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Abstract

Background & Objectives: Policy-makers and decision-makers in health are increasingly turning to health technology assessment (HTA) as a means for determining the efficacy, effectiveness, and cost-effectiveness of medicines. This study examines and compares the outcomes and processes of HTA in four countries—Australia, Canada, England & Scotland—across 27 oncology drug-indications pairs.

Methodology: This study consisted of two phases. In the first, the broad trends in HTA bodies' appraisal outcomes, dates of publication, and evidentiary considerations were surveys. Phase II included a more in-depth review of several oncology medicines in order to develop a more nuanced understanding of the appraisal processes within and between these four countries.

Findings: While there is variability in appraisal outcomes between agencies, there is substantive agreement on the therapeutic and social value of nearly 2/3 of oncology drug-listing pairings. Similarity exists in that NICE, PBAC, pCODR, and SMC apply a mix of both scientific judgments and social values to determining the effectiveness and efficiency of medicines. What the foregoing has demonstrated is that, in many respects, the HTA bodies of Australia, Canada, England, and Scotland vary in in the methodologies used to assess medicines and, in particular, in the rigor of process, interpretation of evidence, and application of additional considerations.

Conclusions: As the burden of cancer disease grows, so does the need for the accurate assessment of the true value of drugs. While there is often agreement on a drug's value, the processes through which such an appraisal is made will require standardization. Failure to do so risks stymieing innovation and inequities in access.

1. Introduction

Health technology assessment (HTA) has been increasingly used across health systems in developed countries as a means to inform healthcare decision-making and policy (Drummond et al 2007). HTA agencies have been borne out of recognition that resources a finite, and thus therapies should be assessed on criteria beyond clinical benefit (Bergmann et al 2013). Rather, these bodies seek to "optimize care using available resources" with "consideration of organizational, societal, and ethical issues" (Nielsen & Busse 2008, 1).

Determining the efficacy, effectiveness, and efficiency of oncology drugs is of particular salience of both developed and developing societies. The Global Burden of Disease 2010 study estimates that cancers account for 7.6% of global disability adjusted life years (DALYs), and the burden of disease attributable to cancer has risen 27.3% between 1990 and 2010 worldwide (Murray et al 2012). The WHO estimates that there are 11 million new cases each yea (Bergmann et al 2013). In 2010, 8 million people died from cancer worldwide, representing an increase of 38% in 20 years (Lozano et al 2012). This translates into considerable costs. In the UK, for example, where NICE is considered a rigorous appraiser of medicines, cancer care spending increased 75% between 2003 and 2010 (Aggarwal & Sullivan 2013). Clearly, with the considerably high need for oncology drugs, HTA will play an increasingly important role in determining which drugs are the most efficacious, effective and efficient (Meropol & Schulman 2007).

The concern, however, is that health technology assessment agencies may fail to determine which drugs demonstrate value for patients. HTA bodies have demonstrated considerable variability in the outcomes of their appraisals (Chabot & Rocci 2014; Kanavos et al 2010; Nicod & Kanavos 2012; Nielsen & Busse 2008). This has several consequences. First, provided that reimbursement authorities adopt the recommendations of the local HTA authority, variability in appraisal outcomes may lead to unequal access across jurisdictions, thereby leading to inequities in access to important medicines (Nielsen & Busse 2008). For the healthcare industry, such variability leads to uncertainty for pharmaceutical companies, which, in turn, creates a disincentive for investment in R&D. A greater burden of evidence for pharmaceutical companies may dissuade firms from entering a market in the first place, or they may pass the costs of

producing such evidence on to the health system. At the same time, concerns of equity, the level of necessity, budget constraints, and the public health impact may justify differences in HTA authorities' approaches to evaluating medicines (Kanavos et al 2010; Nicod & Kanavos 2012).

The system-level, firm-level, and patient-level significance of HTA and of cancer has prompted this study to compare England's National Institute for Health and Care Excellence (NICE), Australia's Pharmaceutical Benefits Advisory Committee (PBAC), the pan-Canadian Oncology Drug Review (pCODR), and the Scottish Medicine Consortium's (SMC) appraisal processes across oncology indications. Similar to the work of Kanavos et al (2010) and van den Aardweg & Kanavos (2013), an initial review for the evidence suggests substantial variation in reimbursement appraisals for the same medicine across all three authorities. However, to our knowledge, no study has exclusively and extensively focused on the health economic assessment of oncology drugs across several countries.

The objectives of this dissertation are several-fold:

1. Compare the evidentiary requirements and methodologies for cost-benefit assessment between NICE, PBAC, pCODR, and SMC.

2. Identify appraisals of medicines that exemplify the similarities and/or differences in the health technology assessment process.

3. Determine the presence of trends across health technology appraisal agencies that are predictive of particular appraisal outcomes.

This paper is structured as follows. The first section presents a review of each of the HTA agencies under consideration. The methods are then presented. Third, results are presented in two subsections: Phase I includes general findings, while Phase II gives a more nuanced analysis that compares the appraisal process of drugs within a particular indication. A discussion highlights key similarities, differences, and implications. The paper then concludes.

2. HTA Bodies

HTA agencies operate within a network of other healthcare actors that, together, determine whether a medicine is allowed to enter a market, who receives the medicine, and who pays for therapies. Regulator bodies such as the European Medicines Agency's (EMA) Committee for

Medicinal Products for Human Use, the Therapeutic Goods Administration (TGA) in Australia, and Health Canada are responsible for assessing drugs on their efficacy and safety. Approval is required from these agencies to receive market authorization (ISPOR 2014a-d). National or regional bodies then negotiate with the manufacturer (or the drug wholesaler) "on drug price, reimbursement status and allocated funding" (Bergman et al 2014, 303). HTA bodies inform these three latter considerations. The degree to which they do so depends on their mandates, and authorities may fall into three different types: advisory, regulatory, or coordinative. With the exception of pCODR (coordinative), all of the HTA bodies surveyed principally fall under the "advisory" label (NICE severs more limited regulatory functions) (Kanavos 2013).,

NICE informs the English and Welsh National Health Service's (NHS) decision-making on medicines and health technologies by developing evidence-based medicine (EBM) guidance, quality standards, and treatment information for actors within the NHS (ISPOR 2014d). EBM includes technological appraisals and treatment/interventional guidelines. A centralized reviewing authority, NICE evaluates technologies that are submitted by the English Department of Health, and its recommendations must be implemented by NHS funds, Primary Care Trusts (PCTs), within three months of an appraisal. NICE's review committee draws upon expertise from academia, providers (physicians and managers), health economists, and statisticians (Kanavos et al 2010; Morgan et al 2006; van den Aardweg & Kanavos 2013).

To date, NICE has appraised 480 interventional technologies (NICE 2014a). NICE is unique among HTA bodies in the respect that its review process adds an additional level of rigor via the requirement that the Evidence Review Group (ERG) conducts an independent review alongside that submitted by the manufacturer (Cairns 2007). As of 2010, NICE's rate of positively recommending drugs for reimbursement stood at 72% (Kanavos et al 2010).

The SMC operates differently than NICE, in several respects. First, the drugs that it reviews are driven by manufacturer submissions. As opposed to NICE's more drawn-out evaluations, SMC attempts to conduct an appraisal as rapidly as possible (Cairns 2007; Kanavos et al 2010). While SMC has an equivalent to the ERG, this group does not conduct its own its own rapid appraisals. This entails that SMC may evaluate a drug several times before NICE even produces its first

review. In addition, SMC principally operates in an advisory role to the Area Drug and Therapeutic Committees (ADTCs) across Scotland (its membership is composed of representatives from these bodies) (SMC 2014b). As of 2010, 68% of SMC's appraisals were positive (Kanavos et al 2010).

pCODR is the newest of all four regulatory bodies, having been founded in 2010. The agency provides guidance, based off of EBM, cost-effectiveness assessments, and patient perspectives, to the Ministries of Health and relevant oncology actors in all provinces and territories (with the exception of Quebec). Manufacturers or "tumor groups" (physician groups) submit evidence for appraisal, and the process is intended to produce rapid review within 5 to 8 months. As of April 2014, pCODR has been subsumed by the Canadian Agency for Drugs and Technologies in Health (CADTH), which conducts the Common Drug Review (CDR) in Canada (pCODR 2014a; ISPOR 2014b).

A centralized review body, PBAC makes recommendations to the Minister for Health and Aging on coverage decisions under the Pharmaceutical Benefit Scheme (PBS) positive formulary (Morgan et al 2006). Similar to SMC, PBAC prioritizes rapidity of appraisals, and has established a fluid-model of review whereby several "final" recommendations might be made before an ultimate funding decision is made based off of clinical benefit considerations, economic evidence (via the Economics Sub-Committee), and budgetary impact (under the Drug Utilization Sub-Committee). The PBAC also considers input from civil society, pharmacists, and clinicians. As of 2010, 74% of all PBAC appraisals resulted in a positive outcome (Kanavos et al 2010; Nicod & Kanavos 2010).

