

The exact wording of the intended purpose in other jurisdictions should be provided. It is preferable that certificates of conformity in other regulatory jurisdictions (e.g. CE marking, FDA, Health Canada) be provided including the number and date of issue of international certificates, as these allow verification of post-market data (e.g. through search of FDA's Manufacturer and User Facility Device Experience (MAUDE)), and may increase confidence in performance and safety claims. The trade name(s) of the device in other regulatory jurisdictions should also be clearly stated, if different from the name used in Australia. If the device has evolved from predicate/s over time the number and dates of certificates for these may be useful in exploring the history of the device. Information on concurrent applications for registration in the other jurisdictions, particularly Europe, the USA and Canada, is helpful if available.

## **Summary of relevant pre-clinical data**

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

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may include an assessment of the adequacy of pre-clinical testing (e.g. bench testing including verification and validation, animal testing) to verify safety and performance for any claims made in the device labelling not adequately substantiated by the clinical data.

### **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 manufacturers 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 Section 4: [Demonstrating Substantial Equivalence](#). Where indirect evidence is presented, the clinical expert must carefully and comprehensively critically evaluate whether there is potential for an adverse impact attributable to the differences between the device and any chosen comparators and include the conclusion based on this analysis in the CER. 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.

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 and/or provide clinical investigation data 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 and decide whether these data still present an accurate, current picture of medical knowledge for this product or treatment method. 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 were generated.



#### **Note**

The CER 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.

### **Overview and appraisal 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, a literature review and/or post-market data (clinical experience) with the device or predicate/similar marketed device with which the manufacturer is claiming substantial equivalence. The CER should include a summary of all the clinical data, including post-market data, with the full clinical investigation reports, literature search and selection strategy provided in the supporting documents. For further information refer to section 2.2.4 and MEDDEV 2.7/1 Rev 4 appendix 6, Appraisal of clinical data.

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## Critical evaluation of clinical data including post market 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 for example. 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 sections [2.2.1](#) and [2.3](#).



- 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.
- It must also be explicitly clear to the clinical assessor whether direct (pertaining to the device) or indirect (pertaining to a predicate or similar marketed device) data are provided. 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.

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

## Risk-benefit analysis

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

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

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

## Conclusions

Essential Principle 14 states that the manufacturer must hold clinical evidence that demonstrates compliance with the other EPs. The conclusion of the CER 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 data on the device and/or predicate/similar marketed device demonstrated to be substantially equivalent which is supportive of the safety and performance of the device
- Confirmation that any differences between the device and the predicate/similar marketed device used for comparison will not adversely affect the benefit risk profile
- Clinical evidence demonstrates the device performs as intended
- Post-market data shows an 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 undesirable effects of the device.

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

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

As stated in Schedule 3 Part 8.6 of the MD regulations:[61](#)

#### Evaluation of clinical data

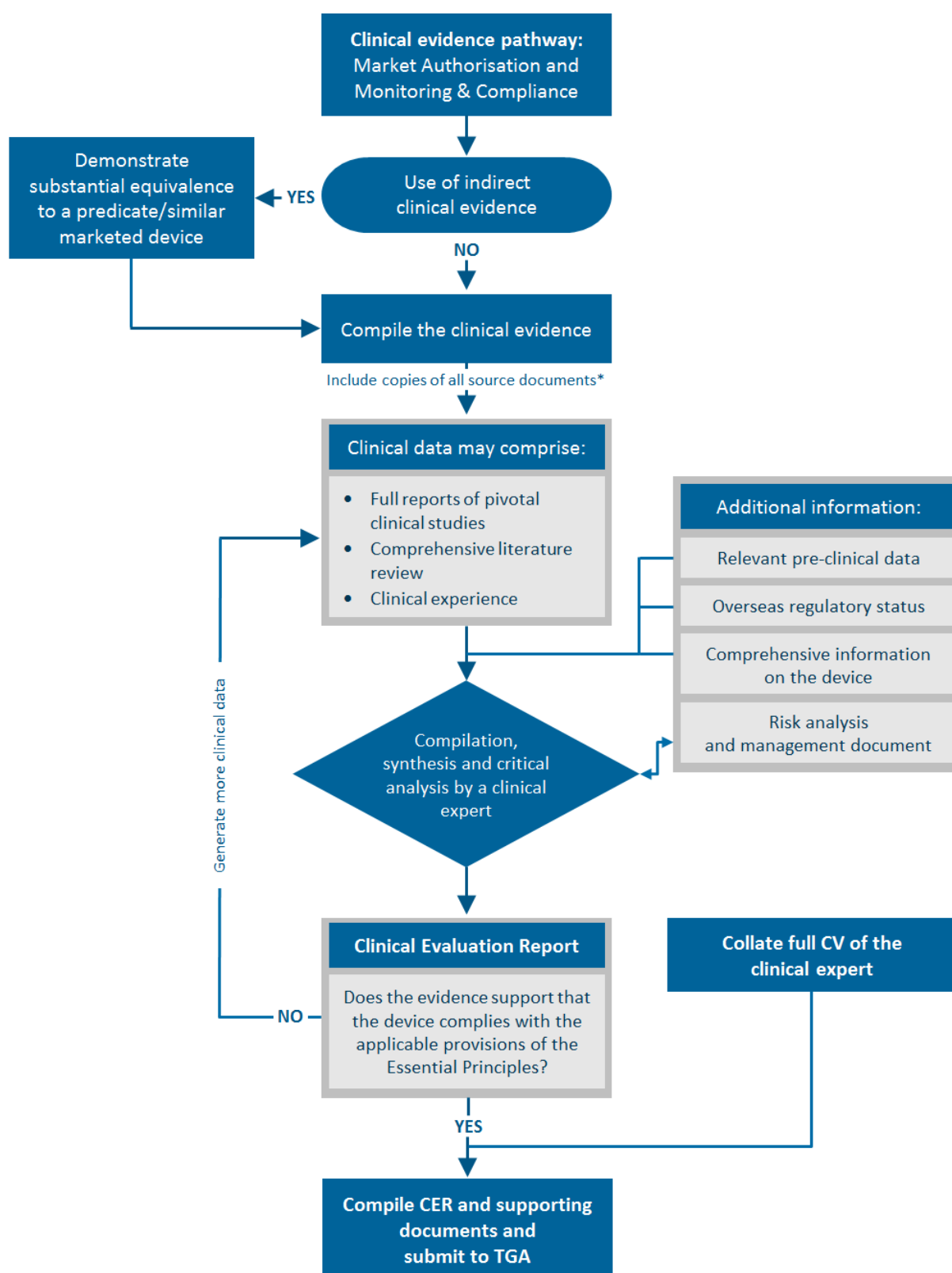
- 1) The manufacturer of a kind of medical device must ensure that the clinical data is evaluated by competent clinical experts.
- 2) The manufacturer must ensure that clinical evidence demonstrating that the device complies with the applicable provisions of the essential principles is documented in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

The name and signature of the clinical expert and the date of signing should be provided clearly demonstrating that he/she has evaluated all the clinical data and endorses all of the CER. A 'competent clinical expert' is someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting. For novel devices, the clinical expert's clinical experience with the device type is expected to be current or recent (preferably within the past two years), to provide confidence in their experience with the current iterations of medical devices that often evolve rapidly with significant changes in functional characteristics and implantation procedures. 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 an 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 should be included with any convergence of interests or potential for conflict with the manufacturer or sponsor noted. For lower class devices which are not typically used by medical practitioners, another health practitioner who uses the device or similar devices in a clinical setting may be deemed, on a case by case basis, as an appropriate clinical expert who is able to critically evaluate all the clinical data and endorse the CER (evidenced by signature and date).

## **3.2. Constructing the CER**

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

**Figure 1: Flow chart for constructing a CER**



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

### 3.3. Supporting documents

The following information on the device must also be provided for pre-market (conformity assessment reviews and applications for inclusion) and post-market reviews in addition to the CER:

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

#### 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. The manufacturer should ensure that all risks identified in the clinical data are included in the risk assessment, that is, all risks relating to patient treatment, method of operation of the device including potential device failures, and risks relating to usability i.e. harm to the patient that results from use of the device but is not caused by the device itself.

Device-related hazards include, but are not limited to, chemical, mechanical, thermal, electrical, radiation, and biological hazards. Use-related hazards<sup>62</sup> refer to hazards associated with user interactions with the device, and include but are not limited to hazards that occur when the device is used as intended by appropriately trained clinicians but there are inherent risks associated with the procedure or use of the device, when the device is not used as intended, users are not suitably trained or equipped to use the device, users are not capable of using the device, or when the user's expectations about the device are not consistent with the intended use of the device.

All ongoing safety concerns (risks) should be specified as to potential causes, the nature, probability, extent, duration, frequency and severity of occurrence. This type of analysis should commence before beginning product development as it generates the safety requirements for the design specification. Once all potential hazards arising from the use of the device for its intended purpose(s) in the target population have been identified, the manufacturer is expected to implement a Quality Management System (QMS) to mitigate and monitor these undesirable effects and hazards.

Strategies to mitigate and minimise these risks such as contraindications or warnings in the IFU, check lists, educational initiatives, patient cards and any others documents supplied with the device should be discussed, including the expected impact of these risk mitigation and minimisation strategies. The manufacturer 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. Sufficient details of the QMS should be provided so that the clinical expert who reviews and endorses the CER can determine whether the potential hazards and undesirable effects associated with the device are being minimised and mitigated adequately. A discussion highlighting how this has been done should be included in the CER.

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<sup>63</sup> can provide further guidance on this.

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## Instructions for use, labelling and documents supplied with the device

Comments on any issues relating to the IFU, product manuals, patient cards, labelling and promotional materials or other documents supplied with the device should be provided in the CER with an assessment by the clinical expert as to whether these are consistent with the clinical data, with particular attention paid to indications for use, target population, contraindications and adverse events. The IFU should include all identified hazards and other clinically relevant information that may impact on the use of the device and sufficient warnings to mitigate risks where possible. Foreseeable safety or performance concerns that may arise from the hazards identified in the IFU, labelling and other documents should have been flagged and incorporated into the overall benefit-risk analysis, and the content of the IFU should take into account who may use the device. For example, self-use devices may require an IFU that is aimed at a different audience compared with devices intended to be used by a medically qualified person.

### Additional information

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

- [Additional information on the device](#)
- [Preclinical data \(if relevant\)](#)
- [Full clinical investigation reports](#)
- [Literature search and selection strategy](#)
- [Full text of pivotal articles from literature review](#)



#### Note

When available, the clinical assessment report from acceptable European notified bodies may aid timely clinical review of the submission.

### *Additional information on the device*

The description of the device should include sufficient detail to satisfying the requirements of Appendix 3 of MEDDEV 2.7.1 Rev 4<sup>28</sup> on “Device description – typical contents”.

### *Preclinical data (if relevant)*

Medical devices may contain elements that cannot be assessed solely through clinical testing, but which are critical to the safety or performance of the device. In such cases, a concise summary of the preclinical data may be required to establish the safety and performance profile for the device. In some cases it may be relevant to include a summary of the following in the supporting documents when recommended for the device type by relevant ISO technical specifications, standards or by other international regulatory agencies such as the US FDA:

- physical and chemical analyses
- engineering assessment
- sterilisation and stability
- microbiology



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- in vivo and in vitro testing
  - engineering studies under simulated conditions of use
  - modelling data
  - Good Laboratory Practices testing

**Note**

For applications for inclusion based on EU certification which are selected for clinical audit only, the TGA clinical assessor is not qualified to review the preclinical information. Such data should be assessed by a suitably qualified expert provided by the manufacturer, and where preclinical data is referenced, details on the type of preclinical testing performed on the device and the relevant standards to which the test adheres must be provided.

***Full clinical investigation reports***

Full reports for the 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 performance 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.

***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. The search strategy should include a summary justification as to how each citation did or did not fit the selection criteria for inclusion.

***Pivotal articles from the literature review***

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

**3.4. Common errors in the CER**

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

- Absence of the required components of the CER and/or referenced attachments and appendices missing
- Intended purpose(s), indication and claims inconsistent between documents i.e. application, IFU and CER list different intended purpose(s)
- Intended purpose(s), indication and claims not supported by clinical data

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- Lack of information about the regulatory history of the device in other countries, for example recalls, withdrawals, removals from market, suspensions and cancellations and the reasons for these in any jurisdiction
  - Information on predicate or previous related devices not included and/or substantial equivalence not demonstrated (if relevant)
  - Insufficient or incomplete clinical investigation(s) data, literature and post-market data with the device or predicate/similar marketed device if relevant.
  - In submissions where a literature review is provided there is:
    - No documented method and/or no demonstrated comprehensive literature review
    - Insufficient information and/or poor quality search protocol that result in inability to reproduce or understand the literature review strategy
    - Provision of a multitude of publications with little or no explanation as to why they are of relevance
    - No identification of device used or indication for use in articles reviewed
    - No summary of study characteristics and findings for each included article
  - Little or no synthesis and critical evaluation of the clinical investigation data, results of the literature review and post-market data:
    - No discussion of relative strengths of the data, for example randomised controlled trials, case control studies, case series
    - Substantial equivalence covering technical characteristics, biological characteristics and clinical use not established to validate the data for a different device (i.e. predicate or similar marketed device) to the device under review
    - Lack of discussion of the validity or otherwise of outcome measures used
    - No endorsement by the clinical expert that the differences will not adversely affect the safety or performance of the device
  - Inadequate critique and summary of the totality of evidence provided for the device
  - No post-market data including adverse events, vigilance reports, complaints, failures in cases where this information is available
  - 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 out-dated
  - Inappropriate selection of clinical experts. The clinical expert who critically evaluates the clinical data and endorses/signs (with date) the CER is expected to be someone with relevant medical qualifications and direct (and for newly developed devices recent) clinical experience in the use of the device or device type in a clinical setting. For some lower class devices which are not typically used by medical practitioners, another health practitioner who uses the device or similar devices in a clinical setting may be deemed, on a case by case basis, as an appropriate clinical expert who is able to critically evaluate all the clinical data and endorse the CER (evidenced by signature and date).

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- 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.

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 are provided for assessment. 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.

The clarity and comprehensiveness of the information provided with a medical device 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 harm ratio of the device.

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

## 4. Demonstrating substantial equivalence

### 4.1. 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.<sup>64</sup> 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 adverse 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. Equivalence should be based on a single device. If this is not possible substantial equivalence of every single device to the device

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under evaluation should be fully investigated, demonstrated and described in the CER.  
Reference MEDDEV 2.7/1 (Rev 4).<sup>28</sup>

#### 4.1.1. 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<sup>65</sup>:

***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:

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

The GHTF makes the following references to intended use:

“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.”<sup>66</sup>

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<sup>67</sup> 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.

#### 4.1.2. 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 evidence:

“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.**”<sup>66</sup> (emphasis added)

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## 4.2. Predicate and similar marketed devices

### 4.2.1. What is a predicate device?

A device may be regarded as a predicate device in relation to a device for the purposes of demonstrating substantial equivalence if all of these apply:

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



#### Note

This differs from the definition used by the FDA where the manufacturer of the predicate device is not required to be the same as the device under assessment.

### 4.2.2. What is a similar marketed device?

A device may be regarded as a similar marketed device in relation to a device for the purposes of demonstrating substantial equivalence if all of these apply:

- It is an existing marketed device
- has a similar structure and design as the device
- has the same intended purpose as the device
- 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 the predicate or similar marketed device. A predicate/similar marketed device should have clinical evidence available to support its safety and performance.

## 4.3. 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 clinical (intended purpose and patient population), technical and biological characteristics of the device.

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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.**”<sup>66</sup> (emphasis added)

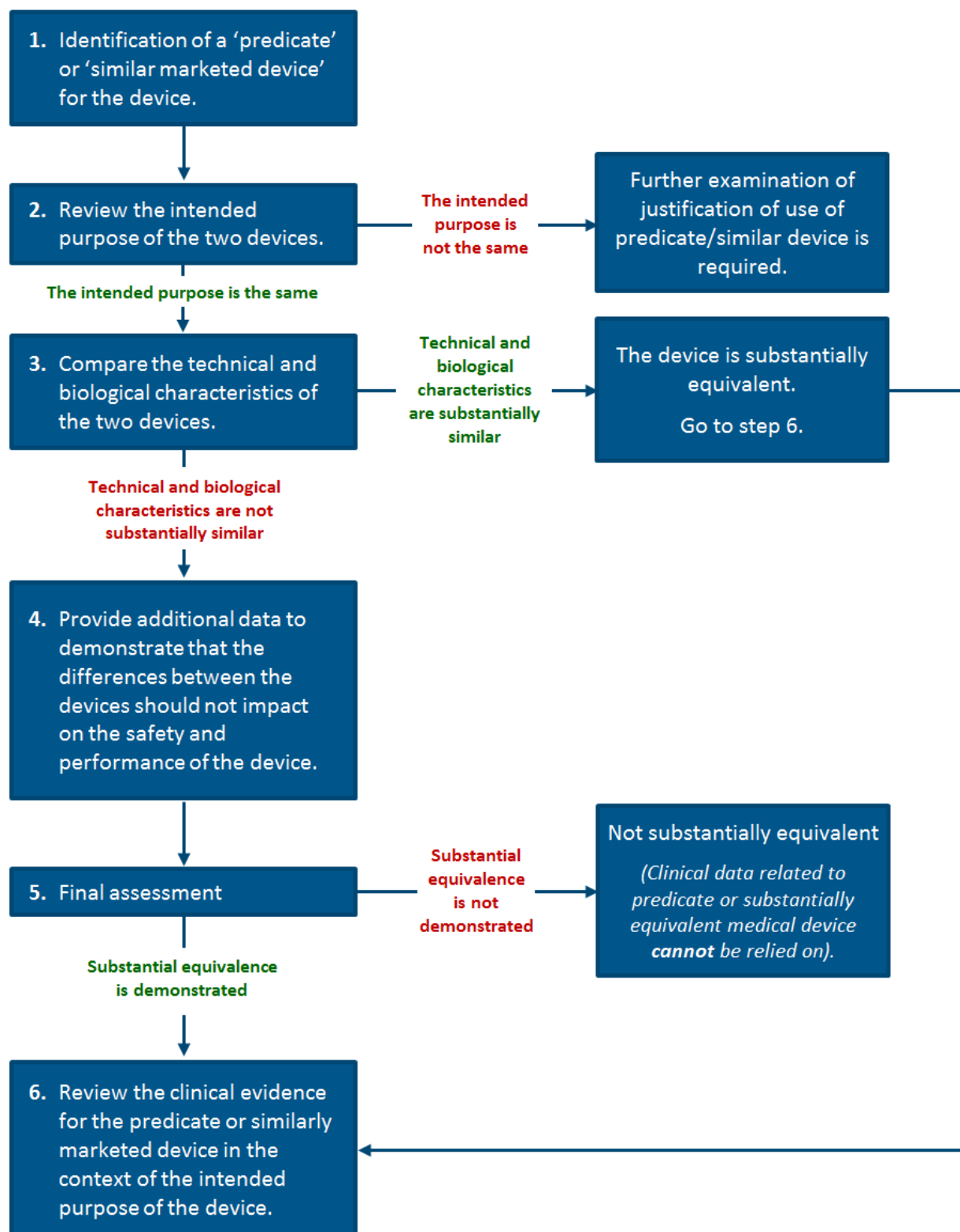
#### 4.3.1. Steps to demonstrate substantial equivalence

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 will only be suitable for inclusion on the ARTG if direct clinical evidence on the device is provided which demonstrates compliance to the EPs.

