

AUSTRALIAN MEDICAL DEVICES GUIDELINES

Clinical Evidence Requirements for Inclusion of Medical Devices in the Australian Register of Therapeutic Goods

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DISCLAIMER

This document is provided for guidance only. It should not be relied upon to address every aspect of relevant legislation. Please refer to the *Therapeutic Goods Act, 1989* and the *Therapeutic Goods (Medical Devices) Regulations, 2002* for legislative requirements.

FURTHER INFORMATION

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INTRODUCTION

This guidance document is one of a series that has been produced to help explain the new regulatory system for medical devices in Australia that commenced on 4 October 2002. The new system has been established by the *Therapeutic Goods Act 1989* as amended by the *Therapeutic Goods Amendment (Medical Devices) Bill 2002* (the Act) and the *Therapeutic Goods (Medical Devices) Regulations 2002* (the Regulations).

Many other guidance documents are available in this series. The series was developed to assist a wide-ranging audience and additional documents can be included if there is enough demand. A separate guidance document is available describing the series.

Although each guidance document has been developed to provide information about particular aspects of the new medical devices regulatory system in Australia, it is expected that a certain amount of cross-referencing to other documents in the series will be inevitable.

This document is intended as a guide to the requirements for clinical evidence needed to support an application for the inclusion of a medical device on the Australian Register of Therapeutic Goods.

THE ESSENTIAL PRINCIPLES AND THE ROLE OF CLINICAL EVIDENCE

The essential principles set out the requirements relating to safety and performance characteristics of medical devices. They define the results to be attained or the risks and hazards to be addressed during product development, but do not specify the technical solutions for doing so. Manufacturers can choose the way to meet these requirements. The mechanics for demonstrating compliance defined for each class of medical device are described in the guidance document on conformity assessment procedures.

When developing a medical device, the essential principles relevant to the device must be considered. For example, essential principles 1, 3, 4 and 6 require that the medical device achieve its intended performance during normal conditions of use and the known and foreseeable risks, and any undesirable side-effects, are minimised and acceptable when weighed against the benefits of the intended performance. More information can be found in the guidance document discussing the essential principles.

These principles, in particular, require that the device concept be first tested using a risk analysis that starts by considering any known patient or user related medical hazard (eg. blood loss, electric shock, etc). For each hazard, the analysis should list all potential causes and determine the probability and severity of their occurrence. Risk mitigation strategies should then be examined and tested. This type of analysis can and should be performed before beginning product development as it generates the safety requirements for the design specification.

Once a design specification that inherently minimises the identified risks has been defined, the manufacturer will need to decide how conformity of the design specification with the relevant essential principles can be demonstrated. Compliance with applicable medical device standards is not mandatory but is one way to establish compliance with essential principles. In many instances this will be achieved through implementation, maintenance and regular inspection of a quality management system by the device manufacturer.

The medical device regulations require medical devices to:

- have clinical evidence that is appropriate for its use and classification;
- demonstrate compliance with essential principles of performance and safety; and
- have undergone a clinical evaluation by the manufacturer as part of the conformity assessment procedure.

Clinical evidence of conformity with the essential principles is generated through an evaluation procedure that is applied by the manufacturer to clinical and other data pertinent to the device. This evidence will form part of the technical dossier. The level and nature of clinical data that forms the basis of the evidence should be appropriate for the use and classification of the medical device.

IDENTIFICATION OF WHAT CLINICAL DATA IS NEEDED

The TGA recognises that a flexible, case-by-case approach should be adopted so that clinical data requirements are commensurate with the intended purpose of the device. Applicants are encouraged to discuss individual device requirements with the TGA.

A properly developed risk analysis is crucial in determining what clinical data is required for a particular device. An outcome of the analysis is the identification of any residual risks. The clinical data are expected to quantify and address those risks.

As a general rule, the data requirements will vary according to the nature and clinical application of the technology used in or by the device. Devices based on new or “unproven” technology and those that extend the intended purpose of an existing technology through a new clinical use, must be supported with clinical investigation data. Devices based on an existing technology and intended for an established and accepted use may rely on literature review.

The TGA recognises that for some long established technologies there may not be clinical trial data of a contemporary standard available. In such cases, the role of the literature review would be to draw together all available trial data, reports of clinical experience, post market reports, adverse event database data and expert opinion to establish the performance and safety of the device. The clinical evaluation may also draw on other information such as the risk analysis, preclinical testing and the history of use of the technology to reduce the reliance on clinical data.