3. Methods

The methodology of this study mirrors that of van den Aardweg & Kanavos (2013). There were two phases of this study. This first phase sought to establish the general health technology assessment methodologies employed by the four agencies in order to gain an understanding of the rationale underlying appraisals. The second, iterative step compared methodologies and appraisals across countries and within indications.

Phase I
Sample Selection

The sample selection component of Phase I identified medicines for inclusion in the entire study. NICE, PBAC, pCODR, and SMC's websites were searched appraisals of oncology medicines between March and April 2014. The search was restricted to appraisals with a final recommendation made in 2007 and onwards in order to capture a reasonable sample size. Each agency had a different search function, thereby complicating the standardization of a case definition. For NICE, technology appraisals were found via hand-searches under all guidance for cancers (NICE 2014b). A hand search of all appraisals was conducted for pCODR and PBAC (PBAC 2014; pCODR 2014b). For SMC, appraisals were found within the malignancy & immunosuppression category (SMC 2014a).

An oncology indication of a medicine was the ultimate criterion for conclusion. Medicines were classified by International Nonproprietary Name (INN), and indications—or the specific disease for which the drug was targeted—were coded for according to ICD-10 classifications (ICD10Data 2014). If a medicine was appraised across several indications, the appraisal for each indication was considered. Only the final appraisal for a medicine in an indication was used for comparisons across agencies in order to account for the aforementioned differences in rapidity of the assessment process.

The degree of overlap of appraisals for medicines was then assessed between all agencies. *Partial* overlap consisted of exact similarity in 1) INN and 2) ICD-10. *Full* overlap consisted of similarity in 3) listing, or the specific population/patient characteristics for which a medicine was appraised. The inclusion of partial overlap allowed for the broad comparison of HTA bodies' methodology and outcomes without sacrificing sample size. Analysis of drug/indication pairs that fully overlapped permitted like-for-like comparisons across countries, which also allowed for the appraisal processes to be considered in greater detail. The distinction between partial and full overlap are made in the text where appropriate. In order to maximize comparability, only overall across three or four agencies was included in this analysis.

Data Extraction and Outcomes of Interest

The author read each appraisal document, and relevant outcomes were extracted into a master file. The author quality-checked this file for accuracy.

There were three broad outcomes of interest: (1) date of market access and appraisal publication; (2) the outcome of the appraisal; and (3) general methodological considerations. The duration between marketing approval and appraisal publication was determined as a proxy for the rigor of each agency's review process. Trends in appraisal outcomes—classified as recommended/list (positive), list with condition (LwC; also considered positive), do not list/not recommended/reject (negative), and defer—allowed for a high-level evaluation of each agency's appraisal process. The methodological considerations were studied in order to more thoroughly investigate and compare each agency's HTA process. Outcomes within this category included: key considerations when making an appraisal (eg safety, efficacy, effectiveness, and health economic evidence); the evidence base; and country-specific factors.

Phase II

The second phase of the study investigated the findings from Phase 1 in further depth through several case studies of medicines that are representative of the overall samples for all four nations. The case studies fall into two categories: 1) universally positively appraised medicines; and 2) tyrosine kinase inhibitors non-small cell lung cancer (NSCLC), which were often used as comparators against each other in appraisals. A caveat must be stated for this last appraisal. PBAC appraised erlotinib in both July 2013 and March 2014 for different listings. The earlier appraisal was for first-line therapy, which was the specific listing in other TKI appraisals, whereas the later submission was last-line treatment. The March 2014 appraisal was accordingly redacted.

4.1: Phase I—General Results

Search Results

The four HTA agencies differ in the volume of drugs considered. SMC is the leader in terms of number of medicines considered (44), indications (27), and total appraisals rendered (52). These numbers are similar between NICE and PBAC, while pCODR assessed 25 medicines across 17 indications. SMC is also the most frequent re-appraiser, followed by pBAC, owing to the aforementioned differences in the degree of manufacturer involvement in the appraisal process.

Table 1: Drugs reviewed across agencies

NICE, n = 31	SMC, n = 44	pCODR, n = 25	PBAC, n = 31
Abiraterone	Abiratrone	Abiraterone acetata	Abiraterone
Aflibercept	Aflibercept	Arsenic Trioxide	Afatinib
Bendamustine	Axitinib	Axitinib	Axitinib
Bevacizumab	Azacitidine	Bendamustine hydrochloride	Bevacizumab
Bosutinib	Bendamustine	Bortezomib	Bortezomib
Cabazitaxel	Bevacizumab	Brentuximab vedotin	Cabazitaxel
Capecitabine	Bortezomib	Cetuximab	Capecitabine
Cetuximab	Bosutinib	Crizotinib	Cetuximab
Crizotinib	Brentuximab vedotin	Dabrafenib	Crizontinib
Dasatinib, nilotinib, and imatinib	Cabazitaxel	Enzalutamide	Dabrafenib
Denosumab	Capecitabine	Eribulin mesylate	Dasatinib
Eribulin	Catumaxomab	Everolimus	Denosumab
Erlotinib	Cetuximab	Ipilimumab	Eribulin
Everolimus	Crizotinib	Lapatinib	Erlotinib
Fulvestrant	Decitabine	Lenalidomide	Everolimus
Gefitinib	Docataxel	Pazopanib hydrochloride	Gefitinib
Imatinib	Enzalutaminde	Pemetrexed	Imatinib
Ipilimumab	Eribulin mesylate	Pertuzumab	Ipilimumab
Lapatinib + trastuzumab	Erlotinib	Regorafenib	Nilotinib
Mifamurtide	Everolimus	Ruxolitinib	Panitumumab
Ofatumumab	Gefitinib	Sunitinib malata	Pazopanib
Pazopanib	Histamine dihydrochloride	Trametinib	Pemetrexed disodium
Pemetrexed	Imatinib	Trastuzumab emtansine	Rituximab
Pixantrone	Ipilimumab	Vemurafenib	Sorafenib
Rituximab	Lapatinib	Vismodegib	Sunitinib
Sorafenib	Mercaptopurine		Topotecan
Topotecan	Mifamurtide		Trastuzumab
Trabectedin	Nilotinib		Vemurafenib
Trastuzumab	Ofatumumab		Vinflunine
Trastuzumab emtansine	Paclitaxel		Vinorelbine
Vemurafenib	Panitumumab		Vorinostate
	Pazopanib		
	Pemetrexed		
	Pertuzumab		
	Rituximab		
	Sunitinib		
	Tegafur/gimeracil/oteracil		
	Temsirolimus		
	Trabectadin		
	Trastuzumab		
	Vandetanib		
	Vemurafenib		
	Vinflunine ditartrate		
	Vismodegib		

With respect to degree of overlap, 22 medicines and across 12 indications partially overlap. The four agencies have thus made a combined twenty-seven distinct appraisals of drug-indication pairs. All four agencies have reviewed 11 of the 27 drug-indication pairings, while 16 of the drug-indication pairs were appraised by three agencies. SMC leads all agencies with an appraisal for all 27 drug-indication pairs. (The drug-indication pairs are numerated and are in the citations).

Table 2: Partial and full (bolded) overlap, with outcomes

			NICE	SMC	pCODR	PBAC
Abiraterone	Castration-resistant metastatic prostate cancer (number of appraisals: 4)	C79.82	List with conditions	List with conditions	List with conditions	List with conditions
Afatinib	Locally advanced/metastatic NSCLC (4)	C34.90	List with conditions	List with conditions	List with conditions	Recommended
Axitinib	RCC (3)	C64.9		List with conditions	Recommended	Not recommended
Bendamustine	CLL (3)	C91.1	Recommended	Recommended	List with conditions	
Bortezomib	Multiple myeloma (4)	C90	Recommended	List with conditions	List with conditions	List with conditions
Cabazitaxel	Metastatic prostate cancer (3)	C61	Not recommended	Not recommended		Not recommended
Capecitabine	Advanced gastric cancer (3)	C16.9	Recommended	Recommended		Defer
Cetuximab	mCRC (4)		Not recommended	List with conditions	Not recommended	List with conditions
Crizotinib	NSCLC (4)	C34.90	Not recommended	List with conditions	Not recommended	Defer
Eribulin	Locally advanced/metastatic breast cancer (4)	C50	Not recommended	Not recommended	List with conditions	Not recommended
Erlotinib	NSCLC (3)	C34.90	List with conditions	List with conditions		Recommended
Everolimus	Breast cancer (3)	C50	Not recommended	Not recommended	List with conditions	
Everolimus	Advanced Renal Cell Carcinoma (3)	C64.9	Not recommended	Not recommended		Not recommended
Everolimus	Neuroendocrin tumors of pancreatic origin (3)	C25.4		Recommended	List with conditions	Recommended
Gefitinib	NSCLC (3)	C34.90	List with conditions	Not recommended		Recommended
Imatinib	GIST (3)	D37.9	Not recommended	List with conditions		Not recommended
Ipilimumab	Advanced melanoma (4)	C34.9	List with conditions	List with conditions	List with conditions	Not recommended
Lapatinib	Breast cancer (4)	C50	Not recommended	Not recommended	Not recommended	List with conditions
Pazopanib	Advanced Renal Cell Carcinoma (4)	C64.9	List with conditions	List with conditions	Recommended	List with conditions
Pazopanib	Soft-tissue sarcoma (3)	C49.8		Not recommended	Not recommended	Recommended
Pemetrexed	NSCLC (3)	C34.90		Not recommended	List with conditions	Not recommended
Rituximab	CLL (3)		List with conditions	List with conditions		Recommended
Sunitinib	Advanced and/or metastatic RCC (3)	C64.9	Recommended	Not recommended		Recommended
Sunitinib	Neuroendocrin tumors of pancreatic origin (4)	C25.4	List with conditions	Recommended	List with conditions	Recommended
Trastuzumab	Metastatic breast cancer (3)	C50	Not recommended	List with conditions		Recommended
Trastuzumab	Metastatic gastric cancer (3)	C16.9	List with conditions	Not recommended		Defer
Vemurafenib	Melanoma (4)	C43.9	List with conditions	List with conditions	List with conditions	Defer