Any application that uses the substantial equivalence process should include a justification from a person with appropriate expertise relevant to the device under assessment to substantiate the proposal put forward by the manufacturer at each step of the substantial equivalence process. In addition it is critical that a clinical expert, specifically someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting, justifies that any differences between the device and the device(s) claimed to be substantially equivalent will not have an adverse effect on the safety, quality and performance of the device. A full curriculum vitae of the clinical expert should be provided.

The following flowchart provides guidance to manufacturers on how to demonstrate substantial equivalence with a predicate device or similar marketed device. *(Next page)*

**Figure 2: Demonstrating substantial equivalence**



### ***Step 1: Identification of a predicate or similar marketed device***

The manufacturer 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

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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 market under the jurisdiction of a comparable regulatory authority due to safety concerns (or when a proposal to cancel due to safety concerns prompts a voluntary recall) are not suitable comparisons. It is incumbent upon manufacturers to be aware of any safety concerns related to the predicate or similar marketed device. If the manufacturer 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 relates to the clinical condition being treated, the severity and stage of disease, the patient population and the site of application to/in the body. This should be clearly stated and provided in the manufacturer or 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 manufacturer or sponsor of the device is applying, and
- the other steps of the substantially equivalent process have been met.

### ***Step 3: Compare the technical and biological characteristics***

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

**“Technical characteristics** relate to the design, specifications, physicochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use and **Biological characteristics** relate to biocompatibility of materials in contact with body fluids/tissues.” <sup>66</sup>

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 technical and biological characteristics as the predicate or similar marketed device. A device that does not have substantially similar technical characteristics as the predicate or similar marketed device may only be considered suitable for the substantial equivalence process if the manufacturer can demonstrate that the differences between the



devices do not adversely impact on the safety and performance of the device in question (refer to [Step 4: Provision of additional data](#)).

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



#### What is considered substantially equivalent?

To be considered substantially equivalent, the differences in the technical and biological characteristics between the predicate/similar marketed device and the device should be minimal. Furthermore, these minimal differences should not be expected to adversely 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 technical 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

**Table 2: Example summary table**

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

Evidence presented	The Device	Predicate or similar marketed device	Impact of difference on safety and performance
<b>Biological characteristics</b>			
{e.g. biocompatibility}			

If the manufacturer considers the technical and biological characteristics of the device and predicate/similar marketed device to be substantially equivalent 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 technical 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 manufacturer to ensure that all information relating to the predicate/similar marketed device is provided for clinical assessment, in particular the clinical data which demonstrate safety and performance of the predicate/similar marketed device must be provided. The manufacturer may not have conducted the research, but they should ensure that the research method, clinical data and all information relevant to the assessment are included.

**If the manufacturer 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. The manufacturer should ensure there is robust clinical evidence to support equivalence where there are technical 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 manufacturer on a regular basis. If a safety concern is identified by the manufacturer for the predicate or similar marketed device which was used to demonstrate compliance with EP 14 for inclusion on the ARTG, the manufacturer 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.[68](#)

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## Part 2 - Requirements for specific high risk devices



### Disclaimer

Part 2 provides guidance to assist industry and clinical researchers to understand TGA's (current) requirements for clinical evidence for particular kinds of high risk medical devices.

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 19](#) 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
- Implantable pulse generators
- Heart valve replacements using a prosthetic valve
- Supportive Devices - Meshes, Patches and Tissue Adhesives

There is also a specific section entitled [Implantable medical devices in the magnetic resonance environment](#).

Manufacturer and sponsors are advised to read this guidance in conjunction with earlier sections outlining general clinical evidence requirements for all devices, including:

- [Legislative basis](#) (Introduction)
- [Clinical evidence](#) (Section 2)
- [Clinical evaluation report and supporting documents](#) (Section 3)
- [Demonstrating Substantial Equivalence](#) (Section 4)

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## 5. Total and partial joint prostheses

Joint prostheses include devices used in 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.<sup>69 70</sup> 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<sup>2</sup> of the MD Regulations.

### 5.1. Summary recommendations

- Joint prostheses are complex medical devices that can be used in combination with other devices or components. Manufacturers are advised to list the common combinations and provide clinical data to support the safety and performance of the device for these nominated configurations.
- For clinical evidence based on an evaluation of predicate or similar marketed device data, manufacturers are advised to submit all relevant documents with a supporting justification by a clinical expert to:
  - establish substantial equivalence between the device and the nominated predicate or similar marketed device, and
  - confirm that any identified differences will not adversely affect safety and performance of the device.
- Manufacturers should provide details of the clinical context within which the clinical data were obtained. The clinical context of the data should be congruent with the indications for use.
- Provision of clinical data:
  - manufacturers who intend to conduct clinical trials should design trials to the highest practical NHMRC level of evidence and trials should be appropriate to inform on the safety and performance of the device for its intended purpose
  - it is recommended that the minimum period for patient follow-up for clinical trials is two years (for reimbursement a defined number of patients are expected to have reached 2 years follow-up)
  - the main clinical outcomes that determine safety and performance are time to first revision and patient scores such as the Harris Hip Score:
    - for revision data, the manufacturers are advised to benchmark the device against devices of the same class as reported by an international joint registry
    - for patient performance data, manufacturers are advised to define the anticipated improvement in patient scores post-surgery (ideally, these should be internationally recognised assessment tool(s) used to measure clinical success)
  - to assess the risk of delayed need for revision surgery, (that is in vivo times greater than two years), the manufacturers should consider using surrogate markers that are predictive of prosthesis failure - alternatively, manufacturers may use post-market data if the device is approved and marketed in Australia or elsewhere

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- when submitting a comprehensive literature review, full details of the search method used should be included with or in the CER with sufficient detail to enable the review process to be reproduced by clinical assessors
  - a well-documented risk analysis and management system should also be provided. All risks identified in the clinical data (investigational, literature and post-market data) should inform and be reflected in the risk documentation. These risks should be rated and quantified before risk reduction activities are assigned such as statements in the IFU and training are implemented to reduce residual risks.
  - For guidance on the conduct of comprehensive literature reviews and on the compilation and presentation of clinical evidence manufacturers are directed to the relevant sections in this document.
  - Compilation of the CER:
    - in compiling the clinical evidence for a joint prosthesis the manufacturer should ensure that a clinical expert, that is someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting, critically evaluates all the clinical data that informs on the safety and performance of the device
    - the clinical expert must review and endorse the CER (evidenced by signature and date) containing the clinical evidence which is sufficient to demonstrate that the requirements of the applicable EPs have been met and the device is safe and performs as intended.

## 5.2. 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<sup>65</sup>

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

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

Joint prostheses pose a significant regulatory challenge because these devices need to have a long *in vivo* life without exposing the patient to unduly high risks of adverse events or undesirable effects.

### 5.3. Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device and/or the predicate or similar marketed device. The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data. Manufacturers should refer to Section 2: [Clinical Evidence](#) for more information.

Direct clinical evidence on the actual device is preferred. 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 Section 4: [Demonstrating Substantial Equivalence](#).

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. Where the device and the predicate share a common design origin, particularly when the device is part of a modular system, the lineage of devices with the same intended purpose should be provided as well.

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## 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.

The characteristics of the prosthesis and the intended purpose(s) are essential to the design of an investigation therefore, when investigations involve a predicate or similar marketed device, direct comparisons of the technical and biological characteristics of the joint prosthesis and the comparator should be demonstrated through testing in order to establish substantial equivalence. 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. The clinical expert should confirm that any identified differences will not adversely affect safety and performance of the device.

Manufacturers are advised to justify the patient numbers recruited according to sound scientific reasoning through statistical power calculation. Some examples of RCTs involving joint prostheses include the UK Knee Arthroplasty Trial (KAT)<sup>71</sup> and the A JOINTs Canada Project.<sup>72</sup>

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

Additional resources regarding the design and conduct of clinical investigation(s) are available on the clinical trial pages of the TGA<sup>73</sup> and FDA<sup>74</sup> 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 [Section 2](#).

## 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 Section 4: [Demonstrating Substantial equivalence](#).

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. A full description of the device used in any given study or adequate information to identify the device (e.g. manufacturer name and model number) should be extractable from the study report. If this is not possible, the study should be excluded from the review.

Section 2: [Clinical Evidence](#) describes the process of performing a literature review, summarised briefly below. As a minimum a literature review should include:



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- 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 on 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 literature report should be prepared which must be critically evaluated and endorsed (evidenced by signature and date) by a competent clinical expert, containing a critical appraisal of 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 to which substantial equivalence has been established, refer to Section 2.2.3: [Post-market data](#).

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 name under which the device is marketed in key jurisdictions such as Canada, USA and Japan, certificate number, date of issue, the exact wording of the intended purpose/approved indication and other relevant details such as MRI designation in other jurisdictions
- any regulatory action including withdrawals, recalls, including recalls for product correction (and the reason for these, such as IFU changes) cancellations or any other corrective actions occurring in the market in any jurisdiction as reported or required by regulatory bodies
- distribution numbers [75](#) of the device(s) including distribution by country and/or geographical region for every year since launch. This may not always be appropriate for high volume devices, those with several components and those which have been on the market for many years
- number of years of use
- for every year since launch, [75](#) the number of complaints, vigilance and monitoring reports and adverse events categorised by type and clinical outcome (e.g. death, serious harm, revision due to loosening, fracture, implant breakage, etc.)
- the post-market surveillance data from national registries from 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 [76](#) as well as Australia.
- explanted joint prostheses returned to manufacturers should be accounted for with an explanation of failures and corrective measures.

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



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

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

## 5.4. Compiling the CER

In compiling the clinical evidence the manufacturers should ensure that a competent clinical expert critically evaluates all the clinical data from clinical investigation(s), literature review and/or post-market data and endorses the CER (evidenced by signature and date), to demonstrate that the clinical evidence is sufficient to comply with the applicable EPs and that the device is safe and performs as intended.

Earlier sections outline the process for collecting clinical data and evaluating the data to derive the clinical evidence and the recommended content and format of the CER. Guidance on defining a predicate or similar marketed device is provided in Section 4: [Demonstrating Substantial Equivalence](#). As time since first approval lengthens predicate data becomes less relevant and should be replaced by data derived from clinical experience with the device.

As per Section 3: [Clinical evaluation report and supporting documents](#) the CER should include the following:

1. [Device description, lineage and version if applicable](#)
2. [Intended purpose/indications and claims](#)
3. [Regulatory status in other countries](#)
4. [Summary of relevant pre-clinical data](#)
5. [Demonstration of substantial equivalence \(if applicable\)](#)
6. [Overview and appraisal of clinical data](#)
7. [Critical evaluation of clinical data including post market data](#)
8. [Risk-benefit analysis](#)
9. [Conclusions](#)
10. [The name, signature and curriculum vitae of the clinical expert and date of report](#)

### Supportive data and information

The following information on the device must also be provided:

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

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

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

## 5.5. Defining clinical success

### Safety

For safety, the primary outcome measure is revision, with revision meaning the replacement of a prosthetic component, refer to Table 4. 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)<sup>53</sup> provides annual reports on the performance of joint prostheses for hip, knee and shoulder and provides the CPR for joint prostheses.



If clinical investigations are conducted, it is recommended that the minimum patient follow-up is two years: this is based on the internationally accepted consensus of orthopaedic surgeons and editors of orthopaedic journals.<sup>77</sup> 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.<sup>78</sup> This supports the concept of the two year minimum patient follow-up in clinical trials. However, manufacturers should be aware that this is the minimum and will not capture information relating to the late failure of a prosthesis. In this situation, manufacturers can assist the clinical assessors by providing adjunct data from surrogate markers. The choice of markers and a justification that these are predictive of future prosthesis failure should be clinically justified.

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

- identify the published early CPR as documented in the AOANJRR (or other national registries) for devices that are in the same class as the device

- determine whether the device or the 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 [79 80](#)
  - 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.[81](#)



#### Note

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

## Performance

Performance related parameters reported in the peer reviewed literature for hip, knee and shoulder prostheses are provided in Table 5.

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

The recommended two year minimum patient follow-up is congruent with the reported time to a stable output for two validated patient scores (these being the Harris Hip Score (HHS) and the Short Form-36 Health Survey (SF 36)). These scores have the greatest change in the first six months post-surgery for patients that have received a unilateral primary total hip replacement and peak or plateau at 18 months and remain high for 5 years.[82](#)



### Note

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

Ideally, manufacturers should define both a Minimum Clinically Important Difference (MCID) and the success margin that can be used to evaluate clinical success. Indicative MCIDs and the expected improvement in function score post-operatively, as well as standardised rating scores are provided for some but not all functional scores, refer to Table 6. 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.

## 5.6. Summary of safety and performance data

### Characteristics of clinical studies of hip, knee and shoulder prostheses

**Table 3: 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 <i>Three systematic reviews</i> <i><a href="#">83</a> <a href="#">84</a> <a href="#">85</a></i>	Knee <i>Five systematic reviews</i> <i><a href="#">86</a> <a href="#">87</a> <a href="#">88</a> <a href="#">89</a> <a href="#">90</a></i> <i>One RCT <a href="#">71</a></i> <i>One registry trial <a href="#">91</a></i>	Shoulder <i>Two systematic reviews</i> <i><a href="#">92</a> <a href="#">93</a></i> <i>Two registry trials <a href="#">94</a> <a href="#">95</a></i>
Number of included studies per systematic review	4 to 236	5 to 34	7 to 29
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

Characteristic of included studies	Hip <i>Three systematic reviews</i> <a href="#">83</a> <a href="#">84</a> <a href="#">85</a>	Knee <i>Five systematic reviews</i> <a href="#">86</a> <a href="#">87</a> <a href="#">88</a> <a href="#">89</a> <a href="#">90</a>  <i>One RCT</i> <a href="#">71</a>  <i>One registry trial</i> <a href="#">91</a>	Shoulder <i>Two systematic reviews</i> <a href="#">92</a> <a href="#">93</a>  <i>Two registry trials</i> <a href="#">94</a> <a href="#">95</a>
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
<b>Patient Follow-up</b>			
Comparative trials e.g. RCTs	3 – 10 years	Immediately post-operative to 19 years. Most at 10 years	2 to years extending out to 19 years
Registry trial	10 years	10 years (median 2.8 years)	1 year extending out to 4 to 7 years

### Reported clinical outcomes of hip, knee and shoulder prostheses

**Table 4: Summary of safety data extracted from systematic reviews on safety and performance of hip, knee or shoulder arthroplasty**

Safety parameter	Hip <i>Three systematic reviews</i> <a href="#">83</a> <a href="#">84</a> <a href="#">85</a>	Knee <i>Five systematic reviews</i> <a href="#">86</a> <a href="#">87</a> <a href="#">88</a> <a href="#">89</a> <a href="#">90</a>	Shoulder <i>Two systematic reviews</i> <a href="#">92</a> <a href="#">93</a>
All cause revision/reoperation (time to first revision and revision rates)	✓	✓	✓

Safety parameter	Hip <i>Three systematic reviews</i> <a href="#">83</a> <a href="#">84</a> <a href="#">85</a>	Knee <i>Five systematic reviews</i> <a href="#">86</a> <a href="#">87</a> <a href="#">88</a> <a href="#">89</a> <a href="#">90</a>	Shoulder <i>Two systematic reviews</i> <a href="#">92</a> <a href="#">93</a>
<b>Revision diagnosis</b>			
Dislocation	✓		✓
Septic loosening	✓	✓	✓
Aseptic loosening	✓	✓	✓
Fracture	✓		✓
Postoperative alignment	✓	✓	
Wear/erosion			✓
<b>Surrogate markers for safety</b>			
Radiostereometric analysis (RSA)		✓	
Radiological findings (radiolucent lines)	✓	✓	

**Table 5: 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 <i>Three systematic reviews</i> <a href="#">83</a> <a href="#">84</a> <a href="#">85</a>	Knee <i>Five systematic reviews</i> <a href="#">86</a> <a href="#">87</a> <a href="#">88</a> <a href="#">89</a> <a href="#">90</a>  <i>One RCT</i> <a href="#">21</a> <i>One registry trial</i> <a href="#">21</a>	Shoulder <i>Two systematic reviews</i> <a href="#">92</a> <a href="#">93</a>  <i>Two registry trials</i> <a href="#">94</a> <a href="#">95</a>
Revision/reoperation (time to first revision and revision rates)	✓	✓	✓

Performance parameter	Hip <i>Three systematic reviews</i> <a href="#">83</a> <a href="#">84</a> <a href="#">85</a>	Knee <i>Five systematic reviews</i> <a href="#">86</a> <a href="#">87</a> <a href="#">88</a> <a href="#">89</a> <a href="#">90</a> <i>One RCT</i> <a href="#">71</a> <i>One registry trial</i> <a href="#">91</a>	Shoulder <i>Two systematic reviews</i> <a href="#">92</a> <a href="#">93</a> <i>Two registry trials</i> <a href="#">94</a> <a href="#">95</a>
Function scores	✓ Harris Hip Score (HHS)	✓ 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)	✓ 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		✓ EuroQoL 5D SF12	✓ SF36
Minimum Clinical Important Difference (MCID) identified in collating evidence for this guidance report.	✓ HHS <a href="#">96</a> Oxford Hip Score (OHS) <a href="#">96</a> WOMAC <a href="#">96</a> EQ-5D <a href="#">96</a> SF 12	✓ OKS <a href="#">97</a> SF 36 <a href="#">98</a> <a href="#">99</a> SF 12 <a href="#">97</a> WOMAC <a href="#">99</a>	✓ WOOS <a href="#">94</a>

## Minimum clinically important differences (MCIDs)

If validated MCIDs are available, manufacturers should provide full documentation and justify their utility when assessing the safety of the device. Alternatively, meaningful MCIDs can be established using either an anchor-based or distribution-based approach. In this case, the manufacturer 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 safe as and to perform as well as a currently available device(s).