WHAT IS CLINICAL DATA AND HOW CAN IT BE GENERATED?

Clinical data may comprise either or both of the following:

- data generated during a clinical investigation program for the device;
- data obtained from a review of the literature, which may include clinical experience with the same or similar devices.

Importantly, the clinical data should demonstrate performance under normal conditions of use and allow evaluation of any undesirable side-effects.

Data generated during a clinical investigation program for the device in question

Data are generated during product development and may include:

- data from all formal clinical trials carried out using finished products; and
- any other experimental use in humans using prototype devices or components for the purpose of developing or investigating the safety and performance of the prototype devices or components.

In some instances it is advisable to supplement data generated from clinical trials with the results obtained from using products supplied to individual patients in Australia through either the Special Access Scheme or the Authorised Prescriber mechanism. This would provide supportive performance and safety data.

There is no requirement that the data has to include data generated from clinical trials conducted within Australia. However, where a trial of a new medical device is conducted in Australia, it must be conducted in accordance with Australian legislative and regulatory requirements (at both Commonwealth and State/Territory level) and Australian ethical standards.

Clinical trials in Australia are conducted under either the Clinical Trial Notification (CTN) Scheme or the Clinical Trial Exemption (CTX) Scheme. Details about each of these schemes can be found in the document “*Access to Unapproved Therapeutic Goods – Clinical trials in Australia*,” available at the following website address
<http://www.tga.gov.au/docs/pdf/unapproved/clintrials.pdf>

Australian ethical standards are set out in the National Health and Medical Research Council’s *National Statement on Ethical Conduct in Research Involving Humans, July 1999*. One of the requirements is that the clinical trial protocol, and therefore conduct, must conform to *ISO 14155 Clinical Investigation of Medical Devices*. (Note: this Standard is being revised in combination with European Standard EN540:1993 and will form a single Standard called *Clinical Investigation of Medical Devices*.)

Clinical trials conducted overseas are required to comply with relevant jurisdictional legislative and regulatory requirements and must be in accordance with the principles of the Declaration of Helsinki as in force in that country at the time the trial is conducted.

Review of the existing literature, which may include clinical experience with similar devices

Such data consists of a review and clinical appraisal of relevant scientific literature. The relevant scientific literature (both published and unpublished) can comprise:

- literature specifically pertaining to the device in question – where available, this must always be included in any review; and/or
- literature for comparative and well-established devices as well as relevant post marketing surveillance. Thus, the literature need not necessarily relate to the device in question if an adequate justification can be provided as to how data for a similar or predicate device can establish the safety and performance of the device in question.

A literature review consists of the following components:

- a compilation, using documented methodology, of the relevant currently available scientific literature consisting of clinical study reports, review papers and expert opinion on the intended purpose of the device and the techniques employed; **and**
- a report, written by an expert competent in the relevant field, containing a critical appraisal of this compilation. Where the review relies in part or wholly on data for a comparable device, the report should also clearly justify that the devices described in the compiled literature are relevant to the safety and performance of the device in question.

It is important that the published literature be able to prove clinical performance and safety of the device in question.

The key elements of a good quality literature review – points to consider

A good quality review is one supported by a detailed search of the literature, using a reproducible search strategy across a range of appropriate scientific databases. The methodology should be documented in a written report. The search output (ie. the citations) should be assessed against clearly defined selection criteria. The report should also summarise how each citation did or did not fit the selection criteria for inclusion in the review. When selecting papers to be included in the assessment of performance and safety, the following aspects should be considered:

- the quality of the literature articles;
- the design of any clinical trials reported in the paper;
- the quality of the data reported in the literature; and
- the clinical significance of the results of those trials.

The quality of the paper can be judged by assessing its scientific impartiality, the completeness of reporting, clarity and logic of argument and the validity of any conclusions drawn in the article.

Clinical trial design is an important consideration. The most desirable clinical trial design is a randomised, double blind, controlled trial. This design has the least source of bias that could potentially contribute to the outcomes observed in the trial. In cases where there are numerous published reports of such trials, it is possible to focus on these trials at the expense of other studies, which, because of their design, will have higher levels of bias.

However, it may be difficult to conduct double-blinded studies with medical devices, particularly for implantable devices, or to use comparator groups. Thus, it may not be feasible to conduct such a trial and therefore a more likely situation may be one in which there are studies which have greater potential for bias and/or few published reports available to support the review. In this case, almost all papers retrieved by the search will need to be assessed. The issue of potential duplication of data in different papers will need to be addressed.