Full overlap exists between 14 medicines and across 10 indications/listings, thereby leading to 15 drug-listing pairings. Three agencies have reviewed nine pairings. pCODR only has reviewed 9 of these pairings.

Process/Timing

The EMA and TGA websites were used to determine the dates of market access for the UK and Australia (EMA 2014; TGA 2014). pCODR included dates of market access in its appraisals.

The time between a drug receiving regulatory approval and the completion of an appraisal is similar between NICE, SMC, and PBAC, which have median lag times (means are not reported due to outliers) of 24 months, 21 months, and 21 months, respectively (see Table 3 below). The median time for pCODR is 6 months. The differences in these values do not entail that Canadian patients have enjoyed access to medicines prior to their counterparts in other countries. Rather,

taking into account dates of market access, medicines are generally available in the UK (and in the European Union in general) before they are in Canada or in Australia.

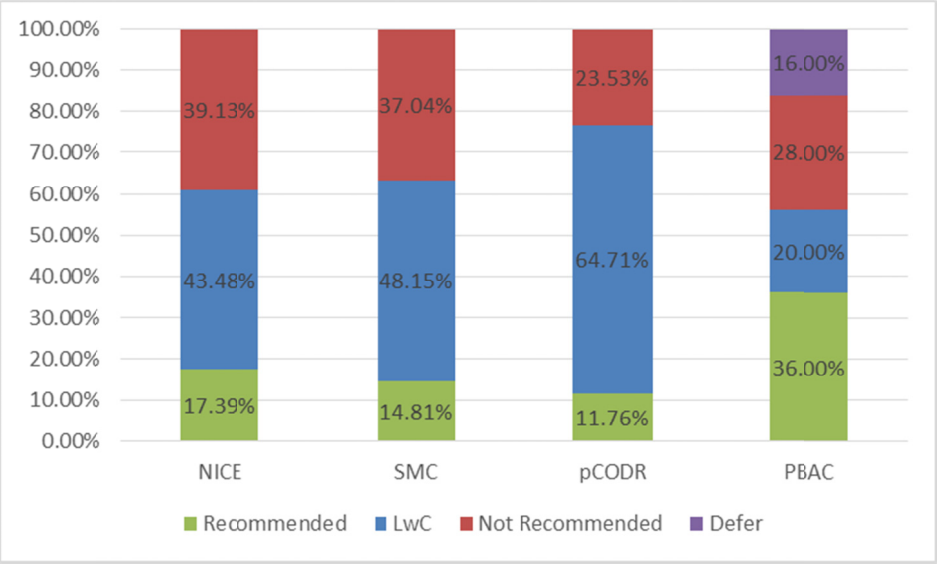
Table 3: Drug-listing pair appraisal dates, marketing authorization date, and lag time

	NICE			SMC		
Drug	**Published**	**MA Date**	**Lag (days)**	**Published**	**MA Date**	**Lag (days)**
Abiraterone	Jun-12	5-Sep-11	270.00	6-Jul-12	5-Sep-11	305.00
Afatinib	Apr-14	25-Sep-13	188.00	7-Feb-14	25-Sep-13	135.00
Bendamustine	Feb-11	3-Aug-10	182.00	4-Mar-11	3-Aug-10	213.00
Bortezomib	Apr-14	26-Apr-04	3627.00	6-Dec-13	26-Apr-04	3511.00
Capecitabine	Jul-10	2-Feb-02	3071.00	10-Aug-07	2-Feb-02	2015.00
Erlotinib	Jun-12	19-Sep-05	2447.00	9-Dec-11	19-Sep-05	2272.00
Everolimus				6-Apr-12	3-Aug-09	977.00
Gefitinib	Jul-10	24-Jun-09	372.00	9-Apr-10	24-Jun-09	289.00
Ipilimumab	Dec-12	13-Jul-11	507.00	8-Mar-13	13-Jul-11	604.00
Pazopanib	Feb-11	14-Jun-10	232.00	4-Feb-11	14-Jun-10	235.00
Rituximab	Jul-10	2-Jun-98	4412.00	4-Dec-09	2-Jun-98	4203.00
Sunitinib	Mar-09	19-Jul-06	956.00	8-Jun-07	19-Jul-06	324.00
Sunitinib	Sep-09	19-Jul-06	1140.00	8-Apr-11	19-Jul-06	1724.00
Trastuzumab	Jun-12	28-Aug-00	4295.00	6-Dec-13	28-Aug-00	4848.00
Vemurafenib	Dec-12	17-Feb-12	288.00	8-Nov-13	17-Feb-12	630.00
Median Lag (days)			731.50			630.00
Median Lag (months)			24.38			21.00
	pCODR			**PBAC**		
	Published	**MA Date**	**Lag (days)**	**Published**	**MA Date**	**Lag (days)**
Abiraterone	Oct-13	28-May-13	147.00	1-Nov-12	1-Mar-12	245.00
Afatinib	May-14	1-Nov-13	182.00	1-Jul-13	7-Nov-13	-129.00
Bendamustine	Feb-13	24-Aug-12	179.00			
Bortezomib	Mar-13	1-Jan-05	3005.00	1-Jul-11	1-Jun-09	760.00
Capecitabine				1-Jul-09	1-Jun-09	30.00
Erlotinib				1-Jul-13	30-Jan-06	2709.00
Everolimus	Aug-12	10-Jan-13	-133.00	1-Mar-14	8-Aug-13	205.00
Gefitinib				1-Jul-13	28-Apr-03	3717.00
Ipilimumab	Apr-12	1-Feb-12	77.00	1-Mar-12	4-Jul-11	241.00
Pazopanib	Aug-13	27-May-10	1190.00	1-Mar-12	30-Jun-10	610.00
Rituximab				1-Nov-10	6-Oct-98	4409.00
Sunitinib				1-Jul-08	14-Sep-06	656.00
Sunitinib	May-12	30-Jun-11	308.00	1-Aug-13	14-Sep-06	2513.00
Trastuzumab				1-Jul-12	14-Sep-00	4308.00
Vemurafenib	Jun-12	15-Feb-12	107.00	1-Mar-13	10-May-12	295.00
Median Lag (days)			179.00			633.00
Median Lag (months)			5.97			21.10

Appraisal Outcomes

The distribution of appraisal outcomes across agencies is presented in Graph 1.The Australian HTA board has been the most "generous," with 36% of the 25 drug-indications appraisals receiving a "list/recommended." PBAC, however, has been the only agency to defer appraisals. Canada has the lowest rate of "list" appraisals (12%), but it does have the highest rate (76%) of positive recommendations (list or list with conditions). NICE claims the highest rejection rate with 40%.

Graph 1: Distribution of appraisal outcomes



Across the drug-indication pairings, only 1 drug was universally given an equivalent appraisal by all reviewing agencies (abiraterone, LwC). Eight drug-indication pairings received a universally positive appraisal from the reviewing agencies. The remaining 18 drug-indication pairings received heterogeneous appraisals. No medicine was universally rejected outright. With respect to drug-listing pairings, the degree of similarity between HTA bodies' appraisals was greater, with 9 of the 15 pairs having received positive appraisals across all of the relevant reviewing agencies. If deferred appraisals are included, 11 out of 15 pairs received universally positive appraisal.

Relating outcomes to the aforementioned timing of appraisals, NICE and SMC appear as the positive-appraisal leaders (van den Aardweg & Kanavos 2013), with 4 positive recommendations each, amongst the 10 drug-listing pairs that received 3 or 4 positive reviews. In these drug-indication pairs, the only negative appraisal came from PBAC.