**Table 6: Example MCID and success margins for performance scores identified from systematic reviews and primary research reports on the safety and performance of hip, knee or shoulder arthroplasty**

Score	Grading	Success margin post-surgery	Minimum Clinical important Difference (MCID)
<b>Hip</b>			
Harris Hip Score (HHS)	Scale 0 to 100 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 <a href="#">96</a>
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) <a href="#">100</a>	range: 5 to 7 <a href="#">96</a>
Western Ontario and McMaster Osteoarthritis Index (WOMAC)			8 <a href="#">96</a>



Score	Grading	Success margin post-surgery	Minimum Clinical important Difference (MCID)
<b>Knee</b>			
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) <a href="#">100</a>	5 [95% CI 4.4 to 5.5] <a href="#">97</a>
Western Ontario and McMaster Osteoarthritis index (WOMAC)			for TKR: ~15 <a href="#">94</a>
<b>Shoulder</b>			
Western Ontario Osteoarthritis of the Shoulder Index (WOOS)			Primary Shoulder replacement: ~ 10% <a href="#">94</a>
Constant Shoulder Score	Ratings; >30 poor 21 to 30 fair 11 to 20 good <11 excellent		
<b>Quality of life</b>			
EQ 5D			Hip: 0.074 <a href="#">96</a>
SF12			4.5 [95% CI 3.9 to 5.2] <a href="#">97</a>
SF36			Multiple MCIDs for specific SF 36 domains <a href="#">98</a>

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## 6. 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.

### 6.1. Summary recommendations

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

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myocardial infarct (MI)); (b) a common primary outcome measure for coronary stents is target lesion revascularisation (TLR) and/or total vessel revascularisation (TVR); and (c) common primary outcome measures for IVC filters are PE (fatal and non-fatal), deep vein thrombosis (DVT) and occurrence of a venous thromboembolism (VTE) distal to the filter.

- It is advised that a clinical justification is provided to support the selection of the primary outcomes and if necessary the use of secondary outcomes or surrogate markers
  - The manufacturer is advised to benchmark the device against devices of the same class as reported in appropriate registers (if available) or provide direct comparative data comparing the device with similar marketed devices
  - For patient performance data, manufacturers are advised to define the anticipated improvement in patient scores post-surgery. Ideally, these should be internationally recognised assessment tool(s) used to measure clinical success, e.g. QoL or exercise stress test
- The manufacturers should consider using surrogate markers that are predictive of implant failure when in vivo times are longer than one year. For example, use of endoleak type II with aneurysm expansion to predict late failure of AAA. However, a clinical justification is needed to support the selection of surrogates and the predictive power of surrogates should be validated
  - It is recommended that the manufacturer supply post-market data if the device is approved and marketed in another jurisdiction to demonstrate long-term safety and performance outcomes
  - When submitting a comprehensive literature review, full details of the search method used should be included in the CER with detail sufficient to enable the review process to be repeated by clinical assessors
  - Risks identified in the clinical data should be appropriately mitigated and/or included in the IFU and other information supplied with the device.
- **Compilation of the CER**
    - in compiling the clinical evidence for a supportive device the manufacturer must ensure that an appropriate clinical expert, that is, someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting, critically evaluates all the clinical data that informs on the safety and performance of the device
    - the clinical expert must then endorse the CER (evidenced by signature and date) containing the clinical evidence to demonstrate that the evidence meets the requirements of the applicable EPs and the device is safe and performs as intended.

## **6.2. 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

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- Inferior vena cava (IVC) filters to prevent pulmonary embolism

### **Arterial stents-carotid, coronary and peripheral**

Arterial stents are metal mesh devices used to correct the pathological narrowing of an artery and to maintain patency e.g., in the neck, heart or vessels of the leg. The aim of a stent is to act as a scaffold to keep the artery open to maintain blood flow and prevent re-stenosis. Using an endovascular approach, a fine wire is inserted into the femoral artery (or other suitable vessel) and passed through the blood vessels into the artery with the blockage. The stent is passed along the wire, often after pre-dilation of the narrowing using a balloon catheter. Stents come in varying diameters, lengths, and shapes and may be self-expandable. They may be “bare metal” (without any coating, often made of stainless steel or cobalt chromium alloy) or “drug eluting” (coated with a drug such as sirolimus or paclitaxel to help prevent restenosis). [101](#) [102](#) [103](#)

### **Implants for abdominal aortic aneurysm (AAA) repair**

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

### **Implants for patent ductus arteriosus (PDA) repair**

Minimally-invasive transcatheter closure of PDAs has become the preferred method of treatment for children beyond the neonatal period, versus surgical closure with ligation or division of the ductus arteriosus through a thoracotomy incision. [104](#) [105](#) 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. [106](#) [107](#)

### **Inferior vena cava (IVC) filters**

IVC filters are intended to prevent pulmonary embolism. The filters are metal alloy devices, generally in an umbrella shape, that are inserted into the inferior vena cava in order to mechanically trap fragmented clots from the deep leg veins to prevent their movement to the pulmonary circulation. Filters are designed to be introduced percutaneously. The latest generation of filters are temporary or ‘retrievable’ and are designed to be removed 2 to 12 weeks after insertion (as specified by the manufacturer) if their use is no longer required. [108](#)

## **6.3. Clinical evidence**

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

It is important to clarify if any changes have been made to the device since the clinical data were gathered and if so to document the changes and to clarify the exact version of the device. Direct clinical evidence on the actual device is preferred. Otherwise indirect clinical evidence may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in Section 4: [Demonstrating Substantial Equivalence](#).

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Where the device and the predicate share any common design origin, the lineage between the devices should be provided as well as a list of other devices that may be used in conjunction with the new device for example the delivery system, such as the catheter system for stents, including any balloons. Manufacturers should refer to Section 2: [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. Manufacturers are advised to justify the number of patients recruited according to sound scientific reasoning through statistical power calculation.

The duration of the clinical investigation should be appropriate to the device and the patient population and medical conditions for which it is intended to be used. Duration should always be justified, taking into account the 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 Section 4: [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. A full description of the device used in any given study must be extractable from the study report or adequate information to identify the device (e.g. manufacturer name and model number). If this is not possible, the study should be excluded from the review.

Section 2: [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

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

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

### Post-market data

Post-market data can be provided for the actual device or for the predicate or similar marketed device, refer to Section 2: [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 other details such as MRI status in other jurisdictions
- any regulatory action including CE mark withdrawals, recalls, including recalls for product correction, suspensions, removals, cancellations, voluntary recalls in any jurisdiction (and the reason for these i.e. IFU changes) or other corrective actions occurring in the market as reported to or required by regulatory bodies
- distribution numbers of the device(s) including distribution by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- the number of years of use
- for every year since launch, the number of complaints, vigilance and monitoring reports and adverse events categorised by type and clinical outcome
- explanted devices returned to manufacturers should be accounted for with an explanation of device failures and corrective measures.

For further details refer to Section 2.2.3: [Post-market data](#). Publicly available post-market data such as adverse event reporting on the FDA MAUDE database and the TGA IRIS should be provided for all devices including those from other manufacturers. The manufacturers should include post-market surveillance data from national jurisdictions where the device is approved for clinical use.

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

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

## 6.4. Compiling the CER

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

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that the clinical evidence is sufficient to comply with the applicable EPs and that the device is safe and performs as intended.

Previous sections outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a CER. These guidance documents apply whether the manufacturer is using direct clinical evidence or relying on indirect clinical evidence for a predicate or similar marketed device. Guidance on defining a predicate or similar marketed device is provided in Section 4: [Demonstrating Substantial Equivalence](#).

As per Section 3: [Clinical evaluation report and supporting documents](#) the CER should include the following:

1. [Device description, lineage and version if applicable](#)
2. [Intended purpose/indications and claims](#)
3. [Regulatory status in other countries](#)
4. [Summary of relevant pre-clinical data](#)
5. [Demonstration of substantial equivalence \(if applicable\)](#)
6. [Overview and appraisal of clinical data](#)
7. [Critical evaluation of clinical data including post market data](#)
8. [Risk-benefit analysis](#)
9. [Conclusions](#)
10. [The name, signature and curriculum vitae of the clinical expert and date of report](#)

### **Supportive data and information**

The following information on the device must also be provided:

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

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

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

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- any further details of post market data

When relying on a predicate or similar marketed device for CV flow implants with the same intended purpose 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
- a supporting justification by a clinical expert is required to establish substantial equivalence between the device and the predicate or similar marketed device, and confirm that any identified differences in the technical and physical characteristics will not adversely affect safety and performance of the device
- the use of more than one 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 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 CER. As time since first approval lengthens predicate data becomes less relevant and should be replaced by data derived from clinical experience with the device.

## 6.5. Defining clinical success

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

### Arterial stents

Table 7 (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 7: 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 <b>OR</b> death or stroke or MI	✓ (1* outcome)	✓**	
TVR and/or TLR		✓ (1* outcome)	✓ (TLR)
Restenosis	✓	✓	✓
Stroke (disabling / major)	✓		
TIA	✓		
MI	✓	✓ (recurrent)	
Facial neuropathy / cranial nerve palsy	✓		
Death	✓	✓	✓
Stent thrombosis (definite or probable; also early or late)		✓	
MACE		✓	
Technical / procedural success		✓	✓
Vessel patency assessed via duplex US and/or angiography			✓
Reintervention			✓
Amputation			✓
Clinical improvement as per the Rutherford Scale			✓
Hemodynamic improvement			✓

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

**KEY:** MI=myocardial infarction, TLR=target lesion revascularisation, TVR=total vessel revascularisation, TIA=transient ischemic attack, MACE= major adverse cardiac events, US=ultrasound, SR=systematic review

\* Outcomes were often divided into <30 day (peri-procedural) or >30 day outcomes

\*\* Outcomes defined in the European Commission MEDDEV 2.7/1 and Academic Research Consortium

## Coronary stents

Outcomes were often divided into <30 day (peri-procedural) or >30 day outcomes. Adverse events within the peri-procedural periods may be related to the procedure while those occurring after 30 days are more likely to represent device-related events. Adverse events for coronary stents and the timing of these may be described differently in the literature. Manufacturers are advised to use standardised definitions for clinical endpoints for coronary stents as defined by the Academic Research Consortium (ARC), in 2007.[110](#) The ARC nominated clinical outcomes have been adopted by the European Commission in their guidance MEDDEV 2.7/1.[28](#) These include, but are not limited to, outcomes listed in Table 7 (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 [110 112](#)
- If MACE is the nominated clinical endpoint, manufacturers are advised to provide a clear definition with clinical justification for the elements included in this composite measure.

Manufacturers should also provide evidence of clinical device success. Typically this will include the successful delivery and deployment of the device, removal of the stent delivery system and final residual stenosis of <50% of the target lesion as assessed by Quantitative Coronary Angiography. Clinical procedural success includes the previous measures associated with stent deployment and stenosis reduction with the additional parameter that there are no ischemia driven adverse events to a maximum of seven days post procedure. [111](#)

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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.<sup>110</sup> This timeline is in line with reported patient follow-up times in the peer-reviewed literature (Table 7 & 9).

### 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

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

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

All will affect the rate at which adverse events occur and whether these rates may be considered clinically acceptable for a given patient cohort.<sup>113</sup>

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

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

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

Procedural success requires a successful deployment of stent and withdrawal of delivery system with a < 30% residual stenosis.<sup>101</sup>

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.

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## 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 7, 8 & 9).

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.<sup>114</sup> 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 revascularisation; 5.9%
- Technical success has been report to be greater than 95%<sup>115</sup>
- Given the physical dimensions of this class of stent, stent fracture may occur at rates in excess of 30% of treated legs.<sup>115</sup> Stent fracture significantly impacts primary patency rates and manufacturers are advised to report these rates
- Patency at 1 and 3 years are reported to be 69 to 79% and 59 to 70% respectively.<sup>116</sup>

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

- define the patient cohort and provide a clinical justification for selected safety and performance parameters
- define the lesion anatomy according to a recognised classification system e.g. TransAtlantic Inter-Society Consensus.<sup>116</sup>

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 9. 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.<sup>117</sup> 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  $\leq 5\text{mm}$  in diameter or  $\leq 5\%$  volume.
- Absence of aneurysm rupture or need to convert to open surgery.

In contrast clinical failure is defined as:

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

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

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

Technical success is defined as the successful deployment and removal of the delivery device without the need for surgical conversion or mortality. Chaikof *et al* <sup>117</sup> further qualified technical success to include:

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

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

### **Implants for PDA repair**

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

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safety and performance values. Manufacturers are advised to provide a justification for the selected clinical outcomes and values that define clinical and technical success.

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

- Clinical success based on the absence of non-trivial residual angiographic shunt is reported to be 90 to 96% for two commercially available devices<sup>118</sup>
- Manufacturers are advised to demonstrate PDA closure rate at implant, 24 hours post-procedure and at appropriate clinical follow-up. Follow-up has been reported at 1, 2 and 5 years. Patient follow-up and assessment method should be supported with a clinical justification
- Major adverse events (e.g. device embolization, device malposition) have been reported to occur at 2.2% (95% CI 1.0 to 3.7).<sup>119</sup>

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

### **IVC filters to prevent PE**

Of primary interest were adverse events, PE (including fatal PE), DVT, and occurrence of a VTE distal to the filter. Manufacturers are advised to provide details of target patient baseline risk for PE, operator experience and technique, medical management goals and the primary study endpoints. These have been shown to be independently associated with adverse events.<sup>120</sup>

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

- Fatal PE is not frequently reported and manufacturers should use appropriate study designs with sufficient power to detect such events when possible. If meta-analysis is performed, then the Peto Odds methods for rare events should be considered.
- Based on the IVC filter registry maintained by British Society of Interventional Radiology (BSIR)<sup>120</sup> more than 96% of filters were deployed as intended. However, manufacturers should report the filter orientation on deployment (i.e. centralised, tilted or abutting the IVC wall).
- Manufacturers should report the dwell time for the device and the impact on retrieval for temporary devices.
- Any structural failure should be reported.
- Manufacturers are advised that DVT was reported to be lower than the 1% in BSIR registry data.<sup>120</sup> However, the clinical profile of the patient cohort may affect this adverse event. Therefore, manufacturers are advised to provide a clinical justification for expected DVT rates in the target population.
- Perforations are the most common long-term adverse event occurring in 0.3 to 14% of filter deployments; the range may reflect differences in IVC filter type.<sup>120</sup>
- The BSIR IVC registry requires notification of filter migration of  $> 10$ mm. Manufacturers are advised to report any filter migrations.

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- Mortality rates reported for the BSIR IVC registry ranged from 4.3 to 12.3% depending on filter type, dwell time and clinical condition of the patient. Manufacturers are advised to provide a clear clinical context for the use of the IVC filter to assist the clinical assessor to determine whether the device has a favourable benefit-risk profile.

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

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



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

## 6.6. Summary of safety and performance data

### Characteristics of clinical studies of CV flow implants

**Table 8: 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:			Implants for AAA repair	Implants for PDA repair	IVC filters
	Carotid (6 SRs) <a href="#">101</a> <a href="#">121</a> <a href="#">122</a> <a href="#">123</a> <a href="#">124</a> <a href="#">125</a>	Coronary(6 SRs) <a href="#">126</a> <a href="#">127</a> <a href="#">128</a> <a href="#">129</a> <a href="#">130</a> <a href="#">131</a>	Peripheral (5 SRs) <a href="#">132</a> <a href="#">133</a> <a href="#">134</a> <a href="#">135</a> <a href="#">136</a>	(4 SRs) <a href="#">134</a> <a href="#">137</a> <a href="#">138</a> <a href="#">139</a> (1 retrospective comparative cohort) <a href="#">140</a>	(1 SR) <a href="#">105</a> (1 retrospective cohort study) <a href="#">104</a>	(2 SRs) <a href="#">108</a> <a href="#">141</a> (1 RCT) <a href="#">142</a>
	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: All Level IV Primary study: Level IV	SRs: Levels II-IV RCT=Level II



Characteristics of included studies	Arterial stents: Carotid (6 SRs) <a href="#">101</a> <a href="#">121</a> <a href="#">122</a> <a href="#">123</a> <a href="#">124</a> <a href="#">125</a> Coronary(6 SRs) <a href="#">126</a> <a href="#">127</a> <a href="#">128</a> <a href="#">129</a> <a href="#">130</a> <a href="#">131</a> Peripheral (5 SRs) <a href="#">132</a> <a href="#">133</a> <a href="#">134</a> <a href="#">135</a> <a href="#">136</a>			Implants for AAA repair (4 SRs) <a href="#">134</a> <a href="#">137</a> <a href="#">138</a> <a href="#">139</a> (1 retrospective comparative cohort) <a href="#">140</a>	Implants for PDA repair (1 SR) <a href="#">105</a> (1 retrospective cohort study) <a href="#">104</a>	IVC filters (2 SRs) <a href="#">108</a> <a href="#">141</a> (1 RCT) <a href="#">142</a>
	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: <a href="#">105</a> n=259 patients in device group; n=551 in control group Primary study: <a href="#">104</a> Level III-2 retrospective cohort with concurrent controls; n=51 in device group; n=130 in control group	SR 2010: <a href="#">108</a> 2 RCTs of 129 and 400 patients (division between arms NR) SR 2014: <a href="#">141</a> n=432 in filter groups; n=4160 in historical control groups RCT 2012: <a href="#">142</a> 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) <a href="#">101</a> <a href="#">121</a> <a href="#">122</a> <a href="#">123</a> <a href="#">124</a> <a href="#">125</a> Coronary(6 SRs) <a href="#">126</a> <a href="#">127</a> <a href="#">128</a> <a href="#">129</a> <a href="#">130</a> <a href="#">131</a> Peripheral (5 SRs) <a href="#">132</a> <a href="#">133</a> <a href="#">134</a> <a href="#">135</a> <a href="#">136</a>			Implants for AAA repair (4 SRs) <a href="#">134</a> <a href="#">137</a> <a href="#">138</a> <a href="#">139</a> (1 retrospective comparative cohort) <a href="#">140</a>	Implants for PDA repair (1 SR) <a href="#">105</a> (1 retrospective cohort study) <a href="#">104</a>	IVC filters (2 SRs) <a href="#">108</a> <a href="#">141</a> (1 RCT) <a href="#">142</a>
	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: <a href="#">108</a> With D&B, assessed studies as low quality SR 2014: <a href="#">141</a> 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: <a href="#">108</a> NR SR 2014: <a href="#">141</a> 34 days to 8 years RCT 2012: 15 (± SD 2) months

