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A comparative study of drug listing recommendations and the decision-making process in Australia, the Netherlands, Sweden, and the UK

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ABSTRACT

Drug listing recommendations from health technology assessment (HTA) agencies often fail to coincide with one another. We conducted a comparative analysis of listing recommendations in Australia (PBAC), the Netherlands (CVZ), Sweden (TLV) and the UK (NICE) over time, examined interagency agreement, and explored how process-related factors—including time delay between HTA evaluations, therapeutic indication and orphan drug status, measure of health economic value, and comparator—impacted decision-making in drug coverage. Agreement was poor to moderate across HTA agency listing recommendations, yet it increased as the delay between HTA agency appraisals decreased, when orphan drugs were assessed, and when medicines deemed to provide low value (immunosuppressants, antineoplastics) were removed from the sample. International differences in drug listing recommendations seem to occur in part due to inconsistencies in how the supporting evidence informs assessment, but also to differences in how domestic priorities shape the value-based decision-making process.

1. Introduction

Health technology assessment (HTA) is frequently used to inform value-based decision-making. Since it involves systematically evaluating health economic evidence, HTA is supported by a growing number of digital resources and regulatory initiatives that promote the sharing of clinical data. In the US, for instance, all applicable clinical trials must submit results to the publicly searchable registry clinicaltrials.gov [1], making submitted data available for use by international appraisers. Regulators, including England's National Institute for Health and Care Excellence (NICE), may also require manufacturers to submit all clinical data within the company's possession anywhere in the world prior to drug review [2]. Evidence from recent comparative studies indicates that a similar set of clinical trials are in fact made available to drug appraisals [3,4], which might lead one to anticipate significant overlap in value-based decision-making on drug coverage around the world.

Contrary to this expectation, a growing body of literature has found that the HTA-based decisions on whether to recommend public reimbursement of new medicines often fail to coincide with one another [5,6]. The literature has generally examined this issue from the perspective of the last available listing recommendation, and has suggested that international differences are accounted by social determinants, including preferences for treatment, disease severity and rarity [7,8] and local clinical practice [4]; as well as methodological factors, including HTA design

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and sufficiency of pharmacoeconomic evidence [7,9], and use of comparative data [4]. As has been previously argued, however, HTA is a complex process that cannot be fully understood if the perspective concentrates exclusively on final listing decisions [10]. Rather, social and methodological factors may impact final listing decisions, but only to the extent that they influence complex HTA processes that occur over time.

These complex processes are reflected in HTA agency listing recommendations, which may evolve as time passes. Periodic reassessment of cost-effectiveness may be mandated [11], but it may also result from an appeal against initial opinions on listing [12,13], ad hoc reassessment initiated by the emergence of new health economic evidence [14], or risk-sharing agreements [2]. In England, for instance, public guidance may be reviewed and re-issued if there is significant new evidence that is likely to change opinions on drug listing [2]. Australian listing recommendations can also be deferred for further review or appealed on 'procedural' or 'merit-based' grounds. Sponsors are also allowed an unlimited number of resubmissions should new information become available, and can request an independent review of negative recommendations [15]. Australian authorities in fact highlight that a decision not to recommend or change listing status "does not represent a final ... view about the merits of the medicine", but rather contributes to an "improved understanding of the listing process" [16].

Therefore, to better understand the causes of disagreement in HTA-based decision-making, we conducted a comparative analysis of drug listing recommendations emerging over time from Australia, England, the Netherlands, and Sweden. Within this framework, we examined interagency agreement in drug listing, and how social and methodological factors pertaining to the assessment process—including therapeutic indication and orphan drug status, time delay between HTA evaluations, health economic value, and comparator—influenced listing recommendations. This analysis found that international differences in drug listing recommendations exist in part due to inconsistencies in how the supporting evidence informs assessment, but also to differences in how domestic priorities shape the value-based decision-making process.

2. Methodology

2.1. Inclusion parameters

This study examined HTA review processes and drug listing decisions from four HTA agencies in Australia (PBAC), England (NICE), the Netherlands (CVZ; 'Zorginstituut Nederland' since 2014), and Sweden (TLV) between 2009 and 2013. These were selected as leading examples of agencies that make similar use of HTA to inform value-based decision-making in drug coverage (Table 1). The five-year period January 2009–December 2013 was chosen in order to pragmatically optimize the size of our sample while also capturing contemporary HTA practice.

2.2. Data extraction

2.2.1. HTA appraisal documents

A stepwise approach was used to identify all drugs that were appraised by the four HTA agencies. This process first identified all unique molecules that were assessed by NICE between 2009 and 2013 ($n = 102$). Of these, reviews for 67 drugs were publicly available as of July 2014 from the PBAC, of which 56 were also found to have been appraised by the CVZ. Of those 56 drugs, the TLV was found to have assessed 43 through July 2014. Since appraisals were publicly available for those 43 drugs from Australian, Dutch, Swedish, and UK HTA agencies, they were used as a common sampling frame in this study. Drug name, indications, listing recommendations, year of assessment, incremental cost-effectiveness ratios (ICERs), and review comparators were then extracted from all appraisal documents corresponding to each of the 43 drugs. If multiple HTA evaluations existed for drug-indication pairs, data was extracted from both the first and last appraisal that had been published through June 2014. For example, Australia's PBAC evaluated the clinical- and cost-effectiveness of sorafenib for renal cell carcinoma in 2006, 2008, 2012, and 2013—the evaluation conducted in 2006 was taken as the 'first' appraisal, while the one published in 2013 was classified as the 'last' available appraisal.

Listing recommendations were classified into four categories: 'List' (L), 'list with restrictions' (LWR), 'deferral' (D) and 'do not list' (DNL). Base case analyses defined restrictions on listing decisions by the presence of any constraint on use in the approved indication that would limit the population eligible for reimbursement. For the TLV, positive approvals that were assigned a '*Generell Subvention*' (general subsidy) were categorized as 'L', while those given a '*Begränsad Subvention*' (limited subsidy) were classified as 'LWR'. System-specific restrictions—e.g. physician prescription, reimbursement authority requirements—were not considered.

Where available, summary ICER measures were also extracted for each drug-indication pair. These consisted of discrete, one-sided directional, or a range of values. If agencies accepted more than one ICER for individual drug-indication pairs—e.g. to reflect treatment across patient subgroups—an inclusive ICER range was derived using the lowest and highest ICER values approved by the agency. Furthermore, if different ICERs were provided for different comparators, the ICER value corresponding with comparators used by other agencies was recorded to permit cross-agency comparison; otherwise, an ICER range was constructed to encompass all comparators that were used. ICERs were converted to U.S. dollar equivalents using historical currency conversion rates from OANDA that corresponded to the year of evaluation [17]. Nominal ICER values were also converted to constant 2013 U.S. dollars using price inflation indices from the World Bank [18]. To permit comparison, analyses were restricted to ICERs that were measured in terms of cost per QALY.

2.2.2. Supplementary sources

Anatomical Therapeutic Chemical (ATC) classifications for therapeutic main groups of drug-indication pairs were