An ideal way of providing an overview of performance data is to construct a hierarchy of evidence, such as that proposed by the *National Health and Medical Research Council (NHMRC) Quality of Healthcare and Outcomes Committee*, as shown on the next page.

Level of evidence	Type of evidence
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

For all safety data, all reports, including individual case reports and overviews relevant to the device should be considered. This would include scientific reports not suitable for assessment of performance due to poor trial design or inadequate analysis but providing safety data about the device. Other safety data may include post-marketing surveillance reports and reports from device adverse event databases.

WHAT IS REQUIRED OF A CLINICAL EVALUATION?

Clinical data must be evaluated to determine if it is sufficient to demonstrate compliance with the relevant essential principles. The technical dossier should indicate how the applicable requirements of the essential principles for the clinical evaluation of the device have been met.

This evaluation must be undertaken by a competent clinical expert in the field relevant to the intended use of the device. The expert must critically appraise the quality, completeness and clinical significance of clinical investigation data and/or literature based data that are pivotal to establishing the performance and safety of the device from data of lesser quality (because of trial design or less clinical significance, but still of a supportive nature).

There may be situations where demonstration of compliance with essential principles is not possible through evaluation of the clinical data alone. This can occur because clinical data from clinical investigation and/or the literature are either lacking or are of poor quality and therefore not sufficiently useful. One option for the manufacturer will be to generate additional clinical investigation data. Alternatively, other forms of data can be considered. The data used for the clinical evaluation is not necessarily limited to clinical data. This will depend on the proposed use of the device and the history of the technology on which the device is based. For example, for a device based on well established technology, it may be possible to use well reasoned argument, based on the risk analysis and pre-clinical data together with the post-marketing history of the device technology to satisfy the need for clinical evidence. It is expected that most established Class I medical devices would be covered by this scenario.

WHAT ABOUT DEVICES ENTERED IN THE ARTG PRIOR TO 4 OCTOBER 2002?

There is a 5-year transition period for medical devices that were registered or listed in the ARTG prior to 4 October 2002. During the transition period these devices can continue to be supplied but, if the sponsor wishes to supply the device after 4 October 2007, an application has to be made to include those goods in the ARTG.

Registered devices

The TGA recognises that registered medical devices have previously undergone an evaluation of clinical safety and efficacy. Although the assessment criteria against which these devices were evaluated may have been different, the standards to which efficacy and safety evaluations were undertaken were generally comparable to the essential principles adopted for the new regulatory system. Thus, the clinical data and corresponding evaluation will still be valid to support an application for an inclusion in the ARTG under the new system.

However, it is likely that the safety data now available about a registered medical device will be greater than at the time of the initial registration. This could have occurred because of the device's market exposure, post market vigilance programs, any post marketing performance or clinical studies that may have been undertaken or new data reported in the literature. Any significant new data, reports or results should be identified and included in the technical dossier to support the application. The dossier should also cross reference the clinical data previously submitted to the TGA.

The revised medical devices legislation requires that appropriate conformity assessment procedures be undertaken for the device, including a clinical evaluation, prior to its inclusion in the ARTG. Once again, the TGA recognises that a clinical expert report will have been submitted previously in support of a registration application. This may form the basis of compliance with the requirement for clinical evaluation. However, for devices registered for more than 12 months, any additional data obtained in relation to the device since its marketing will need to be evaluated. The entire clinical data can be re-evaluated in a single new report, or evaluation of the additional data can be presented as an addendum to or as an update of the original clinical expert report. If the latter is chosen, the report will need to clearly cross-reference the original report. The report must outline how the additional data were identified and assess the significance in relation to conclusions previously reached about the device. The TGA would also expect that the "directions for use" and patient information documents be reviewed and updated as necessary in light of the additional data.

Listed devices

In general, listed medical devices have not been subject to a formal evaluation by the TGA. Under the previous regulatory system they underwent an administrative review which was often based on the assessment of GMP certification and compliance with the advertising provisions in the *Therapeutic Goods Regulations 1990*.

The previously listed device in the ARTG will need full evidence of conformity with the essential principles and conformity assessment procedures to support an application as an inclusion in the ARTG. The general approach, based on the intended purpose, history and classification of the device as described above in the section, "Identification of What Clinical Data is Needed", will apply.

Note: Under the old system the TGA was able to ask for and review clinical safety information prior to listing the product. Where this occurred for a particular device, the information previously submitted would be expected to form part of the evidence base with respect to safety. However, that information would need to be updated in light of the post marketing history of the product and evidence of conformity with other essential principles will be required.