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

## Reported clinical outcomes on selected CV flow implants

**Table 9: 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
<b>Arterial stents:</b> <ul style="list-style-type: none"> <li>– <b>Carotid</b> (6 SRs) <a href="#">101</a> <a href="#">121</a> <a href="#">122</a> <a href="#">123</a> <a href="#">124</a> <a href="#">125</a></li> <li>– <b>Coronary</b> (6 SRs) <a href="#">126</a> <a href="#">127</a> <a href="#">128</a> <a href="#">129</a> <a href="#">130</a> <a href="#">131</a></li> <li>– <b>Peripheral</b> (5 SRs) <a href="#">132</a> <a href="#">133</a> <a href="#">134</a> <a href="#">135</a> <a href="#">136</a></li> </ul>	<ul style="list-style-type: none"> <li>– Carotid: often divided into &lt;30 day (peri-procedural) or &gt;30 day outcomes</li> <li>– Primary: Composite of (a) death or stroke OR (b) death or stroke or MI</li> <li>– Secondary: Death, stroke / disabling / major stroke, TIA, MI, facial neuropathy / cranial nerve palsy</li> <li>– Restenosis</li> <li>– Coronary <ul style="list-style-type: none"> <li>– TVR and / or TLR</li> <li>– Death</li> <li>– Recurrent MI</li> <li>– Stent thrombosis (definite or probable; also early or late)</li> <li>– Various composite endpoints such as MACE</li> </ul> </li> <li>– Peripheral <ul style="list-style-type: none"> <li>– Death, reintervention, amputation</li> <li>– Technical success, vessel patency, TLR, restenosis</li> <li>– Clinical improvement as per Rutherford Scale, hemodynamic improvement, QOL</li> </ul> </li> </ul>
<b>Implants for AAA repair</b> (4 SRs) <a href="#">134</a> <a href="#">137</a> <a href="#">138</a> <a href="#">139</a> (1 retrospective comparative cohort) <a href="#">140</a>	<ul style="list-style-type: none"> <li>– AEs / postop complications, e.g., MI, stroke, renal failure, aortic rupture</li> <li>– Mortality (30-day, aneurysm-related, all-cause)</li> <li>– Reintervention rates including conversion from EVAR to open procedure</li> <li>– Secondary endpoints, e.g., QOL, procedure time, blood loss, blood transfusion, fluoroscopy time, contrast load, recovery time, days in ICU &amp; LOHS</li> </ul>
<b>Implants for PDA repair</b>	<ul style="list-style-type: none"> <li>– AEs</li> <li>– Primary success</li> </ul>

Type of CV flow implant	Outcomes reported in included research
(1 SR) <a href="#">105</a>  (1 retrospective cohort study) <a href="#">104</a>	<ul style="list-style-type: none"> <li>– Residual shunt</li> <li>– Blood transfusion</li> <li>– LOHS</li> </ul>
<b>IVC filters</b>  (2 SRs) <a href="#">108</a> <a href="#">141</a>  (1 RCT) <a href="#">142</a>	<ul style="list-style-type: none"> <li>– AEs</li> <li>– DVT</li> <li>– Fatal PE</li> <li>– PE</li> <li>– VTE distal to the filter</li> </ul>

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

## 7. Implantable pulse generator systems

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

### 7.1. Summary recommendations

- Implantable pulse generator systems (pacemakers including cardiac resynchronisation therapy with or without defibrillation (CRT, CRT-D), implantable cardiac defibrillators (ICDs) and implantable electrical nerve stimulation devices), are complex medical devices that may be used in combination with other devices or components. Manufacturers are advised to list all components and combinations and provide clinical evidence to support the safety and performance of the new device for these nominated configurations.
- Provision of clinical investigation data: Manufacturers who intend to conduct clinical investigations should use study designs to the highest practical NHMRC Level of Evidence, and trials should be appropriately designed to inform on the safety and performance of the device for its intended purpose.
  - For Active Implantable Cardiac Devices (AICDs), patient follow-up in clinical trials should include the peri-operative, acute ( $\leq 3$  months) and chronic ( $> 3$  months) phases, with the patient then monitored during yearly follow-up visits. Follow-up time should be sufficient to identify late adverse events. The nominated follow-up periods should be supported by clinical justification.
  - For implantable devices for pain and other neurological symptom control, patient follow-up for clinical trials should include the peri-operative, acute ( $\leq 3$  months) and chronic ( $> 3$  months) phases. Due to the chronicity of pain and other neurological

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symptoms, performance should be studied for 1 year or longer post device implantation. [143](#)

- The clinical outcomes that determine safety and performance of implantable pulse generator systems vary significantly by device type:
  - The manufacturer is advised to benchmark the new device against devices of the same class as reported by an international registry, if available.
  - Nominated values that indicate safety and performance should be appropriate to patient health status and indicated use and justified by a clinician who is an expert in the field.
  - For patient performance data manufacturers are advised to define the anticipated improvement in patient scores post-surgery or post-treatment. Ideally, these should be by an internationally recognised assessment tool(s) used to measure clinical success e.g. pain assessment via a visual analogue scale.
  - When submitting a comprehensive literature review, full details of the method used should be included in the CER in sufficient detail to ensure the literature review can be reproduced.
  - A well-documented risk assessment and management system should also be provided. All clinical risks identified in the clinical investigation data, literature review and post-market clinical experience should inform and be reflected in the risk assessment documentation. These risks should be appropriately rated and quantified, before assigning risk reduction activities such as statements in the IFU and training materials to reduce inherent risks.
- For guidance on the conduct of comprehensive literature reviews and presentation of clinical evidence, manufacturers are directed to the relevant sections and appendices.
  - In compiling the clinical evidence for an implantable pulse generator system, the manufacturer should ensure that a clinical expert, that is, someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting, conducts a critical evaluation of all the clinical data that informs the safety and performance of the device.
  - The clinical expert must determine whether the clinical evidence is sufficient to demonstrate that the device meets the requirements of the applicable EPs, including that it is deemed to be safe and to perform as intended, and that there is a positive benefit-risk ratio with regard to its use. The clinical expert should then endorse the CER (by signature and date).
- A full curriculum vitae of the clinical expert should be included in the CER.

## **7.2. Defining implantable pulse generator systems**

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

- Active Implantable Cardiac Devices (AICD) including:
  - single and dual chamber pacemakers
  - cardiac resynchronisation therapy pacemakers, with or without defibrillation (i.e. CRT-D and CRT respectively)

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- implantable cardiac defibrillators (ICDs)
  - Electrical nerve stimulation devices
    - only implantable electrical nerve stimulation devices will be covered in this guidance; transcutaneous electrical nerve stimulation (TENS) devices are not included.

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

### 7.3. Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or clinical experience (generally post-market data) from the use of the device (direct evidence) and/or the predicate or similar marketed device (indirect evidence). The intended purpose, clinical indications, claims and contraindications must be supported by the clinical data. Manufacturers should refer to Section 2: [Clinical Evidence](#) for further information.

Direct clinical evidence on the actual device is preferred. Otherwise indirect clinical evidence may be used after substantial equivalence has been demonstrated through a comparison of the clinical, technical and biological characteristics as described in Section 4: [Demonstrating Substantial Equivalence](#).

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

#### Clinical investigation(s)

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

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

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

For implantable devices for pain and other neurological symptom control, patient follow-up for clinical trials should include the peri-operative, acute ( $\leq 3$  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.<sup>143</sup>

For applications based on clinical data from a predicate or similar marketed device, the manufacturer should demonstrate that clinical data are derived from methodologically sound clinical studies and describe any direct relationship that exists between the predicate/similar

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marketed device and the new device with respect to the clinical data. Where the device and the predicate share any common design origin, the lineage between the devices should be provided. Manufacturers are advised to provide all relevant documents with a justification by a clinical expert to establish substantial equivalence and to confirm that any identified differences between the device and the nominated predicate or similar marketed device will not adversely affect the safety and performance of the device.

For further information on demonstrating substantial equivalence refer to Section 4: [Demonstrating Substantial Equivalence](#).

### **Literature review**

The manufacturer should ensure that an internationally recognised method is followed when conducting a systematic literature review. A literature review involves the systematic identification, synthesis and analysis of all available published and unpublished literature, favourable and unfavourable, on the device when used for its intended purpose as outlined in the literature review section in Section 2: [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. All included studies on the device and/or predicate or similar marketed device(s) should have been appraised for reporting quality and potential bias.

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

### **Post-market data**

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

- distribution numbers of the device(s) by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- safety data including medical device vigilance reports, adverse events, and complaints categorised by type and clinical outcome for every year since launch should be reported, including all deaths (all cause, cardiac and sudden cardiac death). Mortality data should include clear definitions of patient death categories and overall mortality rate, and all patient deaths should be supported by sufficient documentation. [144](#)
- the number of years of use



- Examples of registry data for implantable pulse generator systems have been reported in peer reviewed studies from Spain,<sup>145</sup> Denmark,<sup>146</sup> Sweden,<sup>147</sup> France,<sup>148 149</sup> Italy,<sup>150</sup> China,<sup>151</sup> Germany,<sup>152</sup> Poland,<sup>153</sup> the United States,<sup>154</sup> and Australia.<sup>155</sup>
- Any explanted pulse generators returned to manufacturers should be accounted for with an explanation of failures and corrective measures.

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

## 7.4. Compiling the CER

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

Previous sections outline the components that may comprise clinical evidence for a medical device and the recommended process of compiling a CER. These guidance documents apply whether the applicant is using direct clinical evidence or relying on indirect clinical devices for a predicate or similar marketed device. Guidance on defining a predicate or similar marketed device is provided in Section 4: [Demonstrating Substantial Equivalence](#).

As per Section 3: [Clinical evaluation report and supporting documents](#) the CER should include the following:

1. [Device description, lineage and version if applicable](#)
2. [Intended purpose/indications, contraindications and claims](#)
3. [Regulatory status in other countries](#)
4. [Summary of relevant pre-clinical data](#)
5. [Demonstration of substantial equivalence \(if applicable\)](#)
6. [Overview and appraisal of clinical data](#)
7. [Critical evaluation of clinical data including post-market data](#)
8. [Risk-benefit analysis](#)
9. [Conclusions](#)
10. [The name, signature and curriculum vitae of the clinical expert and date of report](#)

### Supportive data and information

The following information on the device must also be provided:

- risk assessment and management document



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

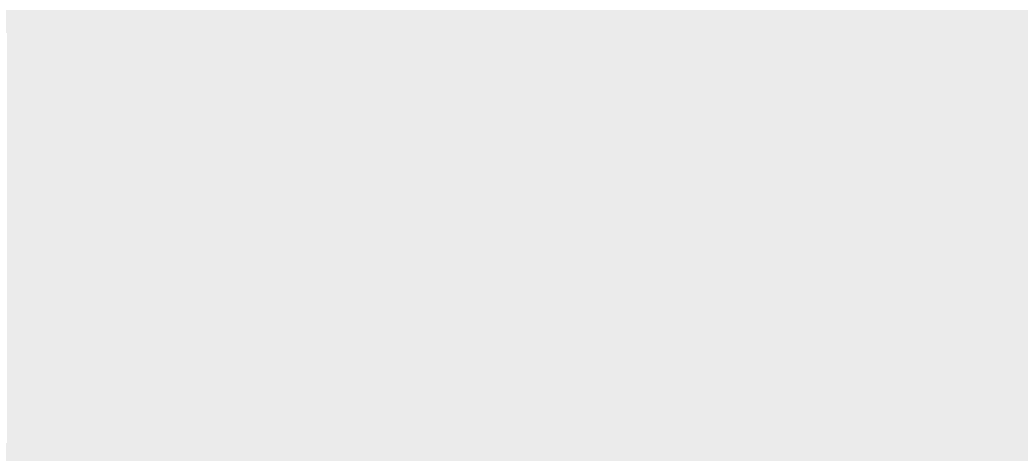
Additional information should be provided as applicable. This may include (but is not limited to):

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

## 7.5. Defining clinical success

### General

Safety and performance data should be provided for the peri-operative, acute ( $\leq 3$  months post-implant) and chronic phases ( $> 3$  months post-implant). Ideally, patients should be assessed with planned yearly follow-up visits.<sup>156</sup> Given the long-term in vivo life of these implantable devices and the potential permanent implantation of some components e.g. leads, manufacturers are advised that long-term follow-up is required. According to peer reviewed literature, typical follow-up periods are three or more years.



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

- unintended biological effects
- external energy sources for example: electric currents, electrostatic discharge
- external cardiac defibrillators
- temperature and pressure
- electromagnetic fields including MR environment
- ionising radiation

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

Irrespective of their placement, implantable pulse generators can be affected by electromagnetic interference (EMI). The risks of altered device function on exposure to electromagnetic fields that are produced either intentionally or as by-products of use of other devices should be assessed. Typical EMI sources include cardioversion, RF ablation, electrosurgery, radiotherapy, use of TENS devices, metal detectors, wireless services (including cellular phones) and MRI environments. Manufacturers are advised to refer to Section 10: [Demonstrating the safety of Implantable Medical Devices \(IMDs\) in the Magnetic Resonance \(MR\) environment](#) and the current version of [ISO 14117<sup>157</sup>](#) (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.<sup>158</sup>



## Active implantable cardiac devices

### *Safety*

Systematic reviews on single, dual-chamber and CRT pacemaker systems either with or without defibrillation capability<sup>159</sup> and ICD systems included the following peri-procedure events and longer term outcomes that were tracked as safety measures: [160](#) [161](#) [162](#) [163](#) [164](#) [165](#)

- procedural complications e.g. pneumothorax, haemothorax, pocket haematoma and infection
- device pocket erosion
- coronary sinus dissection or perforation, damage to arteries and nerves, air embolism, venous thrombosis, cardiac perforation

- 
- pericardial effusion
  - device migration
  - toxic or allergic reaction, e.g. nickel allergy, silicone allergy
  - CRT-D and ICDs; arrhythmia and inappropriate shocks
    - A Health Canada [166](#) guidance report also lists changes to defibrillation thresholds and lead impedances
  - device-related problems
    - leads: dislodgement, reposition, difficult placement, malfunction or fracture
    - sensing problems (loss, oversensing or undersensing)
    - loss of capture
  - extracardiac stimulation
  - CRT and CRT-D: progression to pacemaker syndrome, atrial fibrillation, heart failure or stroke
  - hazards related to use in the MRI environment (refer to Section 10: Demonstrating the safety of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment)
  - death

### ***Performance***

In guidance documents on pacemakers and their associated leads issued by Health Canada [166](#) and US FDA [144](#), and systematic reviews (SRs) [161](#) [159](#) related to CRT-D and ICD evidence, [160](#) [161](#) [162](#) [163](#) [164](#) [165](#) 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](#) [167](#) 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 [144](#)
- avoidance of rehospitalisation (for any reason) after device placement, including heart transplant
- for CRT and CRT-D devices the pacing impedances (low [ $< 200$  ohms] or high [ $> 3000$  ohms] measured using a recognised standard method [ISO 14708-2]) are within the ranges specified by manufacturer
- voltage stimulation threshold (CRT, CRT-D)

- 
- improved cardiac function (CRT, CRT-D) e.g. left ventricle ejection fraction (LVEF), reduced incidences of atrial fibrillation (AF), stroke, heart failure
  - improvement in clinical symptoms

### **Implantable electrical nerve stimulation devices**

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

The different aetiologies of pain and other neurological symptoms can impact on the performance of neurostimulators. Therefore manufacturers are advised to clearly define the target symptom and stimulation loci to assist clinical assessors to evaluate the safety and performance of implantable neurostimulators for pain or the management of other neurological symptoms. Devices can be categorised as either intracranial (e.g. deep brain stimulation [168](#)) or extracranial (e.g. spinal cord, vagal nerve or peripheral nerve stimulators [169 143](#)).

#### ***Safety: intracranial neurostimulators***

Adverse events are variously reported [168 170](#) and include:

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

#### ***Safety: extracranial neurostimulators***

Adverse events are variously reported [169 170](#) and include:

- device-related complications e.g. electrode migration, lead fracture
- distorted or loss of sensation (paraesthesia or numbness)
- dural puncture (spinal cord stimulators)/CSF leak
- infection
- discomfort or pain
- undesired stimulation

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

***Performance: intracranial and extracranial neurostimulators***

The evidence reviewed reported on various outcomes [143](#) [168](#) [170](#) [171](#) 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 [143](#)
- symptom reduction or improvement for non-analgesic neurostimulator indications (e.g. movement disorders such as Parkinsonian tremor, essential tremor, dystonia; urinary or faecal incontinence; epilepsy)
- patient function e.g. QoL, mood, sleep and function scores should be assessed using validated tools such as:
  - Oswestry Disability Index and the Low Back Pain Outcome Scale
  - SF-36
  - Zung Self-Rating Depression Scale
- return to work
- hospital attendance
- patient satisfaction and experience



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

## 7.6. Summary of safety and performance data

### Studies from the peer reviewed literature

**Table 10: Study characteristics extracted from SRs on the safety and performance of selected implantable pulse generators**

Characteristics of included studies	Pacemakers (including CRT) (2 SR) <a href="#">159</a> <a href="#">161</a>	ICDs (5 SRs) <a href="#">160</a> <a href="#">162</a> <a href="#">163</a> <a href="#">164</a> <a href="#">165</a>	Pain management devices (5 SRs or narrative reviews) <a href="#">143</a> <a href="#">168</a> <a href="#">169</a> <a href="#">170</a> <a href="#">171</a>
Number of included studies per SR	Dominant design RCT total included studies n = 45	4 SRs / MAs only included RCTs: range 3 to 8; 1 SR only included cohort studies: n=18	Mixed evidence base with the number of included studies ranging from 11 to 62
Clinical situation(s)	Dual-chamber versus single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome	(a) Primary prevention of SCD in patients w/ CKD at risk of life-threatening ventricular arrhythmias; (b) patients w/ HF; (c) patients w/ ARVD/C; (d) primary prevention of SCD in older patients	(a) Complex regional pain syndrome (b) neuropathic or ischaemic (c) low-back disorders (d) nociceptive or neuropathic pain (e) headaches
Dominant design of included studies	1 SR including 4 RCTs of parallel group design and 28 randomised crossover comparisons	4 SRs included only RCTs; 1 SR included only observational studies	Case series and RCT
Sample size (range) for included studies	RCTs: 58 to 2568 Crossover studies: 8 to 48	Total N in SRs ranged from 610 to 5674	Total N in the SR ranged from 210 to 509
Reported comparisons	Dual-chamber versus single chamber ventricular pacing	(a) Usual medical therapy, placebo or amiodarone; (b) CRT-D (ICD + CRT); (c) “appropriate control” (not specified but could not include ICD or CRT-D)	Medical and/or surgical treatment (appropriate to condition) that does not include SCS.
Patient follow-up	RCTs: 1.5 to 5 years Crossover studies: 48 hours to 8 weeks	Means of 3 months to 3.8 years	Ranged from 1 month to 7.2 years

