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Health Policy Analysis

Assessment of the Quality of the Clinical Evidence in Submissions to the Australian Pharmaceutical Benefits Advisory Committee: Fit for Purpose?

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ABSTRACT

Background: Assessments of the comparative clinical (and cost) effectiveness of new medicines are increasingly being used to inform decisions on their reimbursement. Assessments of added clinical benefit are invariably based on evidence generated to support registration. **Objective:** Our objective was to identify and characterize significant problems relating to the quality of the clinical evidence in submissions to the Australian Pharmaceutical Benefits Advisory Committee (PBAC) seeking subsidy on the Pharmaceutical Benefits Scheme and thus determine whether the evidence presented to the committee was "fit for purpose." **Methods:** We conducted a retrospective analysis of submissions considered by the PBAC between 2005 and 2012 using a published evaluation framework. We developed an additional framework to categorize significant problems in more detail. Significant problems related to the choice of comparator, the unavailability of randomized clinical trial evidence, poor-quality data, a claim of clinical superiority, and a claim of clinical noninferiority. **Results:** We identified 261 significant problems in 479 major submissions. There was a significant problem with the sponsor's choice of comparator in 11% of the submissions. The most common significant problem (29%) was the determination of a medicine's comparative performance in the target patient population. **Conclusions:** The supporting clinical evidence is the foundation of a PBAC submission. We found a poor fit for purpose; on average, one in every two major submissions had a significant problem with the supporting evidence. The findings from our study, if confirmed in other jurisdictions, raise important questions regarding what clinical evidence should be generated to support the reimbursement of new medicines.

Keywords: decision making, evidence, quality, reimbursement.

Introduction

Governments of the developed world currently face challenges in ensuring that their constituents are able to access new and effective health care technologies in a timely and affordable manner. They have promoted the use of health technology assessment (HTA) to facilitate efficient use of their limited public resources. Although some undertake assessments of comparative economic effectiveness ("value for money"), a common denominator for all is an assessment of comparative clinical effectiveness ("level of added clinical benefit") [1]. Assessments of added clinical benefit, be they single or multiple and direct or indirect, are invariably based on evidence generated to support registration. Few have studied whether the clinical evidence generated to support the registration of new medicines is well suited for reimbursement/coverage decision making. Insofar as access to new medicines is becoming increasingly dependent on reimbursement, this is an important public health issue.

Australia has considerable experience in the use of HTA to inform reimbursement decision making. The Pharmaceutical Benefits Scheme (PBS) was established in 1953 under the National Health Act to guarantee Australians subsidized access to essential medicines. The National Health Act also established the Pharmaceutical Benefits Advisory Committee (PBAC) to make recommendations to the Commonwealth Minister for Health regarding the subsidy of medicines on the PBS. The PBAC has 20 years experience in assessing submissions to list new medicines on the PBS or make a substantial change to currently listed medicines (so-called major submissions) in terms of their comparative clinical and economic effectiveness [2].

The main objective of our study was to identity and then characterize significant problems relating to the quality of the clinical evidence in major submissions to the PBAC using the evaluation framework of Hill et al. [3] with information on the submissions from their public summary documents (PSDs) [4].

Conflicts of interest: The views expressed in this article do not necessarily reflect the views or practices of our previous and/or current employers.

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We wanted to determine the type of problems that had a bearing on PBAC's decision making and thus determine whether the clinical evidence presented to the committee was "fit for purpose."

Methods

Because the focus of our study was the quality of the clinical evidence, aspects not directly related to this (i.e., modeling issues, calculation errors, and administrative matters) were not considered.

We deemed a problem to be significant if the issue was serious enough to prevent the PBAC from making a recommendation for the medicine in accordance with the request in the submission at the time. The reason(s) why the PBAC made a decision to recommend (or not recommend) the listing of a medicine is documented in the associated PSD. This does not suggest that there were no significant problems with submissions for medicines that were recommended.

We felt that it was important to distinguish between "significant problems" and "uncertainty." Submissions will always be associated with uncertainty, even those that are recommended. We sought to identify situations in which the level of uncertainty in submissions was so great that it presented a significant problem to the PBAC.

