

# Clinical evidence requirements: comparison between seven HTA agencies and implications for drug manufacturers



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## Introduction

Health Technology Assessment (HTA) agencies appear to have more extensive clinical effectiveness evidence requirements than regulators such as the EMEA/FDA. Furthermore, given the large number of global national and regional HTA bodies, there is likely to be inter-agency variation in the types and standards of evidence preferred by each.

The objective of this study was to determine the extent of the differences in the clinical evidence requirements of major global HTA agencies. This will help to determine whether national differences such as those related to health policy have a strong impact on specific HTA requirements for clinical evidence. This will also be essential to understand whether there are broad similarities between clinical evidence requirements that manufacturers and sponsors can consider as key to all major HTA agencies.

It is essential for technology sponsors/manufacturers to understand how decisions made during the design and execution of clinical trials will influence a range of future country-specific HTA submissions, as these HTA outcomes are the key to widespread market access.

## Methods

A literature search was conducted for clinical evidence requirements from the websites of the following HTA agencies:

- **Australia:** PBAC (Pharmaceutical Benefit Advisory Committee)<sup>1</sup>
- **Canada:** CADTH (Canadian Agency for Drugs and Technologies in Health)<sup>2</sup>
- **England and Wales:** NICE (National Institute for Health and Clinical Excellence)<sup>3</sup>
- **France:** HAS (Haute Autorité de Santé)<sup>4</sup>
- **Germany:** IQWiG (Institut für Qualität Wirtschaftlichkeit im Gesundheitswesen)<sup>5</sup>
- **New Zealand:** PHARMAC (Pharmaceutical Management Agency)<sup>6</sup>
- **Scotland:** SMC (Scottish Medicines Consortium)<sup>7</sup>

These seven agencies were selected as they are considered to be globally well-recognised organisations with readily accessible documentation describing their evidence requirements. Information such as comparator required, the use of surrogate outcomes (SO) and systematic reviews was extracted from the agency submission guidelines. HTA submissions' outcomes were also studied to analyse the pattern of approval for submissions with SO. Economic evidence requirements were considered separately (Balvanyos et al 2010, ISPOR 2010 Poster PHP107).

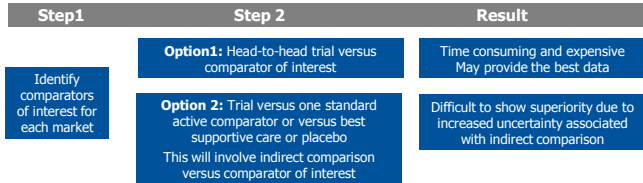
## Results

### Choice of comparator

The choice of the optimal comparator is crucial to the outcome of the HTA, thus should be influenced by HTA requirements as well as by regulatory concerns and other practical considerations. Most agencies considered (NICE, AWMMSG, NCPE, CADTH, PHARMAC) prefer that comparisons are made versus the most routinely used interventions, however PBAC requires a comparison to the interventions most likely to be displaced, and the SMC prefers the comparator that is considered best practice. HAS will also consider the cheapest drugs as appropriate comparators.

Figure 1 below illustrates how early decision-making regarding trial comparators typically influences subsequent HTA outcomes in the countries considered.

**Figure 1: General decision process at Phase III for choosing trial comparators to lead to optimal HTA outcomes**



### Observational studies

While RCTs provide the key evidence for comparative effectiveness, all the agencies (except IQWiG) recognise the additional value of non-RCT studies in reflecting real-world situations and providing long-term data (Table 1).