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

**Table 11: Reported clinical outcomes in the peer reviewed literature on selected implantable pulse generators**

Type of pulse generator	Outcomes reported in the included research or resources
<b>Pacemakers (including CRT)</b> (2 SR) <a href="#">159</a> <a href="#">161</a>	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 <ul style="list-style-type: none"> <li>• Voltage stimulation thresholds</li> <li>• Sensing characteristics</li> <li>• Pacing impedances (Low or high)</li> <li>• Battery longevity</li> </ul>
<b>ICDs</b> (5 SRs) <a href="#">160</a> <a href="#">162</a> <a href="#">163</a> <a href="#">164</a> <a href="#">165</a> <a href="#">166</a> <a href="#">172</a>	Safety (AEs / postop complications): pneumothorax, haemothorax, pocket haematoma, lead dislodgement or reposition or difficult placement or malfunction or fracture, ICD migration, impending ICD pocket erosion, infection, ICD-related infection, pericardial effusion or tamponade, coronary sinus dissection or perforation, damage to arteries and nerves, air embolism, venous thrombosis, cardiac perforation, arrhythmia, inappropriate shocks <ul style="list-style-type: none"> <li>• Mortality (all-cause and ICD-related)</li> <li>• Rehospitalisation (for any reason) after ICD placement including heart transplant</li> <li>• Improvement in clinical conditions</li> <li>• QoL</li> <li>• From Health Canada: defibrillation thresholds and lead impedances (since the device is designed for cardioversion or defibrillation)</li> </ul>
<b>Pain management</b> (5 SRs) <a href="#">143</a> <a href="#">168</a> <a href="#">169</a> <a href="#">170</a> <a href="#">171</a>	<ul style="list-style-type: none"> <li>• Safety intracranial (AEs / postop complications): l risks associated with major surgery, infection, intracerebral or extra-axial haematomas, subdural or epidural haemorrhage, seizure (intraoperative or trial stimulation period), seizure long-term, neurological deficit (short-term &lt; 1 mo), neurological deficit long-lasting, local pain/headache, hardware maintenance e.g. shorten battery life, failed leads, MR environment safety concerns e.g. heating leading to neurological damage</li> <li>• Safety extracranial (AEs / postop complications): device-related complications e.g. electrode migration, lead fracture, loss of paraesthesia, dural puncture (spinal cord stimulators), infection,</li> </ul>

Type of pulse generator	Outcomes reported in the included research or resources
	<p>hardware maintenance e.g. shortened battery life, failed leads, MR environment safety concerns</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• Patient function e.g. QoL, mood, sleep and site specific function scores should be assessed using validated tools such as: <ul style="list-style-type: none"> <li>– return to work</li> <li>– patient satisfaction and experience</li> <li>– analgesic consumption</li> <li>– hospital attendance</li> </ul> </li> </ul>

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

## 8. 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.

### 8.1. Summary recommendations

- Prosthetic heart valves are complex medical devices which are currently made of either synthetic material (mechanical valves) or biological tissues (bioprosthesis) or a combination of both and inserted via open surgery or percutaneously. Manufacturers are advised to provide clinical evidence to support the safety and performance of the particular device and any accessories used to deliver the device.
- Provision of clinical investigation data:
  - manufacturers who intend to conduct clinical trials should design trials to the highest practical NHMRC level of evidence and trials should be appropriate to inform on the safety and performance of the device for its intended purpose
  - to comply with ISO 5840, clinical trials should continue until the minimum number of patients with each valve type have each been followed for a minimum of one year and there are at least 400 valve years of follow-up of each valve type. For modification of an existing valves already on the ARTG the patient years deemed acceptable may in some circumstances be adjusted based on a risk analysis of the changes
  - for evaluating the performance of prosthetic heart valves it is recommended that the Objective Performance Criteria (OPC) as listed in ISO 5840 (and updates) be reported including early (within 30 days post implantation), mid- term outcomes (after 30 days post implantation)<sup>173</sup> and at one year (or two years for reimbursement). The selection should be supported by a clinical justification



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- typical safety and performance values are provided in Table 13, Table 14, Table 15, Table 16 and Table 17 and Table 18.
  - Pre-clinical data demonstrating the mechanical and physical characteristics should be consistent with the intended purpose and anticipated in vivo lifespan of the heart valve replacement.
  - Documentation demonstrating biocompatibility of the device should be provided.
  - For submissions reliant on predicate, or similar marketed device data, manufacturers are required to submit all relevant documents with a supporting clinical justification by the clinical expert that establishes substantial equivalence between the device and the nominated predicate or similar marketed device.
  - When submitting a comprehensive literature review full details of the method, search strategy, inclusion/exclusion criteria for selection of studies and analysis should be included in the CER with sufficient detail to ensure the search can be reproduced.
  - In addition, a well-documented risk analysis and management system must be provided with the CER. The clinical investigation data, literature review and post-market clinical experience should inform the risk assessment documentation. All clinical risks identified in the clinical data should be reflected in the risk assessment documentation. These risks should be appropriately rated and quantified and ideally be presented as risk matrices, before assigning risk reduction activities such as statements in the IFU and training materials to reduce residual risks. The residual risk following risk mitigation implementation should be estimated.
  - Manufacturers should provide details of the clinical context within which the clinical data was obtained. The clinical context of the evidence should be consistent with the indications for use.
  - Compilation of the clinical evidence
    - in compiling the clinical evidence for a prosthetic heart valve the manufacturer should ensure that a competent clinical expert critically evaluates all the clinical data that informs on the safety and performance of the device
    - the competent clinical expert must then endorse the CER (evidenced by signature and date) which demonstrates that the clinical evidence is sufficient to meet the requirements of the applicable EPs and the device is deemed to be safe and to perform as intended
  - The full CV of the clinical expert should be provided

## 8.2. Defining heart valve prostheses

This section includes both conventional heart valves (those that are implanted using open heart surgery) and percutaneous heart valves (those that are collapsed into a catheter and are expanded at the time of implantation).<sup>174</sup> The guidance also applies to 'sutureless' (meaning heart valves with fewer sutures, not without sutures) valve technology whereby the valve is mounted on a self-expanding nitinol frame that is implanted into the aortic annulus following resection of the diseased tissue.<sup>175</sup> Each type of valve has its own associated risk benefit profile that needs to be addressed by the manufacturer.

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

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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).<sup>174</sup>

Manufacturers and applicants are advised to read this guidance section in conjunction with other relevant sections and ISO documentation, ISO 5840:2015 <sup>32</sup> and ISO 5840-3:2013.<sup>178</sup>

### 8.3. Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or post-market data (clinical experience) from the use of the device (direct) and/or 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 from a predicate or similar marketed device may be used after substantial equivalence has been demonstrated through a comparison of the clinical, (intended purpose) technical and biological characteristics as described in Section 4: [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. Manufacturers should refer to Section 2: [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 that manufacturers refer to ISO 5840-1:2015;<sup>176</sup> ISO 5840-2:2015<sup>177</sup> and ISO 5840-3:2013<sup>178</sup> as guides to study design.

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

It is recommended that the clinical study continue until the minimum number of patients of each valve type has each been followed for a minimum of one year (two years if seeking reimbursement). There must be at least 400 valve years of follow-up of each valve type. This is based on guidance in ISO 5840:2015.<sup>32</sup> For modification of an existing valve on the ARTG the patient years deemed acceptable may in some circumstances be adjusted based on a risk analysis of the changes. The manufacturer is responsible for providing justification of the study protocol. The number of patient years should also be documented.

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

### **Literature review**

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

Data on the materials used to construct the prosthesis, its dimensions and geometry and the intended purpose and population will define the construction of search strategies as well as study selection when conducting a comprehensive literature review. This ensures that the searches are complete and the included studies are related to the device and/or 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 or adequate information to identify the device (e.g. manufacturer name and model number) in any given study must be extractable from the study report. If this is not possible, the study should be excluded from the review.

### **Post-market data**

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

Publicly available post-market data such as adverse event reporting on the FDA MAUDE database and the TGA IRIS may be used for devices from other manufacturers. The manufacturer should include post-market surveillance data from national jurisdictions where the device is approved for clinical use. Registries for different prosthetic heart valves have been established in Belgium, France, Germany, Italy, New Zealand and the United Kingdom as well as Australia.<sup>179</sup>  
[180](#) [181](#) [182](#) [183](#) [184](#) [185](#) [186](#) [187](#) [188](#) [189](#) [190](#)

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

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

## 8.4. Compiling the CER

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

As per Section 3: [Clinical evaluation report and supporting documents](#) the CER should include the following:

1. [Device description, lineage and version if applicable](#)
2. [Intended purpose/indications and claims](#)
3. [Regulatory status in other countries](#)
4. [Summary of relevant pre-clinical data](#)
5. [Demonstration of substantial equivalence \(if applicable\)](#)
6. [Overview and appraisal of clinical data](#)
7. [Critical evaluation of clinical data including post market data](#)
8. [Risk-benefit analysis](#)
9. [Conclusions](#)
10. [The name, signature and curriculum vitae of the clinical expert and date of report](#)

### Supportive data and information

The following information on the device must also be provided:

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

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

- additional specifications of the device(s)
- the materials from which the device is made including chemical composition
- other devices that may be used in conjunction with the device

- 
- any aspects of non-clinical testing results that inform the design of the clinical trial should be included in the supporting documents
  - biocompatibility testing, bench testing and animal studies where applicable
  - specific testing of any adjuvant medicinal components may be required especially if these are new chemical entities in the Australian context. This should cover interactions between the device and the medicine, pharmacodynamics and time-release profiles.

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

In submissions to the TGA, it is recommended that manufacturers of heart valve prostheses refer to ISO documents for guidance on the type of information that should be provided with respect to the characteristics of the device, for example 5840-1: 2015, Cardiovascular implants -- Cardiac valve prostheses -- Part 1: General requirements;<sup>176</sup> 5840-2:2015 Cardiovascular implants -- Cardiac valve prostheses -- Part 2: Surgically implanted heart valve substitutes<sup>177</sup> and 5840-3:2013 Cardiovascular implants -- Cardiac valve prostheses -- Part 3: Heart valve substitutes implanted by transcatheter techniques.<sup>178</sup>

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

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

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

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

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

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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 selection of the predicate/similar marketed device. 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 5840:2005 for a more comprehensive list
  - any differences in the technical and physical characteristics should be addressed in the clinical justification to determine whether the difference will affect the benefit-risk profile when the device is used for its intended purpose
  - the use of more than one predicate or similar marketed device is discouraged; however, these may be used if each predicate or similar marketed device is a valid comparator 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.
- The clinical expert should critically evaluate all the clinical data for the device and predicate/similar marketed device and then endorse the CER (evidenced by signature and date) that establishes whether the clinical evidence is sufficient to demonstrate the requirements of the applicable EPs and that the device is safe and performs as intended.

## 8.5. Defining clinical success

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

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

- all-cause mortality
- valve related mortality
- thromboembolism
- valve thrombosis
- all cause reoperation

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

In addition, it is recommended the following outcomes be reported after 30 days:

- all-cause mortality
- all stroke (disabling and non-disabling)
- hospitalisation for valve-related symptoms or worsening congestive heart failure
- a quality of life measure e.g. the New York Heart Association Classification (NYHA) or the Minnesota Living with Heart Failure Questionnaire (MLHF)
- prosthetic valve endocarditis
- prosthetic valve thrombosis
- bleeding, unless unrelated to valve therapy (e.g. trauma) (note: bleeding should be classified as either 'all haemorrhage' or 'major haemorrhage' 'anticoagulant-related haemorrhage')
- reoperation
- thromboembolic events (e.g. stroke)
- structural valve deterioration
- non-structural valve dysfunction/valve related dysfunction (note: valve regurgitation should be reported as 'all paravalvular leaks' and 'major paravalvular leaks' and it should be noted if the dysfunction required a repeat procedure)

At one year the following should be reported:

- Structural valve deterioration
- Thromboembolism
- Major, reversible ischemic neurological deficit (RIND)
- Valve thrombosis

- 
- Anticoagulant-related haemorrhage
  - Prosthetic valve endocarditis
  - Non-structural valve dysfunction/paravalvular leak
  - Re-operation

It is recommended that the following outcomes; valve related dysfunction, prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events and bleeding, be reported in a time-related manner as described in [Guidelines for reporting mortality and morbidity after cardiac valve interventions](#).<sup>191</sup>

The outcomes listed above are a recommended minimum based on a consensus report produced by the [Valve Academic Research Consortium](#).<sup>192</sup> For appropriate definitions, diagnostic criteria and measurement of the above outcomes manufacturers should consult the following documents:

- the Valve Academic Research Consortium Consensus Documents on standardised endpoint definitions for transcatheter aortic valve implantation [173](#) [193](#)
- guidelines by Akins et al (2008) for reporting mortality and morbidity after cardiac valve interventions
- guidelines on the evaluation of prosthetic valves with echocardiography [194](#) [195](#)
- the update of objective performance criteria for clinical evaluation of new heart valve prostheses by ISO (Wu et al 2014) [196](#)

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 [173](#) [194](#) [195](#) (Table 13, Table 14, Table 15, Table 16 and Table 17).

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.<sup>196</sup> For transcatheter valves the number of events for each of the listed outcomes should be similar to or less than those reported in studies published in peer reviewed journals or heart valve registries for a similar type of prosthetic heart valve in the same valve position. Values that are reported need to be supported by clinical justification.

Manufacturers should report early (within 30 days post implantation) and late valve outcomes (after 30 days post implantation) with a follow-up of one year or more (two years if seeking reimbursement) and a minimum of 400 valve years of follow-up for each valve type.<sup>32</sup>

Outcomes are comprised of the most relevant patient endpoints as defined by the Valve Academic Research Consortium (VARC). [173](#)

For surgically implanted valves, manufacturers should refer to the objective performance criteria determined by the ISO for what is considered an acceptable number of events for different outcomes.



For transcatheter valves the number of events for each outcome should be similar to or less than those reported in studies published in peer reviewed journals or heart valve registries for a similar type of prosthetic heart valve in the same valve position.

## 8.6. Summary of safety and performance data

### Reported clinical outcomes on prosthetic heart valves

**Table 12: 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)	✓	✓	✓
Death (cardiovascular cause)	✓	✓	
Repeat hospitalisation		✓	
Myocardial infarction		✓	
Strokes		✓	✓
Transient ischemic attack		✓	
kidney injury/need for haemodialysis		✓	✓
Vascular complications		✓	
Bleeding/haemorrhage	✓	✓	✓
Endocarditis	✓	✓	✓
Atrial fibrillation		✓	✓
Tamponade/pericardial effusion		✓	
Life threatening arrhythmias/arrhythmias requiring intervention		✓	
Haemodynamic collapse/need for haemodynamic support		✓	
New pacemaker		✓	✓

Safety parameter	Surgical Aortic Valve Replacement	Transcatheter Aortic Valve Implantation	Sutureless valve replacement
Device malfunction, misplacement or migration		✓	✓
Non-structural dysfunction	✓		
Structural valvular deterioration	✓		
Injury to valve or myocardium		✓	
Valve-in-valve or second valve required		✓	
Conversion to sutured valve			✓
Conversion to surgical valve replacement		✓	
Thromboembolism	✓		✓
Valve thrombosis	✓		
Reintervention/reoperation or freedom from reoperation	✓		✓
Aortic regurgitation/paravalvular regurgitation		✓	✓
Atrioventricular block			✓
Cross-clamp time	✓		✓
Bypass time	✓		✓
Left ventricular mass regression index	✓		
Life expectancy based on microsimulation	✓		
Event-free life expectancy based on microsimulation	✓		
Successful implantation		✓	

Safety parameter	Surgical Aortic Valve Replacement	Transcatheter Aortic Valve Implantation	Sutureless valve replacement
Length of stay in intensive care		✓	
Length of hospital stay		✓	
<b>Haemodynamic parameters</b>			
Post-operative mean and peak aortic pressure gradient	✓	✓	✓
Effective orifice area index	✓		✓
Left ventricular ejection fraction		✓	
Mean aortic valve area		✓	✓
Change in NYHA* class	✓	✓	✓
6-minute walk test		✓	

\*NYHA: New York Heart Association

**Table 13: Parameters used to assess transcatheter valve function and a guide to what are considered normal values as defined by the Valve Academic Research Consortium**

	Prosthetic Aortic Valve Stenosis		
	Normal	Mild Stenosis	Moderate/Severe Stenosis
<b>Quantitative parameters (flow dependent)<sup>†</sup></b>			
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
<b>Quantitative parameters (flow-independent)</b>			
Doppler velocity index <sup>‡</sup>	>0.35	0.35–0.25	<0.25
Effective orifice area <sup>§</sup>	>1.1 cm <sup>2</sup>	1.1–0.8 cm <sup>2</sup>	<0.8 cm <sup>2</sup>
Effective orifice area <sup>  </sup>	>0.9 cm <sup>2</sup>	0.9–0.6 cm <sup>2</sup>	<0.6 cm <sup>2</sup>
	Prosthesis-Patient Mismatch		
	Insignificant	Moderate	Severe

Indexed effective orifice area <sup>†</sup> (cm <sup>2</sup> /m <sup>2</sup> )	>0.85 cm <sup>2</sup> /m <sup>2</sup>	0.85–0.65 cm <sup>2</sup> /m <sup>2</sup>	<0.65 cm <sup>2</sup> /m <sup>2</sup>
Indexed effective orifice area <sup>#</sup> (cm <sup>2</sup> /m <sup>2</sup> )	>0.70 cm <sup>2</sup> /m <sup>2</sup>	0.90–0.60 cm <sup>2</sup> /m <sup>2</sup>	<0.60 cm <sup>2</sup> /m <sup>2</sup>
	<b>Prosthetic Aortic Valve Regurgitation</b>		
	Mild	Moderate	Severe
<b>Semi-quantitative parameters</b>			
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%
<b>Quantitative parameters<sup>‡</sup></b>			
Regurgitant volume (mL/beat)	<30 mL	30–59 ml	≥60 ml
Regurgitant fraction (%)	>30%	30–49%	≥50%
EROA (cm <sup>2</sup> )	0.10 cm <sup>2</sup>	0.10–0.29 cm <sup>2</sup>	≥0.30 cm <sup>2</sup>

<sup>†</sup>These parameters are more affected by flow, including concomitant aortic regurgitation

<sup>‡</sup>For left ventricular outflow tract (LVOT) >2.5 cm, significant stenosis criteria is <0.20

<sup>§</sup>Use in setting of Body Surface Area (BSA) ≥1.6 m<sup>2</sup> (note: dependent on the size of the valve and the size of the native annulus).

