PFPA Supplement; Assessment of Medical Devices and Vaccines

Purpose

This supplement is provided as a quick reference guide to new content that has been added to PFPA version 2.2 relating to medical devices and vaccines.

We have received many consultation responses over the last few years that have helped inform PHARMAC's evolving approach to the management of medical devices. We appreciate that a one size fits all approach cannot be applied to pharmaceuticals – whether medicines, medical devices, or vaccines – and that we need to understand the implications of their differences.

The Prescription for Pharmacoeconomic Analysis (PFPA) is a guide for anyone assessing the value for money of pharmaceuticals in New Zealand. The methodologies described in the PFPA are intended to be flexible enough that they can be applied in the assessment of all pharmaceuticals, including medical devices, medicines and vaccines.

The PFPA is updated periodically to ensure its methodologies are consistent with best international practice for undertaking pharmacoeconomic assessment. During the most recent update we assessed the applicability of the PFPA to medical devices and vaccines. We have collected a wide range of information through our stakeholder engagement processes and have analysed this information against the current recommendations in the PFPA.

Our analysis of the PFPA identified that the methodologies recommended are generally appropriate for the assessment of medical devices and vaccines – chiefly because they are flexible enough to be able to accommodate the specifics relevant to different types of health technologies. However, there are areas of the PFPA 2.2 that have been updated to reflect methodology changes necessary for the assessment of medical devices and vaccines. This supplement brings together in one place the key changes that are included in PFPA 2.2 and that we think are significant for stakeholders who are specifically interested in the assessment of medical devices or vaccines.

Assessment of Medical Devices

Evidence for Relative Clinical Effect

Chapter 4 of the PFPA discusses evidence for inclusion in an economic model. The PFPA recommends that:

All appropriate evidence relating to the pharmaceutical(s) and population under assessment should be identified, described and quality-assessed. The level of clinical evidence may vary depending on the level of analysis and time available to systematically review the evidence – for less detailed analyses, more opportunistic data may need to be used and less comprehensive critical appraisal undertaken.

Critical appraisal of trials

Chapter 4.4.1 describes the recommended best practice for critical appraisal of trials:

PHARMAC recommends that clinical trials be critically appraised using the Graphic Appraisal Tool for Epidemiology (GATE) framework(1) or other similar frameworks.

The GATE framework involves the following five steps:

1.   Asking focused questions based on PECOT (Population, Exposure, Comparison, Outcome, Time) and RAMMbo (fair Recruitment, fair Allocation, fair Maintenance, fair Measurement of Outcomes).

2.   Searching the literature for best available evidence.

3.   Appraising the study by 'hanging' on the GATE frame.

4.   Assessing study quality.

5.   Applying the evidence in practice.

Details on the GATE framework, including critical appraisal spreadsheets, are available at: https://www.fmhs.auckland.ac.nz/en/soph/about/our-departments/ epidemiology-and-biostatistics/research/epiq/evidence-based-practice-and-cats.html.

Grading the evidence

Chapter 4.4.2 further discusses methods for economic modelling with lower levels of evidence:

PHARMAC acknowledges that in some cases it may be necessary to use lower levels of evidence if this is all that is available. For example, trials on vaccines and medical devices may be of insufficient duration to evaluate long-term efficacy, and may only report intermediate endpoints. As lower-quality evidence increases the level of uncertainty in the analysis, conservative assumptions should be applied and extensive sensitivity analysis undertaken. See Chapter 5 for further details.

While acknowledging some vaccines and medical devices may have lower levels of evidence, it is worth noting that assessments already allow for the fact that many medicines also have lower levels of evidence.

Economic Modelling – Transformation of Clinical Evidence

Use of Surrogate Measures Chapter 5.1.1

Some trials in medical devices and vaccines, like other pharmaceuticals, may report on surrogate endpoints rather than clinically-important outcome measures that affect disease progression, overall survival and quality of life. Therefore, it may be necessary to translate surrogate endpoints to clinically important outcomes. The PFPA recommendations are as follows:

Economic analysis should ideally be based on studies that report clinically important outcome measures. These are valid outcomes that are important to the health of the patient.

In some cases, only surrogate outcomes may be available. These are a substitute for a clinically meaningful endpoint, and measure how a patient feels, functions or survives.

