EVIDENCE REQUIREMENTS FOR CLINICAL EFFECTIVENESS ASSESSMENT OF APPLICATIONS FOR THE PROSTHESES LIST

Prostheses List Advisory Committee

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1. Introduction

The purpose of this paper is to provide a framework to help refine and clarify minimum requirements to apply to evidence that is used to support applications to list devices on the Prostheses List.

We acknowledge that this builds on arrangements that have evolved over a number of years. However, it is timely to re-examine the basis of the Prostheses List Advisory Committee's (PLAC's) decision-making in light of Recommendation 2 of the Review of Health Technology in Australia (the HTA Review), accepted by Government in February 2010, that 'the rigorous consideration of evidence be consistently applied across all Commonwealth HTA processes to ensure sustainability of the Australian Government's health financing arrangements.'[1]

The paper starts by setting out some of the relevant background, before examining essential principles and objectives for a schema of minimum evidence requirements stratified by the level of risk for proposed prostheses' indications. The paper then outlines such a schema suggesting what 'levels' and coverage of evidence ought to apply across risk levels to inform decision-making in any given circumstance.

The objective is not to remove expert clinical judgement from the process, but to support it, consistently and clearly, by appropriate consideration of evidence. From time to time, CAGs and/ or the PoCE may require more or less evidence than described in this paper, in order to consider an application to list a new product on the Prostheses List. Where this occurs, the recommending body should make it clear to the PLAC and the sponsor, the reasons why this has occurred, and the nature of the variance.

2. Background

2.1 The HTA Review

The HTA Review acknowledged that the Commonwealth HTA system is complex and that there are differing approaches to assessment methodologies, evidence requirements and process transparency. The review proposed that the objectives of the Commonwealth should be to 'use

[1] Commonwealth of Australia, *Review of Health Technology in Australia* (December 2009), p.6.

the best available evidence and efficient methods to inform robust decisions about market entry and the subsidised use of health technologies.' Further, the HTA Review suggested that the HTA system should continually improve the evidence base for assessment and be underpinned by key principles.

2.2 The Prostheses List

While essentially the same principles ought to apply across HTA processes for reimbursement purposes, the assessment of prostheses has to be different in practice for a few reasons. Firstly, to perhaps a greater extent than for other aspects of medical care, the performance of a prosthesis may vary depending on the skill of an operator. Secondly, 'blinded' trials are often not possible in the same way that they are in the assessment of pharmaceutical products. Thirdly, some new prostheses and other medical devices may have a shorter life cycle than pharmaceutical products, and are more likely to develop through incremental improvements to established devices, affecting the period of time over which it is useful and reasonable to expect evidence to have been gathered.[2] Finally, devices are generally used in much lower volumes than pharmaceutical products, which have consequences for the quantity of evidence that can be derived.

Nevertheless, we require a process that systematically combines the best available evidence to the assessment of each prosthesis' incremental effectiveness and ultimately its cost effectiveness, relative to an appropriate comparator.[3] The process needs to be consistent, and help to ensure that if the same evidence were assessed again, the same decision would be reached.

3. Principles

In response to the HTA Review, the Government accepted that Commonwealth HTA processes should be:

- sustainable;
- transparent, accountable and independent;
- consultative and reflective of Australian community values;
- administratively efficient;
- flexible and fit for purpose; and
- informed by robust and relevant evidence.[4]

The following are further principles to guide the design of a set of evidentiary requirements specifically for the assessment of prostheses (though they might apply to other processes as

[2] Productivity Commission 2005, *Impacts of Advances in Medical Technology in Australia*, Research Report, Melbourne, pp.245-46.
[3] The intervention that most practitioners will replace in practice.
[4] Commonwealth of Australia, *Review of Health Technology in Australia* (December 2009), p.8.

well). Requirements should:

1. be able to be consistently applied.
    - If the same quality and quantity of evidence with the same results were provided for the same indication then the conclusion of the assessors should be the same.
2. cover *all* relevant evidence required for decision-making, allowing for relevant intended and unintended consequences of devices in given indication/s.
3. be clearly expressed and understood.
    - Applicants should have no grounds for being uncertain about what they need to provide.
4. be consistent with other Commonwealth health technology assessment processes.
    - Where there are differences, there should be an explicit reason, based on factors such as the purpose of the process (e.g. reimbursement versus regulation).
5. note that if there were no evidence of a device's comparative safety or effectiveness, then it cannot be assumed that there is no potential harm or benefit associated with the device's use ('absence of evidence is not evidence of absence').[5]