<sup>||</sup> Use in setting of BSA <1.6 m<sup>2</sup>, <sup>¶</sup> Use in setting of BMI <30 kg/m<sup>2</sup>, <sup>#</sup> Use in setting of BMI ≥30 kg/m<sup>2</sup>

\*\*not well-validated and may overestimate the severity compared with the quantitative Doppler

EROA: effective regurgitant orifice area; PW: pulsed wave

**Table 14: Guide to normal values, intermediate values for which stenosis may be possible and values that usually suggest obstruction in mechanical and stented-biological prosthetic aortic valves\* from Zoghbi et al (2009)**

Parameter	Normal	Possible stenosis	Suggests significant stenosis
Peak velocity (m/s) <sup>†</sup>	<3	3-4	>4
Mean gradient (mm Hg) <sup>†</sup>	<20	20-35	>35
DVI	≥0.30	0.29-0.25	<0.25
EOA (cm <sup>2</sup> )	>1.2	1.2-0.8	<0.8

Parameter	Normal	Possible stenosis	Suggests significant stenosis
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 15: Parameters for evaluation of the severity of prosthetic aortic valve regurgitation from Zoghbi et al (2009)**

Parameter	Mild	Moderate	Severe
<b>Valve structure and motion</b>			
Mechanical or bioprosthetic	Usually normal	Abnormal†	Abnormal†
<b>Structural parameters</b>			
LV size	Normal	Normal or mildly dilated‡	Dilated‡
<b>Doppler parameters (qualitative or semiquantitative)</b>			
Jet width in central jets (% LVO diameter): colour*	Narrow ( $\leq 25\%$ )	Intermediate (26-64%)	Large ( $\geq 65\%$ )
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
<b>Doppler parameters (quantitative)</b>			
Regurgitant volume (mL/beat)	<30	30-59	>60

Parameter	Mild	Moderate	Severe
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 16: Doppler parameters for assessment of stenosis in prosthetic mitral valves from Zoghbi et al (2009)**

	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 <sub>PrMV</sub> /VTI <sub>LVO</sub> <sup>†§</sup>	<2.2	2.2-2.5	>2.5
EOA (cm <sup>2</sup> )	≥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 17: Echocardiographic and Doppler criteria for severity of prosthetic mitral valve regurgitation using findings from transthoracic echocardiograms and transesophageal echocardiogram from Zoghbi et al (2009)**

Parameter	Mild	Moderate	Severe
<b>Structural parameters</b>			
LV size	Normal*	Normal or dilated	Usually dilated‡
Prosthetic valve <sup>  </sup>	Usually normal	Abnormal <sup>¶</sup>	Abnormal <sup>¶</sup>
<b>Doppler parameters</b>			
Colour flow jet area <sup>  #</sup>	Small, central jet (usually < 4 cm <sup>2</sup> or <20% of LA area)	Variable	Large central jet (usually >8 cm <sup>2</sup> or >40% of LA area) or variable size wall-impinging jet swirling in left atrium
Flow convergence <sup>**</sup>	None or minimal	Intermediate	Large
Jet density: CW Doppler <sup>  </sup>	Incomplete or faint	Dense	Dense
Jet contour: CW Doppler <sup>  </sup>	Parabolic	Usually parabolic	Early peaking, triangular
Pulmonary venous flow <sup>  </sup>	Systolic dominance	Systolic blunting§	Systolic flow reversal†
<b>Quantitative parameters<sup>++</sup></b>			
VC width (cm) <sup>  </sup>	<0.3	0.3-0.59	≥0.6
R vol (mL/beat)	<30	30-59	≥60
RF (%)	<30	30-49	≥50
EROA (cm <sup>2</sup> )	<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 valves.

¶ Abnormal mechanical valves, for example, immobile occlude (valvular regurgitation), dehiscence or rocking (paravalvular regurgitation); abnormal biologic valves, for example, leaflet thickening or prolapse (valvular), dehiscence or rocking (paravalvular regurgitation).

# At a Nyquist limit of 50 to 60 cm/s.

\*\* Minimal and large flow convergence defined as a flow convergence radius <0.4 and ≥0.9 cm for central jets, respectively, with a baseline shift at a Nyquist limit of 40 cm/s; cut-offs for eccentric jets may be higher.

†† These quantitative parameters are less well validated than in native MR.

**Table 18: Objective performance criteria (OPC) from the ISO for valve-related complications for new valves or newly modified valves implanted surgically (% per patient-year)\***

Adverse event	Mechanical Valve		Bioprosthetic Valve	
	Aortic	Mitral	Aortic	Mitral
Thromboembolism	1.6	2.2	1.5	1.3
Valve thrombosis	0.1	0.2	0.04	0.03
Major haemorrhage	1.6	1.4	0.6	0.7
Major paravalvular leak	0.3	0.5	0.3	0.2
Endocarditis	0.3	0.3	0.5	0.4

\*Not for transcatheter valves. A new valve is required to have complication rates lower than twice the OPC

## Characteristics of clinical studies on heart valve prostheses

**Table 19: Summary of study characteristics of six systematic reviews on surgical aortic valve replacement identified in a health technology assessment**

Review	Design of included studies	Numbers of studies and patients	Follow-up	Comparison
Kassai et al 2000 <a href="#">197</a>	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 <a href="#">198</a>	RCTs	11 studies 919 patients	NR	Aortic: Stented vs. non-stented bioprosthetic



Review	Design of included studies	Numbers of studies and patients	Follow-up	Comparison
Lund and Bland, 2006 <a href="#">199</a>	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 <a href="#">200</a> Puvimanasinghe et al 2003 <a href="#">201</a>	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 <a href="#">202</a>	Observational	13 studies 6,481 patients	18 years for Carpentier-Edwards pericardial valves and up to 20 years for Carpentier-Edwards porcine supraannular valves	Aortic: Carpentier-Edwards pericardial aortic vs. Carpentier-Edwards supra-annular bioprosthetic
Rizzoli et al 2004 <a href="#">203</a>	Observational	11 studies 1,160 patients	Mean duration: 6.8 years	Tricuspid: Bioprosthetic vs. mechanical valves

NR: not reported

**Table 20: Summary of study characteristics of 57 RCTs\* on surgical aortic valve replacement identified in a Health Technology Assessment.** [174](#)

Total number of patients: 12,379

Valve types studied	Valve comparisons	Average follow-up time
<b>Aortic</b> (n=43)	Most common comparison was bioprosthetic stented vs. bioprosthetic unstented (n=15)	1 year or sooner (69% of studies) >1 to 5 years (24% of studies) > 5 to 10 years (7% of studies)

Valve types studied	Valve comparisons	Average follow-up time
<b>Aortic and mitral</b> (n=11)	Homograft vs. mechanical (n=1)  Mechanical vs. mechanical (n=7)  Mechanical vs. bioprosthetic (n=2)  Bioprosthetic vs. bioprosthetic (n=1)	>1 to 5 years (36% of studies)  > 5 to 10 years (45% of studies)  >10 years (18% of studies)
<b>Mitral</b> (n=3)	All compared mechanical valves	Mean of 5 years

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

**Table 21: Summary of study characteristics of two Health Technology Assessments on transcatheter aortic valve implantation**

Study	Study details	Numbers of patients	Follow-up	Comparison
<b>NICE</b> (2011) <a href="#">204</a>	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

Study	Study details	Numbers of patients	Follow-up	Comparison
<b>Tice</b> (2014) <a href="#">205</a>	HTA including 2 Level II studies <sup>†</sup> , 10 Level III studies <sup>‡</sup> and 16 Level IV studies <sup>§</sup>	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 month to 18 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
<b>Registries</b>	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

<sup>†</sup>Same Level II studies as included in NICE (2011)

<sup>‡</sup> Includes one Level III study which is a meta-analysis

<sup>§</sup> Includes two Level IV studies which are meta-analyses

**Table 22: 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
<b>NICE</b> (2012) <a href="#">206</a>	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
<b>Sinclair et al</b> (2013) <a href="#">207</a>	HTA including 6 studies <sup>†</sup> (all Level IV)	Range from 6 to 140	Range from a mean of 313 days to up to 3 years	NA
<b>Englberger et al</b> (2014) <a href="#">208</a>	Single Level IV (multicentre) study	141	5 years	NA

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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

## 9. Supportive devices - meshes, patches and tissue adhesives

Supportive devices act as scaffolds, reinforcement or buttressing and include all devices that hold, fix or sustain body organs or incisions. The majority of supportive devices are surgical meshes for hernia and gynaecological repair, central nervous system (CNS) patches, and tissue adhesives, but sheeting of various origins is also included.<sup>209</sup>

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

### 9.1. Summary recommendations

- Manufacturers 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.
- Provision of clinical investigational data:
  - manufacturers who intend to conduct a clinical trial should design the trial using the highest practical NHMRC Level of Evidence and trials should be appropriate to inform on the safety and performance of the device for its intended purpose
  - it is suggested that the minimum period for patient follow-up for clinical trials is 24 months for permanent and biological meshes. At the time of writing there is no agreed recommended follow up for patches or tissue adhesives.
  - across the surgical supports the main clinical outcomes that determine safety and performance for hernia repair are recurrence rate, reoperation rate, function and QoL scores, adhesions (particularly for intraperitoneal mesh), mesh degradation, seroma and pain, and for pelvic organ prolapse (POP) and stress urinary incontinence (SUI), cure of stress incontinence and patient scores such as the Pelvic Organ Prolapse Quantification System (POP-Q)<sup>210</sup>
    - for revision data, the manufacturer is advised to benchmark the device against devices of the same class as reported by an international registry, if available
    - for patient performance data, manufacturers are advised to define the anticipated improvement in patient scores post-surgery. Ideally, these should be internationally recognised assessment tool(s) used to measure clinical success, e.g., QoL or cough stress test
  - when submitting a comprehensive literature review, full details of the method used should be included in the CER in sufficient detail to ensure the literature review can be reproduced.

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- for guidance on the conduct of comprehensive literature reviews and presentation of clinical evidence manufacturers are directed to relevant sections in this document.
  - For submissions reliant on predicate, or similar marketed device data, manufacturers and sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between a device and the nominated predicate(s) or similar marketed device(s).
  - In addition, a well-documented risk analysis and management system should also be provided with the CER.
  - Manufacturers should provide details of the clinical context within which the clinical data were obtained. The clinical context of the evidence base should be congruent with the indications of use for which the manufacturer seeks TGA approval.
  - Compilation of the CER:
    - in compiling the clinical evidence for a supportive device the manufacturer should ensure that a clinician who is an expert in the field and experienced in the use of the device critically evaluates all the clinical data that informs on the safety and performance of the device
    - the clinical expert must then endorse the CER containing the clinical evidence (evidenced by signature and date) to demonstrate that the evidence meets the requirements of the applicable EPs and the device is deemed to be safe and to perform as intended.

## 9.2. Defining supportive devices

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

- **Surgical mesh:** this is a textile-based sheet (typically knotted or warp knitted) used as a temporary or permanent support for organs or other tissues. It is used for hernia repair, POP, SUI and many other purposes. The main classes of surgical mesh are biological and synthetic or a combination of these. Types of mesh include bio-mesh, polypropylene, expanded polytetrafluoroethylene (ePTFE), composite polypropylene-PTFE, polyester, composite meshes that combine permanent and absorbable materials such as collagen, polyglactin, polylactic acid and polyglycolic acid and in combination with materials such as titanium. More than one type can be used at once and they can be absorbable, semi-absorbable and non-absorbable. The configuration of mesh varies. Fixation methods include staples, sutures, tackers and glue. [211](#)
- **Patches:** specifically CNS patches, both absorbable and non-absorbable, are impermeable adhesive membranes used in intradural neurosurgical procedures, as an alternative to using autologous grafts or cadaveric implants. These patches are used to reinforce dural closure when there is the risk of postoperative cerebrospinal fluid (CSF) leak.
- **Tissue Adhesives:** these are an alternative to sutures and staples used for closure of wounds and fixation of devices such as surgical mesh, patches and scaffolding to tissues. They may also be used as a sealant for closure, for example, of colostomies. Tissue adhesives are defined as any substance with characteristics that allow for polymerization. This polymerization must either hold tissue together or serve as a barrier to leakage or to control bleeding. Fibrin sealants are the most commonly used adhesives. Other adhesives include cyanoacrylates, albumin-based compounds, collagen-based compounds,

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glutaraldehyde glues and hydrogels.<sup>212</sup> Tissue adhesives can act as a barrier to microbial penetration as long as the adhesive film remains intact.

Any of the supportive devices can include biocompatible coated materials such as silver coating, titanium dioxide, hydroxyapatite, hyaluronate, monocryl, paclitaxel and many other materials.

### 9.3. Clinical evidence

The clinical evidence can be derived from clinical investigation(s) data, a comprehensive literature review and/or post-market data (clinical experience) on the device (direct) and/or the 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 Section 4: [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. Manufacturers should refer to Section 2: [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, patient profiles and morbidity as well as specific indications. In addition the risks, techniques, design of implants and accessories and experience of users should be taken into account. Manufacturers are advised to justify the patient numbers recruited according to sound scientific reasoning through statistical power calculation. Registry data from jurisdictions where the device is marketed may provide useful clinical evidence.

The duration of the clinical investigation should be appropriate to the device, the patient population and medical conditions for which it is intended. Duration should always be justified, taking into account the time-frame of expected complications. Analysis of clinical events should be blinded and independently adjudicated wherever possible.

#### Literature review

A literature review involves the systematic identification, synthesis and analysis of all available published and unpublished literature, favourable and unfavourable, on the device or predicate/similar marketed device when used for its intended purpose(s).

The literature search protocol should be determined prior to implementing the search, detailing the aim, search terms, planned steps and inclusion and exclusion criteria. Data on the materials used to construct the device, their biocompatibility, the device dimensions and geometry and the intended purpose will determine the construction of search strategies as well as study selection. The selection of 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. 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

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criteria for inclusion in the review. This ensures that the searches are comprehensive and the included studies are related to the device in question or substantially equivalent device(s).

A full description of the device used or adequate information to identify the device (e.g. manufacturer name and model number) must be extractable from study report. If this is not possible, the study should be excluded from the review. The overall body of evidence from the literature should be synthesised and critically evaluated by a competent clinical expert and a literature report prepared containing a critical appraisal of this compilation. The full details of the search can be provided in the supporting documents and should be sufficient to allow the search to be reproduced.

### **Post-market data**

Post-market data can be provided for the actual device or for the 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, including the certificate number, date of issue and name under which the device is marketed, the exact wording of the intended purpose/approved indication(s) and any conditions in other jurisdictions
- any regulatory action such as CE mark withdrawals, recalls (including recalls for product correction, and the reason for these i.e. IFU change), suspensions, removals, cancellations, any other corrective action ) anywhere in the world as reported to or required by regulatory bodies
- distribution numbers of the device(s) including by country and/or geographical region for every year since launch. It is accepted that this may not always be appropriate for high volume devices, those with many components or those on the market for many years
- the number of years of use
- for every year since launch, adverse events, complaints and vigilance data categorised by type and clinical outcome (adhesion, tissue damage (erosion, dehiscence etc.), chronic pain, bacterial infection and toxicity due to chemical components of the device)
- the post-market surveillance data from national registries in jurisdictions where the device is approved for clinical use if available
- explanted devices returned to manufacturers should be accounted for with an explanation of device failures and corrective measures.

Publicly available post-market data such as adverse event reporting on the FDA MAUDE database and the TGA IRIS may be used for devices from other manufacturers.

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

The post-market data should be critically evaluated by an appropriately qualified clinical expert, that is, someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting. The CER should then be endorsed by the clinical

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expert (evidenced by signature and date) to enable an understanding of the safety and performance profile of the device(s) in a 'real-world' setting.

## 9.4. Compiling the CER

In compiling the clinical evidence the manufacturer should ensure that a clinical expert in the relevant field critically evaluates all the clinical data from clinical investigation(s), literature review and/or post-market data (clinical experience) and provides a written report, the CER, to allow the clinical assessor to determine whether the clinical evidence is sufficient to demonstrate that the requirements of the applicable EPs have been met and the device is safe and performs as intended.

Section 3.2: [Constructing the clinical evaluation report](#) outlines the components that may comprise clinical evidence (see Section 2) for a medical device, and the process to compile a CER. These apply whether the manufacturer is using direct clinical evidence or relying on indirect clinical evidence based on a predicate or similar marketed device. Guidance on defining a predicate or similar marketed device is provided in Section 4: [Demonstrating Substantial Equivalence](#).

The device description should include sufficiently detailed information to satisfy the requirements of Appendix 3 of MEDDEV 2.7.1 Rev 4 on "Device description – typical contents". For supportive devices this may include, but is not limited to; the material type, chemical composition, biological compatibility testing, coating, porosity, flexibility, tensile strength, durability and dimensions. If biological actives are impregnated the *in vitro* activity should be demonstrated and documented in the submission.

The design of clinical studies to demonstrate the clinical safety and performance of devices that have no equivalent 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 or similar marketed device selection.

As per Section 3: [Clinical evaluation report and supporting documents](#) the CER should include the following:

1. [Device description, lineage and version if applicable](#)
2. [Intended purpose/indications and claims](#)
3. [Regulatory status in other countries](#)
4. [Summary of relevant pre-clinical data](#)
5. [Demonstration of substantial equivalence \(if applicable\)](#)
6. [Overview and appraisal of clinical data](#)
7. [Critical evaluation of clinical data including post market data](#)
8. [Risk-benefit analysis](#)
9. [Conclusions](#)
10. [The name, signature and curriculum vitae of the clinical expert and date of report](#)



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## Supportive data and information

The following information on the device must also be provided:

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

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

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

## 9.5. Defining clinical success

### Meshes

Hernia repair surgery is the most common application for surgical meshes followed by reconstructive surgery for POP and SUI.<sup>[209](#)</sup>

Meshes can be used for either a primary or secondary repair or as suture line reinforcement material. It is imperative that the clinical evidence reflects the indication for use of the mesh under review. Measures such as de novo or worsening prolapse in a non-treated compartment and urinary symptoms may be reported as both safety and performance measures.

### *Safety*

Post-operative complications and/or reoperation are the primary safety outcome measures although subjective measures of success should also be included.

Complications associated with surgical mesh for hernia repair reported in the literature include adhesions, fistula, bowel obstruction, mesh erosion, bleeding, infection, haematoma, seroma and chronic pain. Bowel obstruction is not seen in extra peritoneal mesh placement. Some of these complications may occur with surgery and are not due to the mesh per se.

Complications associated with surgical mesh for POP and SUI reported in the literature include pain, bleeding, organ perforation (such as bladder and urethral perforation), dyspareunia, visceral injury, urinary issues (including retention, voiding dysfunction, urge incontinence, overactive bladder) as well as late events such as mesh erosion and exposure. A summary of the safety data extracted from systematic reviews is provided in Table 23. Clinical experts have

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reported additional complications associated with the use of surgical mesh for POP and SUI which include inflammation, seroma, haematoma, infection, fistula, urinary tract infection, bowel dysfunction, nerve injury, chronic pain and de novo or worsening prolapse in a non-treated compartment.