The existence of a leader-follower relationship, however, is weakened by two considerations. First, pCODR only began issuing appraisals in 2012. Second, Canada generally grants market access after market access granted by the EMA. For the 5 drug-appraisal pairings for which the first appraisal occurred during or after 2012, pBAC was the leader in 2, and NICE, pCODR and SMC in 1 each. Irrespective of time trends, the facts that two-thirds of drug-listing pairs received majority positive appraisals, as well as that three of these were initiated with a negative or deferred ruling, suggest that there exists broad consensus on the value of oncology drugs.

Evidence Considered

All four HTA bodies consider phase III randomized controlled trials as the primary piece of evidence for nearly all appraisals. Individual phase III trials provided either a direct or indirect comparison between the comparators of interest. Where a single trial was insufficient to compare the applicant medicine to the existing treatment options in a particular jurisdiction, the manufacturer (or the ERG) submitted further phase III trials with a common comparator to the primary RCT. The table below presents the appraisals in which an indirect comparison was necessary.

The bodies differ in the extent to which they consider supplementary evidence. NICE, for instance, regularly accepts phase II trials as evidence, particularly in order to evaluate safety and HRQoL. PBAC also regularly conducts systematic reviews that identify, for instance, phase III trials necessary to furnish indirect comparisons or phase II trials for dosage optimization. SMC and pCODR, on the other hand, principally only include a handful phase III trials. Further evidence is presented below.

Table 4: Appraisals' consideration of trials that allow for direct comparisons between sponsored drug and comparators of interest

	NICE	Direct	SMC	Direct	pCODR	Direct	PBAC	Direct
Abiraterone	List with conditions	N	List with conditions	N	List with conditions	N	List with conditions	N
Afatinib	List with conditions	P	List with conditions	N	List with conditions	N	Recommended	N
Bendamustine	Recommended	Y	Recommended	Y	List with conditions	Y	N/A	
Bortezomib	Recommended	N	List with conditions	Y	List with conditions	Y	List with conditions	N
Capecitabine	Recommended	Y	Recommended	Y	N/A		Defer	Y
Erlotinib	List with conditions	N	List with conditions	P	N/A		Recommended	Y
Everolimus	N/A		Recommended	P	List with conditions	N	Recommended	N
Gefitinib	List with conditions	P	Not recommended	N	N/A		Recommended	P
Ipilimumab	List with conditions	N	List with conditions	P	List with conditions	N	Not recommended	N
Pazopanib	List with conditions	N	List with conditions	P	Recommended	Y	List with conditions	N
Rituximab	List with conditions	Y	List with conditions	Y	N/A		Recommended	Y
Sunitinib	Recommended	Y	Not recommended	Y	N/A		Recommended	Y
Sunitinib	List with conditions	Y	Recommended	Y	List with conditions	N	Recommended	Y
Trastuzumab	Not recommended	N	List with conditions	Y	N/A		Recommended	Y
Vemurafenib	List with conditions	Y	List with conditions	Y	List with conditions	Y	Defer	Y

Primary Comparative Effectiveness Measurements

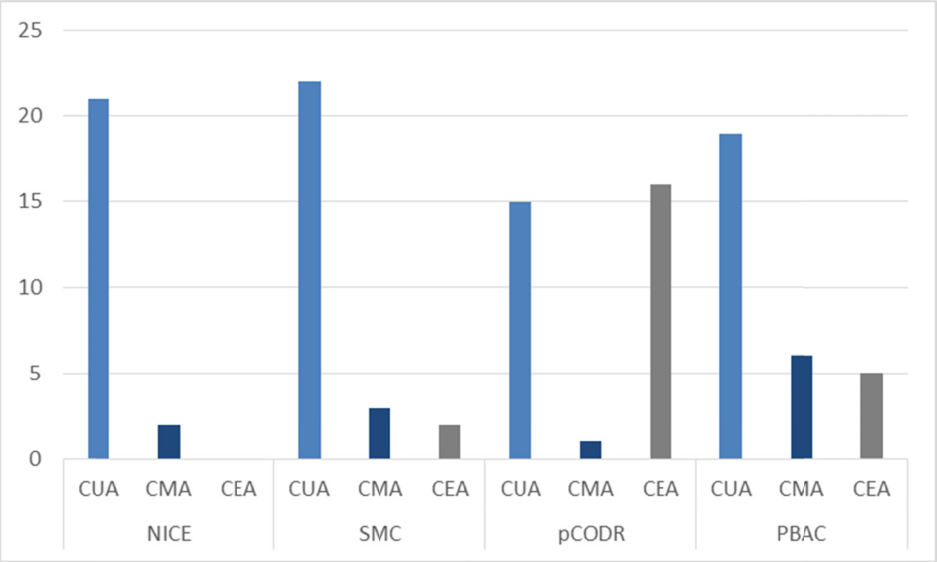
For establishing clinical effectiveness, oncology clinical trials have two primary endpoints: progression free survival (PFS) and/or overall survival (OS). HRQoL has been inconsistently estimated in phase III trials. NICE, pCODR and PBAC evaluate PFS and OS as the primary clinical effectiveness endpoints, which are used to establish clinical superiority, clinical similarity, or clinical non-inferiority (see case studies below for further detail). SMC has often factored in several secondary outcomes from the RCTs into its decisions, including: time to progression; objective response rate; median duration of response; recurrence free survival; and definitive deterioration.

Health Economic Assessment

The four agencies consider cost-utility analyses (CUA), cost-effectiveness analysis (CEA), cost-minimization analysis (CMA), and, to a highly limited extent, budget impact analyses as economic evidence. The type of economic assessments and modeling considered differs across the four bodies (Graph 2). NICE almost exclusively considers CUA; SMC accepts CUA and CMA; pCODR considers CUA and CEA; and PBAC regularly bases decisions off of all three

types. When reporting health economic outcomes, nearly all appraisals report CUA ICERs or the results of cost-minimization analyses. CEA results were only reported in several appraisals.

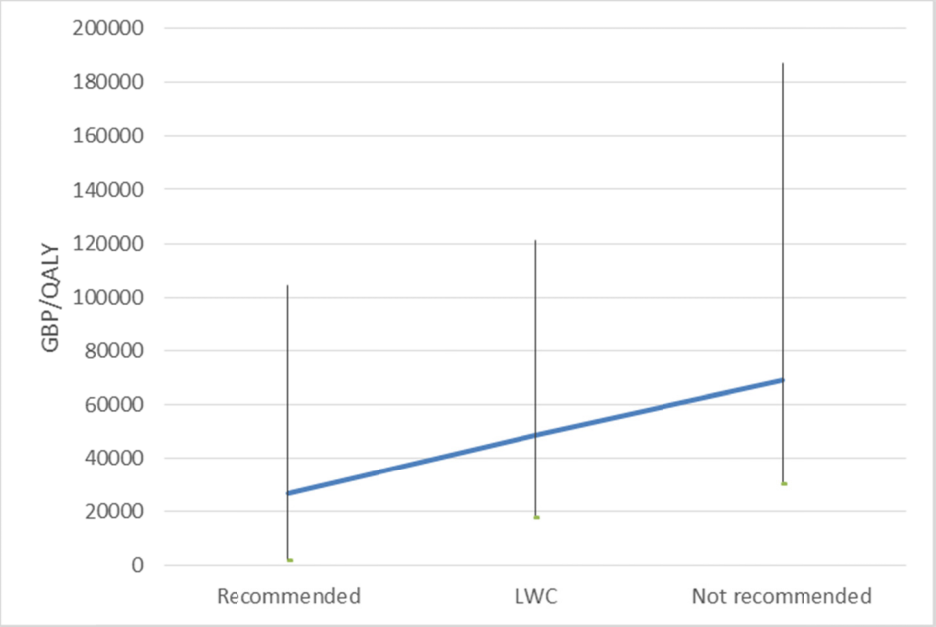
Graph 2: Distribution of CEA types



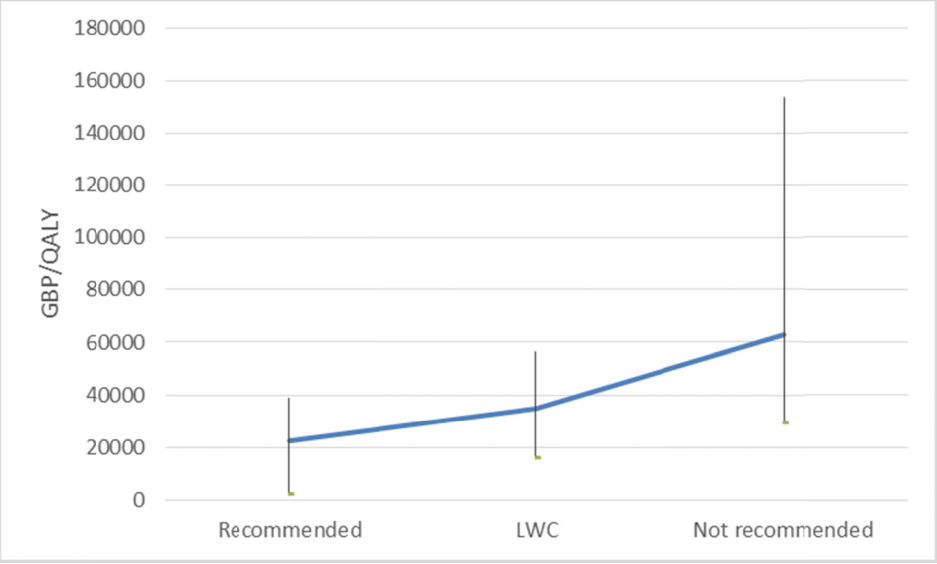
Graphs 3a-d demonstrate the trends in the median and range of the ICERs estimated or reviewed by all four agencies across appraisal outcome. The ICERs point to the at least rough presence of acceptability thresholds in the NICE and SMC decision-making processes. For NICE, recommended oncology drugs generally have a base case ICER below £30,000/QALY, while conditional appraisals were above £50,000/QALY in only three circumstances. In Scotland, recommended drugs rang from £1,790/QALY to £38,925/QALY, LwC from £15,593/QALY to £56,343/QALY, and not recommended from £28,912/QALY to £154,002/QALY. In Canada, the opposite of expectations is true: all but one of the rejected medicines' ICERs are less than the LwC medicines' ICERs. PBAC, meanwhile, reports ICERs as ranges, thereby complicating any comparison.