4. Prerequisites

Some information is needed before evidence can be properly assessed, which might be considered necessary but not sufficient for assessors to do their job. Such information should include:

1. A description of the device (what is it?)
    - Current guidelines refer to 'product brochure with specifications' and 'digital images, exploded and properly labelled, of individual components of the application' and 'surgical technique'. While this information may be necessary it is not, in itself, evidence of the results that the device produces compared to something else. Future iterations of the guidelines could be improved by making this distinction clearer.

2. The relevant indication(s) (what is it for; what does it help to treat?)
    - Demonstrating how a particular MBS item applies to the use of a device is one way that the applicant can articulate the indication to which the device relates.

3. The relevant comparator that would otherwise be used to treat that indication (what will the proposed device be added to or replace, and that it is claimed to be as effective as, or better than?)
    - Decisions about what the Commonwealth should support through reimbursement arrangements, in all contexts – PBAC, MSAC and PLAC – are based on comparative

[5] Altman and Bland 1995; Briggs and O'Brien 2001.

rather than absolute assessments.

5. Evidence

There is general agreement that the level of evidence that should be required to support the assessment of a prosthesis for listing differs according to a number of factors.

This paper sets out a schema that will enable all parties – sponsors, assessors, clinicians, hospitals, insurers, consumers and government – to understand the basis of all decisions to reimburse or not to reimburse prostheses.

The factors discussed here are:

- the ***risk*** to the patient of the prosthesis having unintended consequences,
- the ***claim*** that the sponsor makes in relation to the relative net effectiveness of the prosthesis for the proposed indication/s, particularly to distinguish between net clinical benefit being "not worse than" (non-inferior) and "better result than" (superior to) relevant comparator/s.
- The ***lifespan*** of the device.

5.1 Levels of risk

There is general agreement that the level of evidence that is appropriate to the assessment of a prosthesis varies according to the degree of risk to the patient if the device does not perform as it is intended. That is, the consequences of decisions – through the potential benefits (and harm) associated with the device - are higher for some devices as compared to others, and therefore the levels of evidence required to assess those potential benefits are greater.

The table below describes three categories of risk, the types of prostheses that might fall into each category, and the corresponding TGA class of product.

PL risk levels		**TGA classification**
High	Load bearing prostheses Electronic prostheses Prostheses in direct contact with the heart or central circulatory/nervous system Finger joints Prostheses with a biological effect Prostheses wholly or mainly absorbed into the body Prostheses which undergo chemical changes in the body (not teeth) Prostheses which administer a medicine Active implantable medical devices	All Class III products and some Class IIb products; Active implantable medical devices

PL risk levels		TGA classification
Medium	Prostheses which do not meet the definitions for High or Low Impact, including but not limited to: Intraocular lenses Ureteric stents Gastric bands	Remaining Class IIb and Class IIa products
Low	Clips, staples or screws Plates Grommets Tissue closure prostheses Haemostatic prostheses	

5.2 Claims to be assessed

The claims made for prostheses to support their inclusion on the Prostheses List can be arranged in a small number of categories, the most important consideration being whether the net clinical benefit is claimed to be either no worse than the comparator (non-inferior), or better than the comparator (superior):

1. Non-inferior result

a. ***Different device*:** These products are those which the sponsor is seeking to have listed as part of an existing group, based on the claim that while its device has some characteristics that are different to comparators in the relevant group, it produces a result that is not worse than (equivalent or potentially better than) the relevant comparator/s for the indicated use/s (non-inferior).

The extent to which a device might differ from its comparator may influence the level of evidence that is appropriate, depending on the comparative risk of harm associated with the device's use. A device that is significantly different in design or composition but is claimed to deliver a non-inferior clinical result, may require more evidence than a device that is different only in aspects that the assessors do not consider to be material to the device's comparative safety and effectiveness.