Surrogate measures should only be used in CUAs where no alternative health outcome data are available. Caution must be used when using surrogate measures, as these may not necessarily translate into clinically relevant and effective outcomes.

Indirect Comparisons of trials Chapter 5.2.6

Relevant head-to-head RCT data may not be available for many medical devices, therefore indirect comparisons may need to be used more often. In such cases, it may be necessary to synthesise a head-to-head comparison (2) . For example, a difference in clinical effect between Device A and Device B can be modelled by obtaining separate estimates from trials comparing Device A versus no treatment, and Device B versus no treatment.

When undertaking indirect comparisons there is greater uncertainty in the effectiveness of one treatment over the other. This is because the trials that are being compared may contain very different groups of patients, which may alter the overall treatment effect (3). If indirect comparisons are required in an analysis, conservative assumptions should be applied and these assumptions need to be clearly stated.

Impact of Operator Skills and Experience - External Validity of Trials Chapter 5.2.3

The benefit of some pharmaceuticals, in particular many medical devices, is linked to how that pharmaceutical is applied. The efficacy of such a medicine or device in clinical practice may therefore differ from trials, due to the experience and skill of the operator. For example, if only experienced operators take part in the trial, the efficacy of the pharmaceutical in clinical practice may be lower in the first few years as operators gain the necessary experience and skills. During this 'learning curve', errors and adverse outcomes are potentially more likely (4-6).

In cases where there is evidence of reduced efficacy or safety in clinical practice compared with the trial, the analysis should adjust the efficacy/safety of a pharmaceutical in the first few years, and assume increased efficacy/safety over time as operators gain experience.

Product Modifications – Relevance of Trial Data over Time Chapter 5.2.4

Many medical devices[1] frequently undergo product modifications, some of which may impact on efficacy. Modifications are often incremental, based on emerging clinical evidence or use in clinical practice. Clinical trial data may become less relevant over time as the pivotal clinical trials may have been undertaken at an early stage in the technology's evolution (5, 6).

In cases where products have been modified since the reported clinical trials, it is recommended that the assessment be based on a synthesis of the trial data (to evaluate overall efficacy of product group) and any further evidence available on the impact of product modifications on the efficacy of the device.

Any reported improvements in efficacy and safety should be assessed according to the grades of evidence. For example, any improvements reported by observational studies should be modelled conservatively because observational studies are a lower grade of evidence. If there is no evidence available on the efficacy of the modification, the assessment should be based solely on the initial trial evidence and should not assume any improvements to efficacy and/or safety due to modifications.

Costs Associated with Medical Devices Chapter 7.2.2

Medical devices have costs that may differ to those for medicines and which need to be taken into account.

These costs include, but are not limited to:
- one-off costs:
  - capital
  - disposal of current device(s)
  - costs of switching out devices already in use
  - implementation
- fixed costs**:**
  - hiring additional staff
  - overheads
  - training
- costs associated with use**:**
  - operating costs
  - maintenance and repair
  - consumables.

Further information on measuring medical device costs in New Zealand is included in the *Cost Resource Manual*, available on the PHARMAC website.

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[1] Due to the differences in regulatory approval processes, this section applies mainly to medical devices.

Assessment of Vaccines Chapter 5.4

Assessment of Vaccines

Adjustments to Vaccine Trial Efficacy Data

The following points should be considered when modelling vaccine efficacy (7):

- *Proportion of vaccinated people who will be protected – a proportion of vaccinated people experience the intended effects, and the remainder of vaccinated people do not. For example, a vaccine with 90% 'take' would then produce the intended effect in 90% of vaccinated people, and not in the remaining 10%.*
- *Degree of protection – vaccinated people in whom the vaccine 'takes' may experience the intended effects to a certain degree (ie not 100% protection). For example, a vaccine with 90% 'degree' would produce the intended effect in 90% of vaccinated people in whom the vaccine 'takes hold'.*
- *Length of protection – efficacy may remain constant over lifetime or wane as a function of time.*
- *Age at administration – the immune system shows different responsiveness based on the vaccinated person's age.*
- *Adherence with the vaccination schedule (compliance and time between doses) – this especially needs to be considered for vaccines where compliance with a full schedule is problematic.*
- *Adverse reactions – some people have adverse reactions to a vaccine, which should be taken into account if significant.*
- *Potential loss of potency – this can be due to heat and cold exposure; however, it only needs to be considered if relevant data are available.*
- *Herd immunity – whether the vaccine is likely to provide indirect protection to unvaccinated people through appropriate coverage, as in section 5.4.2 below (further details provided below).*