Graph 3a-d: Distribution of ICERs (Maximum, median, minimum)

a) Median of ICERs increases from positive to negative appraisal in England[1]



b) Median of ICERs increases from positive to negative appraisal in Scotland



[1] Medians taken in order to account for significant skew in the ICER estimates

c) Median ICERs unexpectedly decline from positive to negative appraisals in Canada

d) Median ICERs demonstrate no clear trends across appraisal outcomes in Australia

Within the drug-listing pairs, the only consistent trend in the ICERs across countries is that those from Australia and Canada tend to be higher once converted to GBP. ICERs can, surprisingly, vary between the clinically and socially similar settings of England and Scotland (see case studies below). The finding of dissimilar ICERs is unexpected given the aforementioned overlaps in positive appraisals.

A principal modifier considered in cost-effectiveness analyses were incentives that lowered the costs or, or risks associated with, new drugs (Table 5). NICE and SMC considered financial-based patient access schemes (PAS). NICE and SMC have factored in PAS's in 8 out of 23 and 6 of 27 of drug-indication pairs. PBAC, meanwhile, has contemplated the role of risk-sharing agreements (RSA) within and after the appraisal in 4 of 25 drug-indication pairs. It is the only agency to consider non-financial RSAs.

Table 5: Consideration of PAS's and RSAs by NICE, SMC & PBAC

	NICE	PAS	SMC	PAS	PBAC	RSA
Abiraterone	List with conditions	Y	List with conditions	Y	List with conditions	Y
Afatinib	List with conditions	Y	List with conditions	Y	Recommended	N
Bendamustine	Recommended	N	Recommended	N	N/A	
Bortezomib	Recommended	N	List with conditions	N	List with conditions	N
Capecitabine	Recommended	N	Recommended	N	Defer	N
Erlotinib	List with conditions	Y	List with conditions	Y	Recommended	N
Everolimus	N/A		Recommended	N	Recommended	Y
Gefitinib	List with conditions	Y	Not recommended	N	Recommended	N
Ipilimumab	List with conditions	Y	List with conditions	Y	Not recommended	N
Pazopanib	List with conditions	Y	List with conditions	Y	List with conditions	N
Rituximab	List with conditions	N	List with conditions	N	Recommended	N
Sunitinib	Recommended	N	Not recommended	N	Recommended	Y
Sunitinib	List with conditions	Y	Recommended	N	Recommended	N
Trastuzumab	Not recommended	N	List with conditions	N	Recommended	N
Vemurafenib	List with conditions	Y	List with conditions	Y	Defer	N

4.2: Phase II—Case Studies of Uniformly Positive Appraisals

Abiraterone (*Zytiga*) for metastatic prostate cancer (C79.82), Appraisals 1, 23, 36 & 59

Submission and recommendation timeframe

The manufacturer sought listing abiraterone for castration-resistant metastatic prostate cancer, in combination with prednisone or prednisolone, for men who have progressed or refractory to a docetaxel-containing regimen in all four countries. Abiraterone received marketing approval first in England and Scotland in September 2011. Australia granted access six months later, while Canadian approval came in May 2013. Appraisal times were all less than a year.

Appraisal outcomes

All four HTA bodies recommended abiraterone within the requested listing conditional on the improvement of cost-effectiveness. NICE and SMC explicitly mentioned that the recommendation was conditional upon the availability of PAS's, while PBAC and pCODR recommended abiraterone only on a cost-minimization and cost-effectiveness improvement basis, respectively. pCODR further restricted abiraterone to mildly symptomatic patients with a European Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The main rationales for a positive recommendation were relatively common across all four agencies. Abiraterone demonstrated a net clinical benefit versus several comparators. Oral administration offered a "step change in treatment" was seen to align with a patient advocacy group's desire for convenience (NICE) (30). At the same time, agencies expressed few concerns with abiraterone. NICE considered that the submitted evidence and the model were consistent with the ERG's model, and that there were few major uncertainties with the evidence. PBAC and pCODR, however, were concerned that abiraterone might be used outside of the specific listing. The former suggested that the government enter into a price-volume risk-sharing agreement with the manufacturer in order to mitigate its exposure to financial risk stemming from unexpected use.

Evidence-base & comparative effectiveness

The types and amount of evidence considered differed between the four bodies, as shown in Table 6. Double-blind, phase III randomized controlled trials served as the primary evidence. PBAC considered the widest range of evidence, and 2 of the 13 RCTs—COU-AA-301 and de Bono 2011—considered also served as the clinical evidence undergirding the NICE and SMC appraisals. pCODR, NICE and SMC each relied on 1 principal RCT.

Table 6: Types of evidence, clinical outcomes, and additional considerations when appraising abiraterone

	NICE	SMC	pCODR	PBAC
Abiraterone, C79.82	List with condition	List with conditions	List with conditions	List with conditions
Evidence Considerations	5 phase III, 3 phase II trials	1 phase III trial; "commercially confidential data"	1 phase III trial	13 phase III trials
Clinical effectiveness	OS, PFS, HRQoL	Primary: OS; secondary: time to PSA progression, time to radiological progression, PSA response rate, objective response rate, symptom-related endpoints (HRQoL)	OS, PFS	OS, HRQoL
Adverse events	x	x	x	x
Administration/feasibility	x	x		x
Unmet need/end-of-life	x	x	x	x
Patient choice	x	x	x	
Resource use		x	x	x
PAS	x	x		

PBAC considered the 13 placebo-controlled RCTs in order to conduct an indirect comparison between abiraterone, mitozantrone and cabazitaxel. NICE and SMC also considered mitozantrone as a comparator, as well as treatment with prednisone alone, via both direct and indirect comparative effectiveness analysis. pCODR compared abiraterone to prednisone alone.

Each agency measured OS and PFS as primary endpoints from the RCTs. The only agency to not explicitly factor-in health-related quality of life (HRQoL) was pCODR. SMC also considered the secondary endpoints of time to prostate antigen (PSA) progression, PSA response rate, time to radiological progression, and objective response rate (ORR).

NICE considered evidence from the sub-group from the COU-AA-301 trial that had received prior chemotherapy treatment, as it was believed that this group would be most similar to the treatment groups in UK practice. In this group, as well as in the wider intention to treat (ITT) population, abiraterone was associated with significantly improved PFS and OS compared to prednisone alone. In a different clinical trial, SMC also found significantly improved overall survival compared to placebo in both the wider population and the previously treated group. NICE and SMC both failed to identify any trials that permitted an indirect clinical comparison between abiraterone and mitoxantrone.

PBAC concluded similar findings. In addition, the sponsor's submitted indirect comparisons—with which PBAC agreed—demonstrated that abiraterone was clinical superior and non-inferior compared to mitoxantrone and cabazitaxel, respectively.

In the COU-AA-302 trial, pCODR found that, relative to placebo plus prednisone, abiraterone offered and improvement in quality of life by increased symptom control. Abiraterone was also associated with improvements in the aforementioned primary outcomes.