In the terms used to date in prostheses assessment, these results have been called *substantially clinically equivalent*, or in PBAC terms akin to 'me-too' medicines.

b. ***Identical device*:** These products are those which the sponsor claims are non-inferior because they are the same in all relevant aspects of design and manufacture to the comparator listed device. That is, advocates for these devices would claim that, as

they are identical to already listed devices, they should be assumed, without the need for further clinical evidence, to deliver the same clinical outcomes. These claims will only be considered to be substantiated, when the device is made to the same specifications, from the same material, comes from the same manufacturing production line, and the claim to be identical is certified by the manufacturer common to both devices.

2. Better result

In the terms used to date in the prostheses assessment context, these products produce results that are *clinically superior* for the indicated use/s.

There is a question as to where devices considered to provide *incremental change* ('improved functionality compared to an existing item already on the Prostheses List and lodged by the same sponsor') fit within this schema. If 'improved functionality' cannot be shown to deliver statistically significant improvements in clinical outcomes, then it would follow that such devices should be regarded as delivering a non-inferior result, and assessed accordingly.

5.3 Lifespan of the device

A third factor that might affect the level of evidence required to properly assess a device is the period for which the device remains active or functional. So, for example (other potential factors being equal), a device that is intended to remain functional in a patient for 20 years might require evidence of comparative effectiveness gathered over a longer period of time than a device that is accepted as having a use, or delivering a benefit, over say two years. That is not to say that evidence should be based on data gathered over the entire lifespan of the device (although this might be ideal). Rather, risks should be managed by requiring that the period over which data are gathered is proportionate to the expected lifespan of the device.

Clearly, registries, such as Australia's National Joint Replacement Registry, have a role in providing access to consistently gathered and presented data in this regard.[6] The use of all relevant data, including registry data, to support applications for devices to be listed on the Prostheses List, is encouraged.

Examples of indicative minimum lengths of clinical follow-up that would be predictive of performance might be:

[6] Other examples include: the European Arthroplasty Register; the UK National Joint Registry (ODEP 10 ratings); the Swedish National Hip/Knee Arthroplasty Register; the Norwegian Joint Registry; the Canadian Joint Replacement Register; and the New Zealand National Joint Register (since 2005).

Major joint replacement prostheses	2 years
Implantable cardiac devices	2 years
Bioresorbable screw	1 year
Polypin resorbable bone pin	1 year
Mesh	1 year

5.4 Classifications of devices for prescribing levels of evidence

The purpose of this analysis is to determine whether the levels of evidence appropriate to any particular device can be clearly and uniformly described. Based on the preceding discussion, the following table includes some basic examples but, in theory, it should be possible to classify every type of device in this manner.

Type of device	Level of risk	Nature of claim	Lifespan of device	Level of evidence required
Hip	High	Non-inferior result	20 years	
Hip	High	Better result	20 years	
Grommet	Low	Non-inferior result	6 months	
Grommet	Low	Non-inferior result	12 months	

6. Levels of clinical evidence

Having determined the factors that might serve to classify devices in terms of the categories that would warrant equivalent evidentiary standards, the next step would be to determine, for each category, what those standards or levels should be.

The current application documentation provides some guidance of such standards, either generally or in relation to specific types of devices. This includes, for example:

- Evidence must demonstrate ‘successful use in a human setting’;
- Where a superior clinical outcome over a comparator is claimed, ‘a level 3 or better study/clinical evidence with 12 months’ follow-up is required.’

Minimum periods of registry data might be another requirement. There is scope to introduce more consistency across the prostheses assessment processes.

The National Health and Medical Research Council has established categories of evidence, ranging from ‘evidence obtained from a systematic review of all relevant randomised controlled trials’ to ‘evidence obtained from case series, either post-test or pre-test/post-test.’ These may be

useful yardsticks to keep in mind, but there may be value also in considering the levels and quality of evidence that the PLAC can reasonably expect to receive, to inform its advice.

The following table sets out this approach, hinging on the nature of the claim for the device, and the level of risk. The life cycle of a device is not presented here as an explicit variable, but might still influence the type or quantity of evidence deemed appropriate in any given circumstance. For the sake of simplicity, the category of 'medium' risk devices is also removed.