Herd Immunity and Vertical Transmission

PHARMAC recommends herd immunity be included in CUA models if vaccine coverage is likely to be high enough to achieve herd immunity and if the inclusion is likely to affect the relative cost-effectiveness of the intervention. Some pharmaceuticals such as vaccines change the population risk of infection. The general case is herd immunity, but the issues also apply to vaccines intended to reduce vertical transmission.

Herd immunity is defined as the indirect protection of unvaccinated individuals in a largely vaccinated population. When a high percentage of the population is protected against a pathogen, it is difficult for a disease to infect new hosts because there are so few new people to infect. This can effectively stop the spread of disease in the community. The extent of protection through herd immunity, therefore, depends on the amount of infection in the community. Once herd immunity is achieved through appropriate coverage, vaccination will more than proportionally reduce the incidence of infection, increase the average age at infection and increase the length of the inter-epidemic period. Models that do not account for herd immunity may underestimate the true effects of vaccination in a population (8, 9).

A key parameter in a vaccine economic model is the 'force of infection' – the probability that susceptible individuals become infected per unit of time. In a static model, the force of infection is constant over time, whereas in a dynamic model it can change over time (8, 10). Vaccination reduces the proportion of people in the susceptible stage. Therefore, as more

people are vaccinated, the proportion of infectious people will decrease, and hence the probability that a susceptible person will come into contact with an infectious person will also decrease. As a result, the force of infection declines.

In a dynamic model, the force of infection is recalculated each time period. The consequence of a decline in the force of infection due to vaccination is that if susceptible persons are infected, the infections will occur, on average, at a later age. The age at infection continues to shift as long as the probability of infectious persons contacting with susceptible persons continues to decline. Dynamic models are particularly useful if herd immunity is important (8, 10, 11).

All dynamic models share the same distinguishing feature – that the risk of infection is dependent on the number of infectious agents at a given point in time. In a dynamic model, the probability of an individual acquiring an infection is dependent on:

- *the contact patterns of the individual (ie interaction between individuals)*

- *how infectious the infection is*

- *the distribution of the infection within the population over time*

- *vaccination coverage (ie the proportion of the eligible population who receive vaccination).*

As outlined above, the age at infection continues to shift as long as the probability of infectious persons coming into contact with susceptible persons continues to decline. This age shift can by itself have beneficial public health effects or detrimental effects (if infection is more severe in adults than in children). Therefore, it is important to assess whether the net effect of herd immunity is positive or negative (7, 11).

PHARMAC recommends including herd immunity in assessments of vaccines if:

- *vaccine coverage is likely to be high, and therefore herd immunity is likely to occur. The level of coverage required for herd immunity, which will vary across antigens, therefore needs to be assessed prior to economic modelling*

- *the inclusion of herd immunity is likely to have an impact on the relative cost-effectiveness of the vaccine.*

Static models may be appropriate if:

- *herd immunity does not play an important role (ie the additional effectiveness per additional person vaccinated is constant).*

Costs Associated with Vaccines

In all cases the recommendations in chapter 7 of the PFPA should be used for economic modelling. Specific costs to consider when modelling vaccines may include:

The direct costs associated with funding a new vaccine (in addition to the cost of the vaccine) may include the cost of:

1. storage (e.g. refrigeration) and transportation – this cost only needs to be included if the infrastructure is not already in place;

2. administration of the vaccine – in most cases this should be based on the Ministry of Health immunisation subsidy (see Cost Resource Manual for details on current subsidy). The amount is also dependent on whether the vaccine can be administered at the same time as other vaccines;

3. wastage – dependent on the number of doses in a vial, the duration and frequency of immunisation sessions, any distribution failures, and the number of vials discarded due to expiry (refer to section 7.2.2 of the PFPA).

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