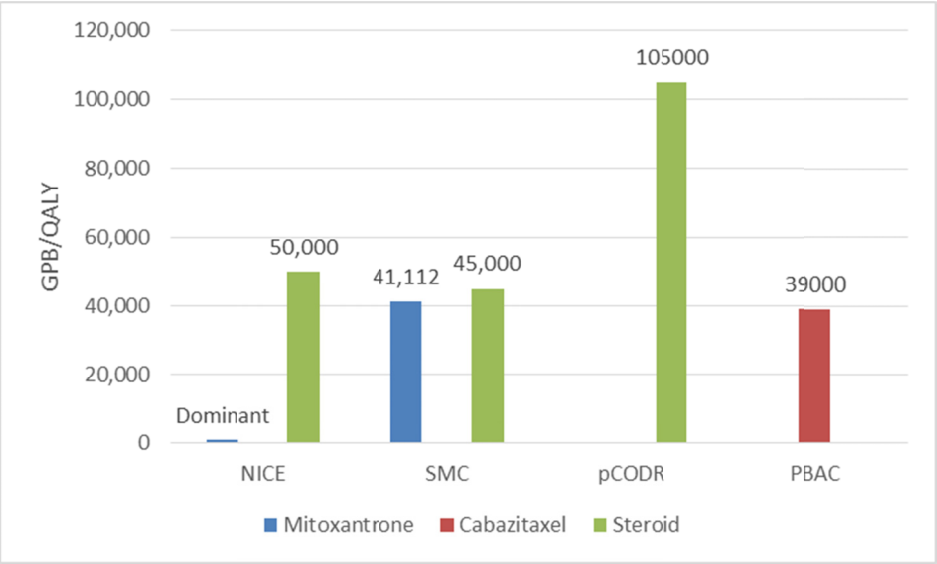
Economic assessment

Each agency considered CUAs, but the specific design of the models differed across agencies. NICE and the ERG, for instance, received and developed a simple decision model, while PBAC evaluated a Markov model. The survival primary endpoints were used to calculated probabilities. Utility values derived either from the manufacturer's algorithm (NICE and SMC) or clinical trials (PBAC and pCODR). The economic assessment panels of all agencies noted varying degrees of sensitivity in the model to changes in utility values, overall survival outcomes and treatment discontinuation.

Graph 4 supports the aforementioned evidence on the disparaties in ICERs across countries, even when common comparators are considered. Based on the ERG's analysis, NICE determined that abiraterone was less than £50,000/QALY against prednisone alone, and that it was dominant to mitoxantrone. SMC, meanwhile, reported that the cost-effectiveness ratio was between £41,000/QALY and £46,000/QALY against the same comparators used in NICE's analysis. The equivalent ICERs in Canada and Australia were, respectively, about £100,000/QALY (compared to prednisone) and £65,000-£130,000/QALY [2] (no specific value given; compared to mitoxantrone and prednisone). PBAC found that abiraterone was cost-effective compared to cabazitaxel on a cost-minimization basis.

[2] Convesion: 0.60GBP = 1.00CAN$/AUD at the time of appraisal

Graph 4: ICERs between abiraterone and several comparators across HTA agencies



Other considerations

For this appraisal, three additional considerations were factored into the final appraisals:

1. All agencies estimated the toxicity profiles of abiraterone. Each noted that abiraterone's side effects, which included hypertension, fluid retention, nausea, and constipation, were generally tolerable. NICE declared that adverse events were "few." PBAC noted no difference in side effects between abiraterone and placebo, and that abiraterone had a superior safety profile compared to cabazitaxel, which was taken into account in making a recommendation based off of the cost-minimization analysis.

2. Three of the agencies considered whether or not abiraterone might address unmet need within the indication. NICE determined that abiraterone qualified as an end-of-life, or "rule of rescue," treatment, which paved the way for the committee to give a positive listing despite the drug's relatively high ICER. Similarly, SMC factored in the lack of treatment options and high unmet need as "decision modifiers" to justify the high ICER. PBAC, however, asserted that abiraterone did not qualify for this status under its criteria because of the availability of cabazitaxel.

3. SMC, PBAC and pCODR assessed the impact of abiraterone on health system's resources. pCODR considered that because abiraterone was not replacing another treatment in this setting, its potential budget impact was higher. As mentioned above, PBAC also took into account the financial implications of abiraterone's use in treatment algorithms outside of its recommended listing.

Pazopanib (*Votrient*) for advanced renal cell carcinoma (64.9), Appraisals 17, 35, 30 & 77

Submission and recommendation timeframe

The listing sought from all four HTA bodies was pazopanib for first-line patients with advanced renal cell carcinoma. Further specificity was added for the SMC submission, which required patients to be treated with a cytokine therapy, as well as the submission to pCODR, which required patients to have good performance status.

Market access was granted in Australia, Canada and the EMA in May/June 2010. SMC and NICE were first to issue appraisals (February 2011; a 7 month delay), while issued its appraisal in the following month after a 21 month delay. pCODR had over a 3 year delay, owing to the fact that the body had yet to be founded at the time of marketing authorization.

Appraisal outcomes

NICE, PBAC, and SMC listed Votrient with conditions, while pCODR recommended pazopanib within the sponsor's requested listing. NICE and SMC's recommendations were conditional on the availability of a PAS. NICE further restricted the recommendation to patients with ECOG status 0 or 1 who had not previously received cytokine-based therapy. PBAC's recommendation was restricted to "[p]atients who have developed intolerance to sunitinib of a severity necessitating permanent treatment withdrawal."

Rationales for the positive recommendations included pazopanib's superior effectiveness, in terms of PFS, compared to placebo, as well as its similar effectiveness compared to existing clinical practice (sunitinib). SMC, pCODR, and PBAC viewed pazopanib's adverse event profile

positively, as it was sufficiently different from suntinib's profile to offer patients an additional treatment option. The non-inferiority and relatively similar adverse event profile entailed that listing pazopanib resulted in net savings for at least PBAC and SMC.

Agencies were cautious in their interpretation of the clinical trial data because the open-label RCTs (see below) allowed for crossing-over of patients upon disease progression, thereby potentially confounding the primary endpoint of overall survival. The rank-persevering structural failure time (RPSFT) method was used to estimate survival. All agencies, with the exception of pCODR, considered the uncertainties inherent in indirect comparisons between pazopanib and sunitinib. As a result, NICE and PBAC viewed the evidence for determining clinical non-inferiority in terms of PFS and OS as especially weak. PBAC was, however, reassured because of the RCT's applicability to the Australian setting. The uncertainties in the clinical evidence translated into meaningful sensitivities in the economic evidence.

Evidence-base & comparative effectiveness

The HTA authorities drew from a diversity of clinical studies for the comparative effectiveness assessment (Table 7). The manufacturer submitted the placebo-controlled VEG105192 to NICE, PBAC and SMC. NICE used seven additional studies in order to conduct an indirect comparison between pazopanib and sunitinib. PBAC's evidence also came from MRC-RE01 and A6181034 in order to conduct an indirect comparison between pazopanib and sunitinib. pCODR assessed clinical evidence from the COMPARZ and PICES studies, which provided direct comparisons of sunitinib and pazopnaib.

For all agencies' assessments, the primary comparator was sunitinib. NICE and SMC also compared pazopanib to interferon-alfa and best supportive care (BSC), which were the other active treatment options in the United Kingdom.

From the trial data, pazopanib was associated with statistically significant improvements in PFS compared to PFS in patients on placebo. Even with the aforementioned uncertainty and the needed usage of the RPSFT method to estimate overall survival, the agencies that considered

indirect comparisons were confident that sunitinib and pazopanib had similar efficacy. PBAC assessed pazopanib to have a more favorable clinical benefit by concluding that the evidence was sufficient to demonstrate clinical non-inferiority. HRQoL data was presented in the clinical trials submitted to all of the agencies.

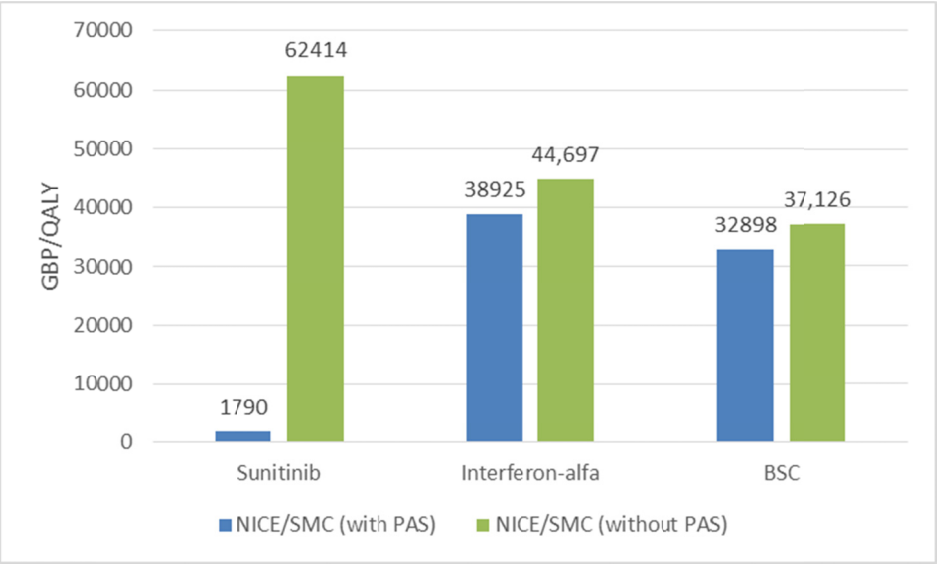
Table 7: Types of evidence, clinical outcomes, and additional considerations when appraising pazopanib

	NICE	SMC	pCODR	PBAC
Pazopanib, C64.9	List with conditions	List with conditions	Recommended	Recommended
Evidence Considerations	8 phase III; 1 extension study	1 phase III trial	2 phase III trials	3 phase III trials
Clinical effectiveness	PFS, OS, HRQoL	PFS, OS, objective response rate, duration of response, and HRQoL	PFS	PFS, OS
Adverse events	x	x	x	x
Innovation	x			x
Unmet need/end-of-life	x	x	x	x
Patient choice	x		x	x
Resource use		x	x	x
PAS	x	x		
Place in the treatment pathway	x		x	

Economic assessment

NICE, pCODR and SMC primarily relied on CUAs. Under PAS's that provided a 12.5% discount on list prices, NICE and SMC both determined that pazopanib cost £1,790 per quality-adjusted life year gained compared to sunitinib. Graph 5 below displays ICERs for both NICE and SMC, both in the presence and absence of a PAS. pCODR did not disclose an ICER, citing confidentiality. PBAC conducted a cost-minimization analysis after determining clinical non-inferiority between pazopanib and sunitinib. It determined that pazopanib was only cost-effective where patients had failed sunitinib-based therapy.