Nature of claim	**Risk**	**Requirement on decision-maker**	**Minimum level of clinical evidence**
Non-inferior claim	Low	Convincing bioengineering argument to conclude equivalence	Design and manufacture evidence (same as comparator); No clinical data
Non-inferior claim	High	Subjective comparison between evidence of new device and comparator device for indicated use. Increased risk of wrong conclusion depending on level and strength of evidence and ability to adjust for differences in observed, predictive patient risk factors.	Design and manufacture evidence; "Single-arm" clinical data, ie clinical follow-up for that device, with patient data on risk factors presented. Subjective comparison of expected outcomes with existing devices for indicated use/s.
Better ('superior') result	Low	Increased risk of wrong conclusion depending on level and strength of evidence and ability to adjust for differences in observed, predictive patient risk factors.	Design and manufacture evidence; Non-randomised comparative clinical data, ie clinical follow-up for that device and its comparator in contemporary use including relevant patient risk factors, background therapy and technique used in practice.
Better (superior) result	High	Greater confidence in comparability of evidence with adequate randomisation and blinding and coverage of the duration and scope of outcomes relevant to assessment of net clinical benefit.	Design and manufacture evidence; Multiple independent sources of data with minimum periods of follow-up, including comparative data and relevant patient risk factors, background therapy and technique used in practice. Randomised control trials where

			available.

The principle of adequate coverage of the scope and duration of relevant outcomes to inform assessments of net clinical benefit for the indicated use (e.g unintended as well as intended consequences) sits alongside consideration of minimum levels (comparability) of evidence in the above table.

Some categories of devices that are high risk and would therefore normally require a minimum of 2 years supporting evidence, in certain circumstances, may not require this level of evidence for the device to be recommended for listing. Examples of these types of devices are those designed specifically for revision or oncology surgery. This is because the overall utilisation of these types of devices is comparatively low and therefore the available evidence normally available for these types of devices is also low.

7. Assessment pathways

In light of the Government's direction that evidence requirements be applied consistently across HTA processes, there might also be opportunities to better align PLAC and Medical Services Advisory Committee (MSAC) mechanisms, depending upon the nature of the applications that come forward. There is already some relationship between the committees where a prosthesis does not have an associated procedure eligible for reimbursement through the Medicare Benefits Schedule, in that PLAC's ultimate advice is contingent on the conclusion of MSAC's processes.

Claim	**Assessment Pathway**
Device claimed to be non-inferior to a listed comparator	CAG/PoCE ⇒ PLAC
Device claimed to be superior, with no comparator	PASC ⇒ ESC ⇒ MSAC CAG/PoCE } ⇒ PLAC

There may be further scope to harmonise the work of the committees, to ensure that devices are assessed as efficiently and appropriately as possible in circumstances where a prosthesis is claimed to be superior to a listed comparator. For example, this might involve drawing on health economic assessment expertise and established MSAC processes[7] to assist with analysis of

[7] The **Protocol Advisory Sub-committee (PASC)** is a standing sub-committee of MSAC with membership including decision analysis, health economics, epidemiology, public health, consumer and clinical expertise. Its purpose is to determine Decision Analytic Protocols – that is, defining the decision option(s) or question(s) for public funding of a proposed new medical technologies and procedures prior to final lodgement of an application for its consideration by MSAC.

The **Evaluation Sub-committee (ESC)** is a standing sub-committee of MSAC with membership including health economics, epidemiology, public health, consumer and clinical expertise. Its purpose is to provide advice on the quality, validity and relevance of internal and external assessments for applications being considered by MSAC.

claims of clinical superiority (and for higher benefits), or in the case of novel devices, assessing their comparative worth to ensure that the additional cost of the new device produces sufficient additional benefit to maintain the cost-effectiveness of the procedure as a whole.[8]

8. Conclusion

This paper proposes a principled approach and a schema to aid the evolution of the assessment of prostheses for reimbursement purposes by introducing a more consistent, clear and coherent approach to the consideration of evidence.

[8] These scenarios are offered as examples only at this stage. The more precise detail of how the committees and their supporting structures might interact in specific circumstances will be worked up separately.