The secrecy provisions of the National Health Act bind the PBAC and submissions are treated as "commercial in confidence." The signing of the Australia-United States Free Trade Agreement in early 2005 facilitated the release of further information regarding the basis for PBAC's determinations regarding the subsidy of medicines on the PBS in PSDs from mid-2005 [2].

PSDs are available only for submissions related to PBAC considerations on the listing of medicines; they are not available for other submissions for PBAC considerations, such as those relating to pricing arrangements for listed medicines. We included all published PSDs associated with submissions (initial submissions and resubmissions) for medicines and vaccines seeking a listing on the PBS. We excluded submissions with PSDs for the following:

- Vaccines seeking a listing on the National Immunisation Program [5].
- Fixed-dose combination products seeking a listing on the PBS.
- Medicines seeking a listing on the Life Saving Drugs Program [6].
- Medicinal preparations (e.g., nutritional supplements) or devices seeking a listing on the PBS.
- New strengths or formulations of medicines already listed on the PBS.
- Nonprescription medicines seeking a listing on the PBS.
- Medicines seeking a change to an existing therapeutic relativity to another listed medicine.
- Medicines for which the applicant was not the medicine's sponsor.

The largest proportions of the submissions we excluded were for fixed-dose combination products, National Immunisation Program vaccines, and Life Saving Drugs Program medicines. Insofar as the (current) PBAC guidelines consider fixed-dose combination products and National Immunisation Program vaccines as separate product types, they are subject to different evidence requirements and hence their exclusion from the analysis is justified. The exclusion of submissions for Life Saving Drugs Program medicines is justified insofar as they are also subject to additional decision-making criteria.[6]

We sought to identify the types of problems in submissions as used by Hill et al. [3] that had been first described by O'Brien [7] and are summarized in Table 1.

Hill et al. found that problems with the supporting clinical evidence were the most common of all problem categories, but they did not conduct further analysis to obtain deeper insights. We developed additional frameworks in an attempt to understand these problems at their core (Tables 2 and 3).

One of us (M.J.W.) developed a coding template. We coded each eligible PSD using the template independently; differences in opinion were resolved by consensus.

Some PSDs were for submissions with multiple requests that were associated with different target patient populations (e.g., treatment-naive and treatment- experienced patients), different proposed main comparators, and different clinical claims. In these situations, we examined each request for each patient population because there might have been a significant problem with one request but not the other.

Some submissions were associated with requests in the form of options. We examined all options because there may have been significant problems in those that were not accepted by the PBAC.

Determinations for all problem categories were made on the basis of the clinical evidence presented in the submission. In situations in which the submission did not include any clinical data for PBAC's preferred main comparator, a determination on the estimate of comparative clinical efficacy could not be made.

Results

The PBAC published 598 PSDs for submissions considered between July 2005 and November 2012; we excluded 119 (20%) submissions, resulting in a study sample of 479 (80%) submissions (Fig. 1).

Some submissions were excluded for more than one reason. We identified 261 significant problems in the 479 submissions, an average of 0.54 significant problems per submission (Table 4). The 479 submissions were associated with 483 PBAC outcomes. Eighty-two percent of the submissions with a significant problem were associated with a rejection by the PBAC. Some submissions were recommended despite having one or more problems with the supporting clinical evidence. Invariably, they were recommended on a different clinical and economic basis than proposed by the sponsor. Submissions with no major problems with the supporting clinical data might have been rejected by the PBAC for another reason, such as uncertain or unacceptable cost-effectiveness.

There was a significant problem with the sponsor's choice of comparator in 11% of the submissions. There was no clear temporal pattern, with at least one problem occurring at all bar two PBAC meetings.

Randomized clinical trial evidence was not available for 4% of the submissions. The most common significant problem (140 or 29% of all submissions) was the determination of the medicine's comparative performance in the target patient population. Some submissions had multiple problems insofar as they contained multiple comparisons with different clinical claims (i.e., a claim of clinical superiority vs. comparator A and a claim of clinical noninferiority vs. comparator B).

There were a few examples in which the initial submission did not clearly identify the target patient population for the proposed medicine, and it took one to two resubmissions to resolve this problem.

Most of the problems related to the medicine's comparative performance with respect to efficacy, with only a few examples