Graph 5: Pazopanib vs sunitinib ICERs with and without a 12.5% cost-reduction under a PAS



Other considerations

For this appraisal, three additional considerations were factored into the final appraisals:

1. All agencies noted that pazopanib had a different adverse event profile compared to sunitinib. PBAC, for example, noted that pazopanib "likely had similar … safety outcomes compared to sunitinib" (3). After pCODR's survey of patient groups, the committee gave pazopanib a positive listing in part because patients valued the option to switch treatments if they had previously experienced poor tolerability with sunitinib.

2. PBAC explicitly considered the level of innovation of pazopanib. It noted that sunitinib was approved with a higher ICER because, at the time, there were not alternative treatments (and thus also high unmet need in the Australian setting). With the decision to list sunitinib, PBAC considered that pazopanib could not be afforded the same cost-effectiveness allowances.

3. A final major consideration of all agencies was the end-of-life implications of pazopanib. SMC explicitly cited EMA's expedited approval of pazopanib in order to fill this gap.

NICE, however, determined that its end-of-life criteria did not apply, owing to the availability of sunitinib.

4.3: Phase II Case Study—Appraisals for Tyrosine Kinase Inhibitors

Afatinib (*Giotrif*), erlotinib (*Tarceva*) & gefitinib (*Iressa*) for non-small cell lung cancer (C34.90), Appraisals 2, 10, 13, 24, 37, 44, 46, 60, 69 & 73

Submission and recommendation timeframe

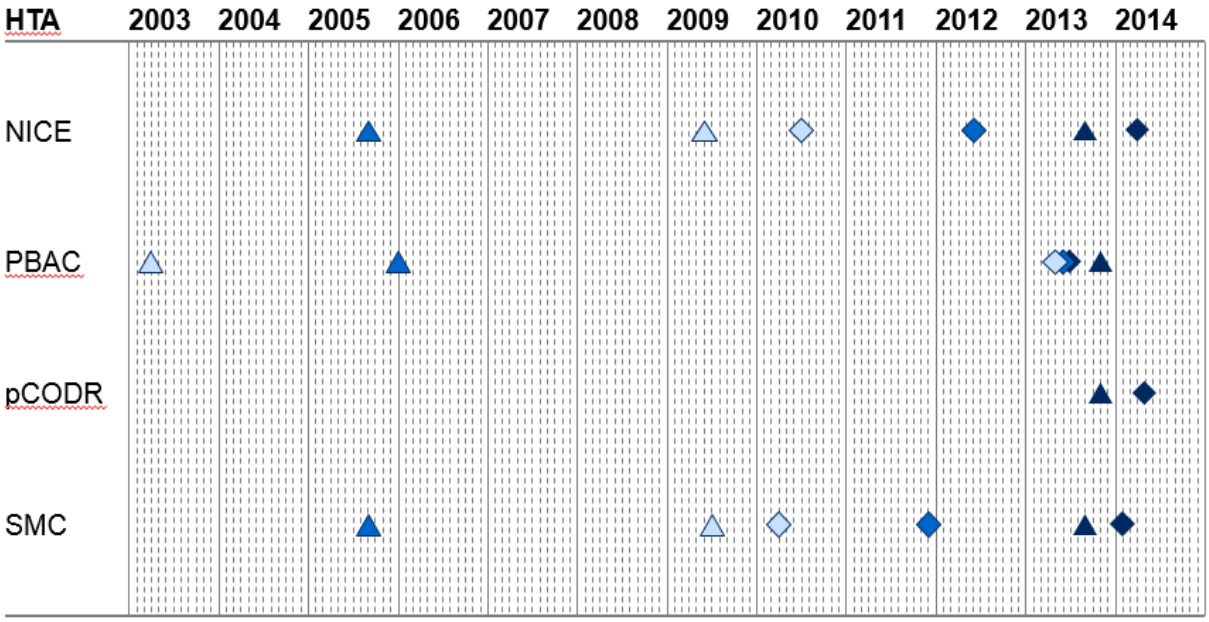
Afatinib, erlotinib, and gefitinib belong to the class of drugs called tyrosine kinase inhibitors (TKIs), which target the etiologic mechanism of NSCLC in patients who are epidermal growth factor receptor tyrosine kinase (EGFR-TK) tumor mutation-positive. They are reviewed as a case study not only because they share intended listing, but also because they are used in several appraisals as comparators to each other, thereby also permitting the comparison of the health technology assessment process within agencies.

The timeline below presents the market access and appraisal dates for all countries, where triangles are MA dates, diamonds are appraisal dates, navy blue is afatinib, royal blue is erlotinib, and sky blue is gefitinib. Generally, lag times had a large range of for example 6.2 to 80.3 months in the UK. NICE, PBAC, and SMC reviewed all three TKIs, while pCODR only reviewed afatinib. All appraisals assessed TKIs on a first-line basis.

Appraisal outcomes

All TKI appraisals resulted in a positive review, with the exception of gefitinib in Scotland. For NICE, the appraisal for each TKI was conditional on the availability of PAS's. Afatinib was further restricted to patients who had not received any TKI-based therapies, thereby preventing the use of afatinib after erlotinib or geftinib. While the late entrants were regarded as being only incremental in innovation, the decision to list three TKIs offered patients choice should they have adverse reactions with one of the drugs.

Figure 1: timeline of market authorization and appraisal date



In Scotland, erlotinib was not compared to any of the other TKIs, and it was deemed more clinically effective than platinum-based chemotherapy regimens, with the additional upside of oral administration. Afatinib was found to be clinically superior compared to erlotinib, but the lack of unmet need encouraged the SMC to recommend afatinib contingent on the availability of a PAS. Finally, the manufacturer neither provided sufficiently robust economic case or a reasonable enough ICER for SMC to result in a positive listing for gefitinib.

PBAC recommended all drugs for funding, thereby making them clinically interchangeable on a first-line basis. Australia approved afatinib, erlotinib and geftinib on a cost-minimization basis against each other. The manufacturers also offered budget- and volume-capping risk-sharing agreements for both afatinib and gefitinib, and PBAC recommended that a volume-based agreement should be sought for erlotinib. PBAC considered that offering access to more than one TKIs would deliver a net benefit to patients and be consistent with clinical practice guidelines.

Finally, pCODR gave afatinib a positive recommendation conditional on pemetrexed-cisplatin's status as the main treatment option.

Evidence-base & comparative effectiveness

While the paucity of clinical trials entailed that the agencies generally overlapped in terms of the evidence considered, the HTA bodies interpreted the evidence (see Table 8) quite differently.

Table 8: for TKIs, the HTA agencies overlap in the evidence considered, but reach different conclusions on comparative effectiveness

	NICE	SMC	pCODR	PBAC
Relative clinical benefit between TKIs	Clinical similarity	Clinical similarity	Clinical similarity (afatinib	Clinical non-inferiority
Phase III Trials--Gefitinib	IPASS	IPASS	N/A	IPASS
	First-SIGNAL		N/A	First-SIGNAL
	NEJGSG002		N/A	NEJGSG002
			N/A	Study 0054
	WJTOG3405		N/A	WJTOG3405
Phase III Trials--Erlotinib	EURTAC	EURTAC	N/A	EURTAC
	OPTIMAL	OPTIMAL	N/A	OPTIMAL
Phase II Trials--Afatinib		LUX Lung 2		
Phase III Trials--Afatinib	LUX Lung 3	LUX Lung 3	LUX Lung 3	LUX Lung 3
	LUX Lung 6	LUX Lung 6	LUX Lung 6	LUX Lung 6

NICE relied on phase III clinical trials that compared afatinib, erlotinib and gefitinib to platinum-based chemotherapy (Lux Lung 3 & 6; EURTAC & OPTIMAL; and IPASS, respectively), with the common endpoints of PFS, OS and, with the exception of IPASS, HRQoL. For the IPASS study, NICE relied on a survey from 105 members of the general public, which was then used to derive utility values. Thus, NICE compared the three TKIs through indirect comparisons.