The manufacturer should report all post-surgical complications and serious adverse events or failures that have been found with the use of the mesh or 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 used in POP repair was identified:

- Austrian Urogynecology Working Group registry for transvaginal mesh devices for POP repair [216](#)

In addition a number of registers for surgeries that involve meshes for hernia repair were identified:

- Swedish hernia register [217](#)
- Herniamed, a German internet-based registry for outcome research in hernia surgery [218](#)
- Americas Hernias Society Quality Collaborative (AHSQC) in the USA [219](#)
- European Registry of Abdominal Wall Hernias (EuraHS) [220](#)
- ClubHernie in France (note – French language) [221](#)

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. [222](#) [223](#) However, manufacturers should be aware that late adverse events of a device can occur many years after implantation.

Safety parameters should be established *a priori* with nominated values clinically justified by a clinical expert experienced in the use of the device.

### **Performance**

It is useful to divide success into objective success measures and subjective success measures, such as clinician reported outcomes and patient-reported outcomes. Performance related parameters reported in the peer reviewed literature for surgical meshes include recurrence rates, reoperation rates, functional scores, quality of life scores and pain. For absorbable devices, clearance and metabolism times are also provided in Table 25. Other measures for performance are objective success measures (including anatomic success measure such as POP-Q) and subjective success measures such as quality of life outcomes. An important outcome is de novo or worsening prolapse in a non-treated compartment and, specifically in regards to SUI, de novo or worsening urinary symptoms should be included as a measure of performance.

### **Primary repair**

Recurrence and reoperation rates can be used to measure clinical success in primary repair surgery.

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Recurrence rates of 15-25% are frequently reported after mesh repair of a hernia.<sup>224</sup> The rates of reoperation vary based on the indication, patient characteristics and surgical procedure undertaken, therefore, depending on these characteristics, rates within this range may be considered acceptable. A satisfactory result of biologic mesh application is a recurrence rate of 18% or below and seroma formation of 12% or less.<sup>225</sup>

Importantly, patient follow-up periods must be comparable to accurately compare recurrence rates as a function of supportive devices.<sup>224</sup>

#### *Primary and secondary outcomes*

Clinical success is often evaluated by patient-oriented assessment tools that determine functional outcomes. It can also be evaluated by primary outcomes or secondary outcomes, and it is important to make a distinction between these two. Functional scores provide an aggregate of patient reported domains (e.g. pain) with an objective measure of mesh success (e.g. current size of hernia) and represent a clinically meaningful grading of mesh performance. However, for procedures using surgical mesh, the short-term performance of a device may be dominated by procedural variables; therefore sufficient time should lapse to isolate device-specific improvements.

Measures of performance that may be of use include the Ventral Hernia Working Group (VHWG) grading system and the Pelvic Organ Prolapse Quantification System (POP-Q). POP-Q is a validated staging system for pelvic organ prolapse and currently the most quantitative, site-specific system with high reported inter-observer reliability.<sup>226</sup> The VHWG has a staging system which predicts both risk and likely outcome in terms of both recurrence and SSO. It is made up of the VHWG grading system plus a defect size component to predict SSO and recurrence and has been validated for clinical application.

Where validated measurement tools are not used, manufacturers can assist the clinical assessor by providing data based on surrogate markers. The choice of surrogate markers and the validation of these to predict future complications or failure should be clinically justified and consistent with the proposed therapeutic indications.

Examples of surrogate markers for mesh performance are:

- Reoperation for recurrence in hernia surgery <sup>227</sup>
- For hiatal hernia, radiological or endoscopic absence of a recurrent hernia (defined as >2cm in size) <sup>211</sup>
- For POP, examples of surrogate markers of performance include: recurrent prolapse, ongoing pain including dyspareunia, de novo urinary or bowel symptoms.
- For SUI, de novo or worsening urinary symptoms



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

Minimum benchmarks that need to be reached to demonstrate the device is performing as expected and is equivalent to already marketed products should be used. For prolapse, at one year POP-Q stage II or greater is considered to be surgical failure and POP-Q stage I was

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considered a surgical cure.<sup>228</sup> For hernia, at the time of writing, there are no benchmarks for performance.

## **Patches**

Central Nervous System (CNS) patches, both bioabsorbable and non-absorbable, are impermeable adhesive membranes used in (intradural) neurosurgical procedures, as an alternative to using autologous grafts or cadaveric implants. These patches are used to reinforce dural closure when there is the risk of postoperative cerebrospinal fluid (CSF) leak.<sup>229 230</sup>

### ***Safety***

For safety, the primary outcome measures are CSF leak, CSF fistula and deep wound infection. Other complications associated with CNS patches (studies reviewed tested for these effects but their occurrence was very rare) include adverse or allergic effects, hydrocephalus, brain tissue scarring, new epileptic seizures and mortality, refer to Table 24. The manufacturer 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, manufacturers should be aware that 3 months is the minimum and will not capture information relating to the late failure of a patch. At the time of writing there are no benchmarks for CNS patches. Manufacturers should define a minimum performance marker based on the literature and clinical expertise, providing a clinical justification for the parameters and values that have been selected.

### ***Performance***

Performance related parameters reported in the peer reviewed literature for patches are provided in Table 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. improvement in POP-Q stage) and represent a clinically meaningful grading of mesh performance. No such tool has been found for application of CNS patch. The most useful functional measure for CNS patches is the existence of cerebrospinal fluid leakage. Manufacturers should define a minimum performance marker based on the literature and clinical expertise, providing a clinical justification for the parameters and values that have been selected.

## **Tissue adhesives**

### ***Safety***

Chronic pain, infection, inflammation, tissue damage, bleeding and leakage of bile and other fluids are primary outcome measures for tissue adhesive surgeries, refer to Table 24. Chronic pain can be measured with Visual Analogue Score (VAS) as mild, moderate or severe persisting from 3 months to 1 year.<sup>231</sup> Secondary outcomes reported in the literature are numbness, discomfort, patient satisfaction, QoL (measured with SF12), length of hospital stay, and time to return to normal activities. The manufacturer should report any post-surgical complications and failure of the adhesive or 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.<sup>232</sup> Another study found a

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recurrence rate of 2.3% at 15 months.<sup>233</sup> Thus a recurrence rate <2.3% in 15-18 months may be acceptable. Rates for tissue adhesives other than those containing fibrin glue are not readily evident, at time of writing. Patient follow-up periods must be comparable when using recurrence rates as a measure of performance of tissue adhesives.<sup>224</sup> Nominated recurrence rates need to have a rigorous clinical justification provided by a clinical expert with experience in the use of the device or device types who takes into account current research when evaluating all of the clinical data in the CER.

### **Performance**

Recurrence is one performance related parameter reported in the peer reviewed literature for tissue adhesives (Table 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 manufacturers define a minimum performance marker based on the literature and clinical expertise and provide a clinical justification for the parameters and values that have been selected.



When documenting patient performance scores for tissue adhesives, it is recommended that manufacturer provide a clinical justification for the follow-up period used. At the time of writing 15-18 months follow-up has been reported in the literature.

As assessment tools of device performance may not be available, manufacturers can assist the clinical assessors by providing data on direct markers.

Examples of direct markers for performance of adhesives are:

- achievement of haemostasis/ increased number of patients reaching haemostasis – measured as no evidence of bleeding from exposed surfaces <sup>234</sup>
- presence of haematoma/ seroma during study, visual perception of oedema 1-7 days post-operatively
- fluid drainage 24h post-operatively, volume of blood loss or transfusion, and resection surface complications such as intra-abdominal fluid collections detected by CT scan <sup>235</sup>
- reduction in drainage volume <sup>235</sup>
- 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 <sup>234</sup>



Manufacturers should, where possible, use validated measurement tools. If selecting and reporting surrogate markers of performance manufacturers should provide a clinical justification for the selection and validation of these to predict device complications or failure.

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## 9.6. Summary of safety and performance data

### Characteristics of clinical studies on supportive devices

**Table 23: 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 Laporoscopic v. open surgery Comparing mesh materials Biologic v. non biologic mesh Human-derived v. porcine-derived biologic mesh Self-gripping mesh or suture fixation	Mesh v. conventional repair Mesh v. vaginal colpopexy Mesh v. anterior or posterior colporrhaphy	NA	Fibrin sealant v. staples Fibrin sealant v. Tranexamic acid Fibrin sealant v. control
Quality of included evidence as reported	Poor to satisfactory	Low to high	NA	Inadequate to good
Patient Follow-up Comparative trials e.g. RCTs	1 month to 10 years	3 months to 3 years	NA	7 months to 4 years

## Reported clinical outcomes in the peer reviewed literature

**Table 24: Summary of safety data extracted from systematic reviews on supportive devices**

Safety parameter	Vaginal surgical mesh	Hernia surgical mesh	Patches	Tissue adhesives
<i>Death</i>			✓	✓
<i>Urinary issues</i>	✓		N/A	N/A
<i>Pain</i>	✓	✓		
<i>Chronic pain</i>		✓	N/A	✓
<i>Infection</i>		✓	✓	✓
<i>Bleeding</i>	✓	✓		✓
<i>Organ perforation</i>	✓			N/A
<i>Dyspareunia</i>	✓		N/A	N/A
<i>Material exposure</i>	✓		N/A	N/A
<i>Visceral injury</i>	✓		N/A	N/A
<i>Mesh erosion</i>	✓	✓	N/A	N/A
<i>Haematoma</i>		✓	N/A	✓
<i>Seroma</i>		✓	N/A	✓
<i>Bile leak</i>	N/A	N/A	N/A	✓
<i>Cytotoxicity</i>	✓		N/A	✓
<i>CSF leakage</i>	N/A	N/A	✓	
<i>Adhesions</i>	N/A	✓	N/A	N/A
<i>Fistula</i>	N/A	✓	N/A	N/A
<i>Bowel obstruction</i>	N/A	✓	N/A	N/A
<i>Hydrocephalus</i>	N/A	N/A	✓	N/A

Greyed cells (N/A) indicate that the safety parameter is not applicable to that device class



**Table 25: Summary of performance data extracted from systematic reviews, RCTs and primary research reports on the safety and performance of supportive devices**

Performance parameter	Surgical Mesh - Gynaecological	Surgical Mesh - Hernia	Absorbable devices	Patches	Tissue Adhesives
Revision/reoperation (recurrence rates)	✓	✓	✓	✓	✓
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		

## 10. Implantable devices in the magnetic resonance environment

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

- Active Implantable Medical Devices (AIMDs)
  - implantable permanent pacemakers (PPM)
  - implantable cardioverter defibrillators (ICD)
  - cardiac resynchronisation therapy (CRT) devices
  - implantable loop recorders (ILR); and
  - the associated leads.
- Passive Implantable Medical Devices (PIMDs), including but not limited to:
  - orthopaedic implants such as hip or knee implants
  - cardiovascular stents

- 
- heart valves
  - neurovascular aneurysm clips or coils
  - interventional guidewires or catheters

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

### 10.1. Summary recommendations

- AIMDs and many PIMDs, for example orthopaedic implants, are complex medical devices forming systems of multiple independent components. The unique configuration of components for each device system may have consequences for the safety of the device system in the MR environment. Therefore, manufacturers are advised to provide appropriate evidence to support the safety and identify the risks and hazards of each unique device system separately. Due to the nature of their materials, currently available AIMDs can only be marked as ‘MR conditional’ or ‘MR unsafe’. PIMDs can be marked as ‘MR safe’, ‘MR conditional’ or ‘MR unsafe’.
- For IMDs claimed to be ‘MR conditional’ under specified conditions of use, these conditions must be clearly articulated in the submission and in the IFU, and/or other supporting documents with evidence supporting any reported thresholds.
- For PIMDs, the use of non-clinical data alone suffices to meet the requirements for the applicable EPs. Clinical data are not required.
- A well-documented risk analysis and management system and quality management system should be provided with the CER.
- Provision of clinical data for AIMDs if applicable:
  - Post market data or clinical investigations from another jurisdiction where the device is already approved can provide useful clinical evidence and are acceptable. This includes clinically indicated MRIs provided that potential sources of bias have been minimised. Studies should be appropriate to inform on the safety and performance of the device for its intended purpose in relation to MR conditional use.
  - examples of appropriate safety outcomes are provided in Table 26 - Section 10: [Safety of active implantable medical devices in the MR environment](#).
  - when submitting a comprehensive literature review, full details of the method used should be included in the CER in sufficient detail to ensure the literature review can be reproduced.
  - for guidance on the presentation of clinical evidence and conduct of comprehensive literature reviews manufacturers are directed to relevant sections.

### 10.2. 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*”<sup>236</sup> In this context, the term “MR environment” refers to the physical space surrounding a MR magnet, which is affected by the static, gradient and radiofrequency (RF) electromagnetic fields.<sup>236 237</sup> Standard F2503-13 defines three terms to classify the safety of medical devices in the MR environment:

- **MR safe:** An item that poses no known hazards resulting from exposure to any MR environment.<sup>236</sup> A medical device can only be classified as MR safe if it is composed of materials that are electrically non-conductive, non-metallic, and non-magnetic (e.g. glass, plastic, silicone). Such devices may be determined to be MR safe based on scientific rationale rather than test data;
- **MR conditional:** An item with demonstrated safety in the MR environment within defined conditions.<sup>236</sup> 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 26 (below).<sup>238</sup>
- **MR unsafe:** An item that poses unacceptable risks to patients, medical staff or other persons in the MR environment.<sup>236</sup>

**Table 26: 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	•		
Vibration/discomfort, device damage	•	•	
Device interactions/therapy delivery, device reset, device damage	•	•	•
Device case heating/discomfort, tissue necrosis		•	•
Unintended cardiac stimulation/arrhythmia induction, asystole		•	•
Lead electrode heating/therapy delivery, sensing			•

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

### 10.3. Evidence requirements

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

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

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

Other information that should be provided for IMDs includes:

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

### **Requirements for PIMDs**

For PIMDs claimed to be ‘MR conditional’, the following experimental data are required using non-clinical testing methods specified in the standards below or equivalent methods,[239](#)

- 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 [240](#)
- 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 [241](#)
- Heating by RF Fields: ASTM F2182-11a, Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging [242](#)
- Image Artifact: ASTM F2119-07 (Reapproved 2013), Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants [243](#)

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

All testing protocols should be described with the following elements:

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

- 
- results (summarised and raw form).

### Regulatory status in other jurisdictions

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

### Post-market data

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

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

## 10.4. 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.

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

**Active implantable medical devices**

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

- a. either:
  - i. to be, by surgical or medical intervention, introduced wholly, or partially, into the body of a human being; or
  - ii. to be, by medical intervention, introduced into a natural orifice in the body of a human being; and
- b. to remain in place after the procedure.

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

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

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

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

**Permanent pacemakers (PPM)** are pacing devices used to regulate abnormal heart rhythm. PPMs deliver low-energy electrical impulses to treat bradyarrhythmias. They may include one pacing lead for single-chamber right ventricular pacing, or two pacing leads for right ventricular and right atrial pacing.[159](#) [166](#)

**Implantable cardioverter defibrillators (ICD)** are capable of delivering both low-energy impulses for pacing, and high-energy impulses for defibrillation.[244](#) ICDs are typically implanted in patients at risk of life-threatening ventricular arrhythmias, in whom a high-energy impulse is required to restore normal rhythm.[160](#) [162](#) ICDs typically have a larger battery than a PPM, and include one lead for right ventricular pacing and defibrillation, +/- another lead for right atrial pacing.[244](#)

**Cardiac resynchronisation therapy (CRT)** devices are pacing devices used to regulate the lack of synchrony between the left and right ventricles. CRT devices are typically used to treat patients with advanced heart failure. They include either two or three pacing leads for right

ventricle, left ventricle, +/- right atrial pacing. CRT devices may also deliver high-energy impulses to correct life-threatening arrhythmias (CRT-Ds).<sup>245</sup>

**Implantable loop recorders (ILR)** are single-lead cardiac monitoring devices. They can be used as a temporary tool to diagnose patients with unexplained palpitations or syncope, or for long-term monitoring of patients with unresolved syncope who may be at risk of atrial fibrillation.<sup>246</sup> Unlike other classes of active implantable cardiac devices, they are not capable of pacing or defibrillation.

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

- the materials from which the device components are made, including the chemical composition
- the dimensions and geometry of the device components
- the list of other devices that are likely to be used in conjunction with the device.

## 10.5. Summary of safety and performance data

### Selection of included studies

**Table 27: Summary of primary studies report in narrative reviews on the safety of AIMDs in the MR environment** <sup>247 248 249 250 251 252 253 254</sup>

Characteristics of included studies	Evidence reported in narrative reviews
<b>Dominant design of included studies</b>	3 RCTs, 1 case-control and 38 case series investigations were included in narrative review articles
<b>Sample size range for included study designs</b>	RCTs: 263-466 Case-control: 65 Case series: 1 to 272
<b>Patient follow-up</b>	Range 0-12 months (median 3 months)
<b>Safety outcomes reported</b>	<b>Force and torque</b> <ul style="list-style-type: none"> <li>– Generator movement</li> <li>– Lead dislodgement</li> <li>– Lead damage</li> <li>– Force (Newtons)</li> </ul> <b>Vibration</b> <ul style="list-style-type: none"> <li>– Generator movement</li> </ul>



Characteristics of included studies	Evidence reported in narrative reviews
	<ul style="list-style-type: none"> <li>– Patient discomfort due to vibration</li> </ul> <p><b>Device interactions</b></p> <ul style="list-style-type: none"> <li>– Reed switch activation/deactivation</li> <li>– Diminished battery voltage (<math>\geq 0.04</math> V)</li> <li>– Power-on-reset</li> <li>– Temporary communication failure with device</li> <li>– Device reprogramming</li> <li>– Pause in pacing</li> <li>– Signal (image) artefacts</li> </ul> <p><b>Device case heating</b></p> <ul style="list-style-type: none"> <li>– Detectable heat increase near generator</li> </ul> <p><b>Lead electrode heating</b></p> <ul style="list-style-type: none"> <li>– Increase in pacing capture threshold (<math>\geq 0.5</math> V)</li> <li>– Increase in cardiac enzyme level (Troponin-I)</li> <li>– Decrease in atrial sensing amplitude <math>\geq 50\%</math>, or amplitude lower than 1.5 mV <a href="#">255</a></li> <li>– Decrease in ventricular sensing amplitude <math>\geq 50\%</math>, or amplitude lower than 5.0 mV <a href="#">256</a></li> <li>– Change in pacing lead impedance (<math>\geq 50</math> <math>\Omega</math>)</li> </ul> <p><b>Unintended cardiac stimulation</b></p> <ul style="list-style-type: none"> <li>– Inappropriate pacing</li> <li>– Induction of arrhythmia</li> <li>– Heart palpitations</li> </ul>

# Appendix 1: CER and supporting documents

## CER

The following list outlines the recommended heading structure for the CER.