**Table 1: Value of observational studies to major HTA agencies**

HTA agency	Inclusion of observational data	Good quality observational studies (cohort studies and case-control studies) provide:
CADTH	✓	<ul style="list-style-type: none"> <li>• Real-world data</li> <li>• Supplementary information to RCTs, including:</li> </ul>
HAS	✓	<ol style="list-style-type: none"> <li>1. Estimating relative treatment effect over longer time horizons</li> <li>2. Measuring outcomes that have not been included in the RCTs</li> <li>3. Allowing observation of a new treatment on compliance and treatment switching patterns</li> </ol>
IQWiG	(x)	
NICE	✓	<ul style="list-style-type: none"> <li>• Supplementary data for models, e.g. utility data (as long as it can be shown that the patients and health states adequately match those in the clinical trial)</li> </ul>
PHARMAC	✓	<ul style="list-style-type: none"> <li>• Useful data for situations in which RCTs are unavailable</li> </ul>
PBAC	✓	<ul style="list-style-type: none"> <li>• IQWiG considers observational studies justified in exceptional cases</li> </ul>
SMC	✓	

## Conclusions

In general, this review of seven HTA agencies showed that there were more similarities between their clinical evidence requirements than differences. Rather than providing highly specific guidance, most agencies focused on the need for good rationale for clinical decisions.

When designing clinical trials, manufacturers need to keep in mind that comparators, study design and surrogate outcomes should meet both regulatory and HTA standards. The differences between the agencies' requirements are subtle and mean that manufacturers need to put together a strong evidence-based clinical evidence package that will require limited adaptation to meet various country requirements. Furthermore, these will have to be considered in conjunction with the pharmacoeconomic requirements of each agency in order to ensure alignment of the evidence (see Poster PHP 107).

### Systematic reviews

Systematic reviews (SRs) of clinical evidence are generally considered essential to present comparative effectiveness data. Contrary to the other agencies, HAS does not require a SR and bases its assessments mainly on pivotal clinical trials provided by the manufacturer, however it does prefer that a SR is also submitted. NICE and IQWiG also differ from the other agencies as they perform or commission their own SRs in addition to assessing those provided by the manufacturer. In terms of methods of synthesising data from systematic reviews, CADTH and NICE had the most detailed guidelines.

### Use of surrogate outcomes

#### • Validity of surrogate outcomes

All HTA agencies are cautious in their interpretation of SO and require manufacturers to provide evidence linking the surrogate outcome to final patient-relevant outcomes. Table 2 presents subtle differences in guidance.

**Table 2: Consideration of surrogate outcomes by HTA agencies**

HTA agency	Statement of validity of surrogate outcome
CADTH	SO is considered valid only if there is a "strong, independent, consistent association" with an important patient outcome, and there is "evidence from randomized trials that... improvement in the surrogate endpoint has consistently led to improvement in the target outcome."
HAS	Individual submissions provide specific opinion on a case by case basis
IQWiG	SO are only considered as proof of additional benefit of an intervention and clear proof is required to show "strong, consistent and unidirectional association between the change in the SO and the change in the patient-relevant outcome"
NICE	The identification and the use of SOs needs to be "appropriate"
PHARMAC	If SOs have been used, the strength of evidence extrapolating the specific SO to clinically relevant patient outcomes must be described
PBAC	PBAC has developed a framework for assessing SOs and the impact of these on uncertainty in HTA submissions
SMC	If SOs have been used, the association between surrogate markers and health benefits or disadvantages to patients must be discussed

#### • Pattern of approval for submission with surrogate outcomes

Except for HAS, which has accepted more SOs in various disease areas than the other agencies, there is no obvious pattern across agencies in approval rates for SO-based submissions and it appears most are generally evaluated on a case by case basis.

## References

1. Pharmaceutical Benefits Advisory Committee (PBAC): <http://www.health.gov.au/internet/main/publishing.nsf/Content/public-summary-documents>
  2. Canadian Expert Drug Advisory Committee (CEDAC) : <http://www.cadth.ca/index.php/en/cdr/search>
  3. National Institute for Health and Clinical Excellence (NICE) : [www.nice.org.uk](http://www.nice.org.uk)
  4. Haute Autorité de Santé (HAS): [www.has-sante.fr](http://www.has-sante.fr)
  5. Institut für Qualität Wirtschaftlichkeit im Gesundheitswesen (IQWiG) : [www.iqwig.de](http://www.iqwig.de)
  6. PHARMAC (Pharmaceutical Management Agency): <http://www.pharmac.govt.nz/>
  7. Scottish Medicines Consortium (SMC): [www.scottishmedicines.org.uk](http://www.scottishmedicines.org.uk)
- All websites were accessed in June 2010