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

Section	Included	Author(s)	Page(s)
1. Device description, lineage and version ( <i>if applicable</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
2. Intended purpose / indications, and claims	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
3. Regulatory status in other countries	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
4. Summary of relevant pre-clinical data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
5. Demonstration of substantial equivalence ( <i>if applicable</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
6. Overview and appraisal of clinical data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
7. Critical evaluation of clinical data including post market data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
8. Risk-benefit analysis	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
9. Conclusions	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
10. Name, signature and curriculum vitae of clinical expert and date of report	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		

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## Supporting documents

The following information on the device must also be provided for pre market (conformity assessment reviews and applications for inclusion) and post-market reviews in addition to the CER.

Section	Included	Author(s)	Page(s)
Risk assessment and management document	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
IFU, product manual and all other documents supplied with the device.	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		

## Additional information

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

Section	Included	Author(s)	Page(s)
Additional information on the device	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
Preclinical data (if relevant)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
Full clinical investigation reports	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
Literature search and selection strategy	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		
Full text of pivotal articles from the literature review	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A		

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## Appendix 2: Glossary and abbreviations

### Glossary

**Adverse event:**<sup>25</sup> any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational device or the comparator.

NOTE 2: This includes events related to the procedures involved.

NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

**Application audit:** The Act enables the Regulations to prescribe certain kinds of applications that are to be selected for audit. These kinds of applications must be selected for audit by the Secretary. However, the Secretary may also select for auditing any other application under section 41FH of the Act. The TGA has established two levels of application audit, Level 1 and Level 2:

- **Level 1:** Targeted for completion within 30 days - The TGA will consider:
  - the original or correctly notarised copy of the manufacturer's Australian Declaration of Conformity
  - Copy of the latest and current conformity assessment evidence for the medical device
  - Information about the device, including copies of the label, instructions for use and advertising material such as brochures, web pages and advertisements
- **Level 2:** Targeted for completion within 60 days – The TGA will consider all of the documentation considered in a Level 1 audit. In addition, the TGA will consider:
  - the risk management report
  - the clinical evaluation report
  - efficacy and performance data for medical devices that disinfect including those that sterilise other medical devices.

**Assessor:** a medically qualified person who reviews the clinical evaluation report and supporting documents provided to the TGA with applications for inclusion, review of conformity assessment procedures and post market reviews of medical devices.

**Australian Register of Therapeutic Goods (ARTG):** The ARTG is the register of information about therapeutic goods for human use that may be imported, supplied in or exported from Australia. All medical devices, including Class I, must be included in the ARTG before supply in Australia. There are limited exceptions to this requirement specified in the legislation.

**Biological characteristics:** relates to use of the materials or substances in contact with the same human tissues or body fluids. Evaluators should consider biological safety (e.g. in compliance to ISO 10993) as well as other aspects necessary for a comprehensive demonstration of equivalence. A justification explaining the situation should be provided for any difference.

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**Clinical data:**<sup>28</sup> the safety and/or performance information that is generated from the clinical use of a device. Clinical data are sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which substantial equivalence to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which substantial equivalence to the device in question can be demonstrated. (with addition of 'substantial').

**Clinical evaluation:**<sup>28</sup> a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for Use.

Note: In exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.

**Clinical evidence:**<sup>34</sup> The clinical data and the clinical evaluation report pertaining to a medical device.

**Competent clinical expert:** Someone with relevant medical qualifications and direct clinical experience in the use of the device or device type in a clinical setting.

For some lower class devices which are not typically used by medical practitioners, another health practitioner who uses the device or similar devices in a clinical setting may be deemed, on a case by case basis, as an appropriate clinical expert who is qualified to critically evaluate and endorse the CER.

**Clinical Evaluation Report (CER):**<sup>64</sup> A report by an expert in the relevant field outlining the scope and context of the evaluation; the inputs (clinical data); appraisal and analysis stages; and conclusions about the safety and performance of the device. The clinical evaluation report should be signed and dated by the clinical expert.

**Clinical investigation:**<sup>25</sup> systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device.

Note: 'clinical trial' or 'clinical study' are synonymous with 'clinical investigation'.

**Clinical investigation data:**<sup>34</sup> 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).

**Clinical performance:**<sup>25</sup> behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to the appropriate subject(s).

**Clinical Safety:**<sup>28</sup> freedom from unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use.

**Clinical use:**<sup>28</sup> use of a medical device in or on living human subjects. NOTE: Includes use of a medical device that does not have direct patient contact.

**Conformity Assessment:**<sup>257</sup> The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority,

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to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles.

Conformity assessment is the name given to the processes that are used to demonstrate that a device and manufacturing process meet specified requirements. In Australia this means that the manufacturer must be able to demonstrate that both the medical device and the manufacturing processes used to make the device conform to the requirements of the therapeutic goods legislation.

Conformity assessment is the systematic and ongoing examination of evidence and procedures to ensure that a medical device complies with the Essential Principles. It provides objective evidence of the safety, performance, benefits and risks for a specified medical device and also enables regulatory bodies to ensure that products available in Australia conform to the applicable regulatory requirements.

The Conformity Assessment Procedures allow risk based premarket assessment for devices. All manufacturers of all medical devices are required to meet manufacturing standards and all manufacturers, except those manufacturing the lowest risk devices, are audited and are required to have their systems certified. The level of assessment is commensurate with the level and nature of the risks posed by the device to the patient, ranging from manufacturer self-assessment for low risk devices through to full TGA assessment with respect to high-risk devices.

**Conformity assessment certificate:** A certificate to demonstrate that the conformity assessment procedure has been assessed.

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

**Hazard:**<sup>28</sup> potential source of harm.

**Incident:**<sup>28</sup> any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

**Indications for use:**<sup>258</sup> The disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

**Intended purpose:** 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 (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

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encompass products that are intended for general laboratory use that are not manufactured, sold or presented for use specifically as an IVD.

**Kind of medical device:** A single entry in the ARTG may cover a range of products that are of the same kind rather than individual devices. At present, medical devices (with the exception of Class III and Active Implantable Devices (AIMDs) and Class 4 IVDs and Class 4 in-house IVDs) are included as a group in the ARTG under a single entry if they: have the same sponsor; have the same manufacturer; have the same medical device classification; have the same nomenclature system code (GMDN code).

**Manufacturer:** Refer to section 41BG of the Act.

**Medical device:** A medical device is:

- (a) any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:
  - i. diagnosis, prevention, monitoring, treatment or alleviation of disease;
  - ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;
  - iii. investigation, replacement or modification of the anatomy or of a physiological process;
  - iv. 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; or
- (aa) any instrument, apparatus, appliance, material or other article specified under subsection (2A); or
- (ab) any instrument, apparatus, appliance, material or other article that is included in a class of instruments, apparatus, appliances, materials or other articles specified under subsection (2B); or
- (b) an accessory to an instrument, apparatus, appliance, material or other article covered by paragraph (a), (aa) or (ab).

Refer to section 41BD of the Act for remainder of the definition.

**Medical device classifications:** Medical devices are classified 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.

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

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**Post market surveillance:** Once a device has been included in the ARTG, the sponsor has ongoing responsibilities. These include monitoring and reporting to the TGA adverse events, vigilance reports, complaints, performance issues and regulatory actions in other jurisdictions. Please refer to Sections 22 and 23 of the ARGMD.

**Risk:**<sup>28</sup> combination of the probability of occurrence of harm and the severity of that harm

**Risk management:**<sup>28</sup> systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.

**Serious adverse event:**<sup>28</sup> adverse event that

- a) led to death
- b) led to serious deterioration in the health of the subject, that either resulted in
  - 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function, or
  - 3) in-patient or prolonged hospitalization, or
  - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP [Clinical Investigation Plan], without serious deterioration in health, is not considered a serious adverse event.

**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 manufacturer is seeking to demonstrate substantial equivalence. Such a device may not be manufactured by the manufacturer.

**Sponsor:** Refer to Section 3 of the Act.

**Substantial equivalence:** Substantial equivalence confirms that the new device is 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 technical and biological characteristics.

**Technical characteristics:**<sup>64</sup> these relate to the design, specifications, physicochemical properties including energy intensity, deployment methods, critical performance requirements, principles of operation and conditions of use.



## Abbreviations

Abbreviation	Meaning
AAA	Abdominal aortic aneurysm
AE	Adverse event
AICD	Active implantable cardiac device
AIMD	Active implantable medical device
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ARGMD	Australian Regulatory Guidelines for Medical Devices
ARTG	Australian Register of Therapeutic Goods
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (Royal Australasian College of Surgeons)
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
BMS	Bare metal stent
BSIR	British Society of Interventional Radiology
CE	Conformité Européenne (European Conformity)
CEBM	Centre for Evidence-Based Medicine
CDMSNet	Canadian Medical Devices Sentinel Network
CDRH	Center for Devices and Radiological Health [USA]
CER	Clinical Evaluation Report
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPR	Cumulative Percent Revision
CRT	Cardiac Resynchronisation Therapy
CSR	Clinical Study Report

Abbreviation	Meaning
CTA	Computed tomography angiography
D&B	Downs & Black [quality assessment tool]
DES	Drug-eluting stent
DVT	Deep vein thrombosis
EU	European Union
EUDAMED	European Databank on Medical Devices
FDA	Food and Drug Administration [USA]
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GMDN	Global Medical Device Nomenclature [System]
HBD	Harmonisation By Doing
HDE	Humanitarian device exemption
ICMJE	International Committee of Medical Journal Editors
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IDEAL	Innovation, Development, Exploration, Assessment, Long-term study [Collaboration]
IFU	Instructions For Use
ILR	Implantable Loop Recorder
IMDRF	International Medical Device Regulators Forum
IRIS	Medical device Incident Reporting and Investigation Scheme (TGA)
ISO	International Standards Organization

Abbreviation	Meaning
IVD	In vitro diagnostic
KAT	Knee Arthroplasty Trial
LOHS	Length of hospital stay
MA	Meta-analysis
MACE	Major adverse cardiac events
MAUDE	Manufacturer and User Facility Device Experience database
MCID	Minimum clinically important difference
MDR	Medical Device Reporting (Program) [USA]
MedSun	Medical Device Surveillance Network [USA]
MHLW	Ministry of Health, Labour & Welfare [Japan]
MHRA	Medicines and Healthcare Products Regulatory Authority [UK]
MI	Myocardial infarction
MLHF	Minnesota Living with Heart Failure Questionnaire
MPMDB	Marketed Pharmaceutical and Medical Devices Bureau [Canada]
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NB	Notified Body [EU]
NCAR	National Competent Authority Report
NHMRC	National Health and Medical Research Council
NHS	National Health Service [UK]
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa scale [quality assessment tool]

Abbreviation	Meaning
NR	Not Reported
NYHA	New York Heart Association Classification
OPC	Objective Performance Criteria
PAL	Pharmaceutical Affairs Law [Japan]
PCT	Pacing Capture Threshold
PDA	Patent Ductus Arteriosus
PE	Pulmonary Embolus
PMA/PMAS	Pre-Market Approval or Pre-Market Approval Supplement [USA]
PMCF	Post-Market Clinical Follow-up
PMDA	Pharmaceuticals and Medical Devices Agency [Japan]
PPM	Permanent Pacemaker
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PMS	Post-market Surveillance
POP-Q	Pelvic Organ Prolapse Quantification System
QMS	Quality Management System
QOL	Quality Of Life
QUADAS	Quality Appraisal of Diagnostic Accuracy Studies
RANZCR	Royal Australian and New Zealand College of Radiologists
RCT	Randomized controlled trial
RF	Radiofrequency
RIND	Reversible Ischemic Neurological Deficit
RSA	Radiostereometric analysis

Abbreviation	Meaning
SAR	Specific Absorption Rate
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guidelines Network
SSO	Surgical Site Occurrence
SR	Systematic Review
STARD	Standards for Reporting of Diagnostic Accuracy
STED	Summary Technical Document
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient Ischemic Attack
TGA	Therapeutic Goods Administration
TLR	Target Lesion Revascularisation
TVR	Total Vessel Revascularisation
UK	United Kingdom
USA	United States of America
VARC	Valve Academic Research Consortium
VHWG	Ventral Hernia Working Group
VTE	Venous Thromboembolism
WHO	World Health Organisation

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## Appendix 3: Source material

### Search Method: Identification and selection of clinical studies

The search method used by ASERNIP-S to identify, retrieve and review the evidence that supports this guidance document was a pragmatic adaption of a rapid systematic review.<sup>[259](#)</sup>

Selection criteria were established *a priori* and include publication type, type of medical device under review, intended purpose of the medical device, adverse events (safety), and clinical outcomes related to device performance.

Using the PubMed Clinical queries tool, representative articles were identified through scoping searches. These results informed the selection of appropriate text words and subject headings.

All searches were executed using the Ovid platform for Medline, Embase and the Cochrane library and Evidence-based medicine databases. Through the application of search filters for study type (Systematic Reviews, Randomised Controlled Trials and Registry trials) search results were restricted to appropriate level evidence.

For joint prostheses - Search title: Total and partial joint arthroplasty: Search terms: Shoulder surgery[MeSH], Shoulder Joint/surgery[MeSH]; Knee surgery [MeSH]; 'knee Joint' surgery[MeSH]; hip Joint surgery [MeSH]; arthroplasty[MeSH]; ((shoulder OR hip OR Knee) adj2 replacement). [text word]; ((shoulder OR hip OR Knee) adj2 joint).[text word]; ((shoulder OR hip OR Knee) adj3 arthroplasty)[text word]; ((shoulder OR hip OR Knee) adj3 surger?)[text word].

For cardiovascular devices for patency and functional flow- Search title: Cardiovascular devices for patency and functional flow: Search terms: Heart [MeSH]; aneurysm [MeSH]; aorta[MeSH]; Venae cavae[MeSH]; 'Ductus Arteriosus, Patent'[MeSH]; vascular.[text word]; endovascular.[text word]; cardiovascular. [text word]; heart.[text word]; cardiac.[text word]; ; 'vena cava'. [text word]; aorta.[text word]; 'Patent ductus arteriosus'. [text word] ; aneurism.[text word]

Selected CV flow implants included the following types:

- Arterial stents (carotid, coronary and peripheral)
- Implants for AAA repair
- Implants for PDA repair

For implantable pulse generators - Search title: electrical impulse generators: Search terms: Pacemaker, Artificial[MeSH]; Biological Clocks[MeSH]; Tachycardia, Ectopic Atrial[MeSH]; implantable cardioverter-defibrillators[MeSH]; Defibrillators, Implantable[MeSH]; Tachycardia, Ventricular[MeSH]; Ventricular Fibrillation[MeSH]; Pain Management[MeSH]; Postoperative pain[MeSH]; Analgesia, Patient-Controlled[MeSH]; Magnetic Field Therapy[MeSH]

Selected implantable pulse generators of the following types:

- Active Implantable Cardiac Devices (AICD) including:
  - single and dual chamber pacemakers
  - cardiac resynchronisation therapy pacemakers, with or without defibrillation (i.e. CRT-D and CRT respectively)

- 
- implantable cardiac defibrillators (ICDs)
  - Electrical nerve stimulation devices

For heart valve prostheses- Search title: Heart valve replacement using a prosthetic valve:  
Search terms: Heart valve prosthesis [MeSH]; heart valve prosthesis implantation[MeSH]; (valv\$ adj3 prosth\$).[text word]; (valv\$ adj3 bioprosth\$).[text word]; (artificial adj3 valv\$).[text word]; (mechanical adj3 valv\$).[text word]; (bioprosth\$ OR prosth\$ OR mechanical).[text word]; (aortic adj3 valv\$).[text word]; (mitral adj3 valv\$).[text word]; (pulmon\$ adj3valv\$).[text word].

For supportive devices- Search title: Supportive devices – meshes, patches and tissue adhesives:  
Search terms: Surgical mesh [MeSH]; Bioabsorbable Implants; Absorbable Implants [MeSH]; Coated Materials. Biocompatible [MeSH]; Tissue scaffolds [MeSH]; Tissue adhesives [MeSH]; Fibrin Tissue Adhesive [MeSH]; Blood patch, Epidural [MeSH].

For active implantables in the magnetic resonance environment - Search title: safety of active implantables in the magnetic resonance environment: Search terms: Magnetic Resonance Imaging[MeSH]; magnetic resonance [text word]; MRI [text word]; MR [text word]; Cardiac Pacing, Artificial[MeSH]; Pacemaker, Artificial[MeSH]; defibrillators, implantable[MeSH]; safe\*[text word]; performance [text word]; efficacy [text word]; heat\* [text word]; scar\*[text word]; burn\*[text word]; artefact\* [text word]; ;dislodge\*[[text word]; interference [text word]; ICD [text word]; Defibrillator [text word]; pacemaker\* [text word] ; resynch\* [text word]; cardiac monitor [text word] ; loop recorder [text word]; ICM [text word].

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

Evidence from both the targeted internet searches and peer reviewed literature focused on study designs that are based on solid scientific principles which generate clinical evidence on the safety and performance of the device. Such evidence sources include, but are not limited to, controlled clinical trials, case control studies, case series and post-market registry data.

Summaries of exemplar articles documenting clinical research on the safety and performance of the device types have also been presented. Reports were selected based on recency and relevance and to be representative of those currently used in clinical practice in Australia.

Searches were restricted to English language articles published between January 2009 and June 2014 with updates for some topics to January 2015. All citations were retrieved and initial selection was based on title and abstract with potentially relevant articles retrieved in full text for final selection.

## Identified study designs

Based on the [NHMRC levels of evidence study](#),<sup>59</sup> designs used to evaluate the safety and performance of high risk medical devices range from systematic reviews of RCTs to case-series reports (Level IV). Irrespective of level of evidence the quality of reporting varied from low to high as assessed by validated quality tools.

In summary, the clinical evidence in this document includes:

- systematic reviews of RCTs, comparative cohort trials and cases-series

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- given the diversity of included evidence these systematic reviews do not meet the Level I classification as prescribed by the NHMRC
  - RCTs (Level II)
    - when practical, this should be the preferred study design
    - clinical trials of a RCT design are reported for the high risk devices and included in the evidence base
  - observational studies (Level III)
    - these are a valid alternative to RCTs<sup>260</sup> provided appropriate matching of treatment groups is performed, e.g. through the application of propensity scores <sup>261 262</sup>
  - case series (Level IV)
    - these can inform on the safety and performance of the high risk devices and have a high sensitivity for adverse events
  - post-market registries
    - these are established for some of the high risk devices and provide a valuable resource for post-market safety and performance data from other jurisdictions that can be used to support a pre- or post-market review of safety and performance of a high risk device.



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## Appendix 4: References

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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 (i.e. % 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.

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## Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Medical Devices Branch, Therapeutic Goods Administration	24/02/2017

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6203 1605  
<https://www.tga.gov.au>

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