Given that gefitinib was the first reviewed, it was only compared to platinum-based chemotherapy. Indirect comparisons were conducted for erlotinib (compared to gefitinib), while afatinib was compared to the other TKIs in its appraisal. Both appraisals proceeded similarly. In the latter, NICE concluded that afatinib "is likely to have similar clinical efficacy to erlotinib and gefitinib," and therefore it "is considered to be a reasonable alternative treatment option compared to erlotinib and gefitinib" (24-25). Similar efficacy was a weaker outcome than the manufacturer sought though its indirect, mixed treatment comparison (MTC), which aimed to demonstrate non-inferiority between the TKIs. However, the MTC was rejected on account of poor methodology in estimating the proportional hazards and of non-applicability of the study population to the UK setting. Consulting with clinicians, NICE determined that afatinib was clinically similar to the other TKIs.

PBAC also used the Lung 3 & 6 trials for the afatinib appraisal, the EURTAC trial for the erlotinib appraisal, and the IPASS trial (in addition to three other RCTs) for the gefitinib appraisal. All drugs were compared to the other TKIs, as well as to platinum-based chemotherapy. The TKIs were deemed to have superior clinical outcomes, as well as a different toxicity profile, compared to chemotherapy.

Given that NICE and PBAC considered nearly the same evidence, the latter also undertook indirect comparisons. In its appraisal, afatininb was compared to both erlotinib and gefitinib; erlotinib to gefitinib; and gefitinib to afatinib and erlotinib. Uncertainty in the indirect comparisons was driven by differences in the chemotherapy doublets across trails. Nevertheless, PBAC concluded that chemotherapy doublets themselves were likely to be clinically non-inferior to each other. This translated into a conclusion of non-inferiority between all three of the TKIs.

The SMC utilized the same clinical evidence as NICE for afatinib and erlotinib. All three TKIs were compared to platinum-based chemotherapy doublets, including pemetrexed/cisplatin and gemcitabine/cisplatin. Afatinib and erlotinib, but not gefitinib, were deemed to significantly improve PFS over platinum-based chemotherapy. The appraisal of afatinib was the only one of the three to (indirectly) compare TKIs (with erlotinib). Using a MTC similar to that used in NICE's afatinib appraisal, SMC cited uncertainties in the baseline characteristics of the patients from in the studies, and that some of the population was not EGFR-TK mutation positive. However, unlike NICE, SMC decided that these weaknesses were relatively minor, and that the MTC was valid. Yet, the same conclusion was reached: the MTC demonstrated that afatinib was clinically similar to erlotinib and gefitinib.

pCODR's lone appraisal of TKI was for afatinib, and it drew its evidence from the Lux Lung 3 & 6 studies. The principal comparator was gefitinib because of its use in many of Canada's provinces. The manufacturer submitted an indirect comparison between afatinib and gefitinib, which, similarly to NICE and SMC, was criticized because it "lacked clinical validity as uncertainty was created by the heterogeneity of patients' EGFR mutation status across the trials being compared" (7). The conclusion was that afatinib was clinically similar to gefitinib.
Table 9 summarizes the comparative effectiveness comparisons that each agency considered.

Table 9: Comparators used in appraisals of TKIs

Appraisal/Comparator	Afatinib	Erlotinib	Gefitinib	Platinum-Based Chemo
Afatinib		NICE, SMC, PBAC	NICE, pCODR, PBAC	NICE, SMC pCODR, PBAC
Erlotinib	PBAC		NICE, PBAC	SMC, PBAC
Gefitinib	PBAC	PBAC		SMC, PBAC

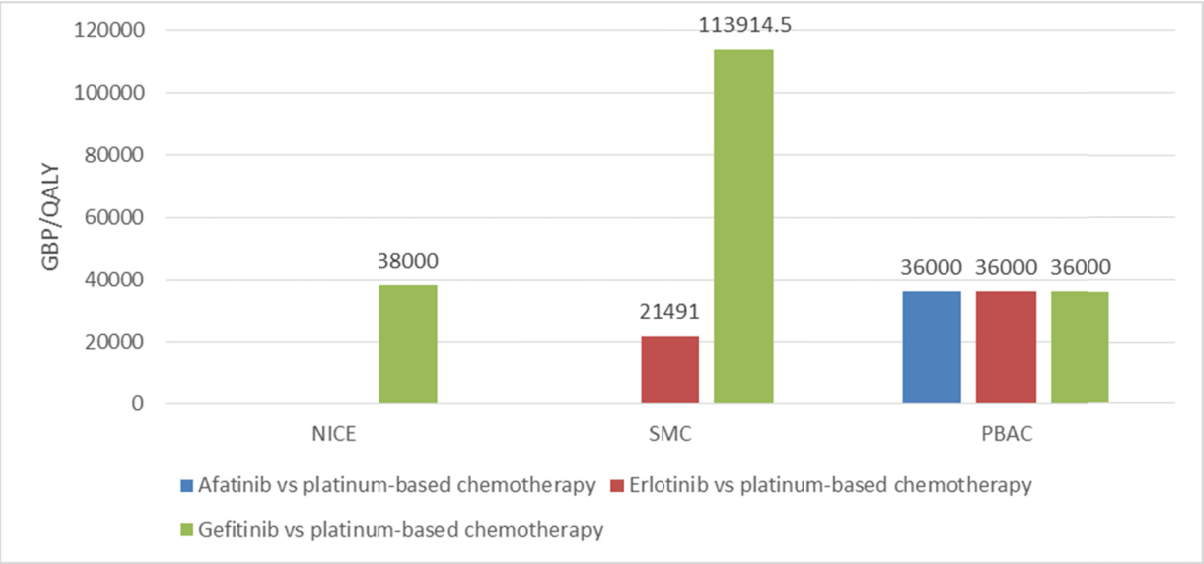
Economic assessment

Cost-utility analyses were conducted for comparisons between TKIs and platinum-based chemotherapy, while all agencies conducted cost-minimization analyses for evaluating the cost-effectiveness between the various TKIs on the basis of clinical similarity or clinical non-inferiority.

Opposite to the previous case studies, the cost-effectiveness data from appraisals demonstrates that NICE and SMC substantially differed in their estimates of base-case ICERs between TKIs and platinum-based chemotherapy (Graph 6). NICE determined that gefitinib's base-case ICER ranged between £27,000/QALY and £49,000/QALY (midpoint presented in the graph below) compared to platinum-based chemotherapy under the PAS. For erlotinib, NICE considered that the uncertainties in the model and the lack of clear overall survival benefit over gefitinib permitted an analysis on a cost-minimization basis. Afaitinib received a positive recommendation despite the economic assessment group's inability to model its cost-effectiveness due to the inappropriate population and methods for determining the progression probabilities in the model. Afatinib was therefore approved on the basis of similar clinical efficacy as an additional treatment option.

SMC likewise considered both cost-utility and cost-minimization models. Gefitinib had a relatively high ICER that ranged from £74,000/QALY to £154,000/QALY depending on the chemotherapy comparator, while, with a PAS, erlotinib was viewed as a cost-effective option at less than £22,000/QALY. Despite concerns over the uncertainty in the mixed-treatment comparison between TKIs, a cost-minimization analysis of afatinib versus erlotinib was deemed reasonable on the basis of similar PFS and OS benefits. This analysis only found that afatinib was only cost-effective over erlotinib under a PAS.

Graph 6: Comparison of ICERs between TKIs and platinum-based chemotherapy



pCODR found that, because of the uncertainty in clinical evidence via indirect comparisons, the CUA models were highly sensitive to the relative clinical benefit between the two drugs, and thus analyses were conducted on a cost-minimization basis. This determined that afatinib could be cost-effective. However, these results were caveated by the fact that the cost of gefitinib varied across jurisdictions.

The cost-utility models evaluated by PBAC demonstrated a range of ICER estimates over platinum-based chemotherapy because of the various assumptions made in the models, as well as the uncertainties of the indirect comparisons between treatments. For all of the cost-utility analyses, the range of probable ICERs centered around $45,000-75,000/QALY, or about £36,000/QALY (the midpoint is presented in the graph below; based on above conversaion rate of 0.60GBP to 1.00 AUD). PBAC adopted a cost-minimization analysis for all three of the appraisals, and required that in order to receive reimbursement, that all three TKIs were cost-minimized against each other. Most explicitly in the gefitinib appraisal, PBAC leveraged this consistent judgment in order to facilitate the PBS to extract a lower price from the manufacturer.

Other considerations

With respect to adverse reactions, NICE concluded that all three TKIs had similar overall

toxicity, but different adverse event profiles. Afatinib, for instance, had higher rates of diarrhea and rash. Variation in adverse event was viewed as advantageous for the DoH. NICE also considered that the gefitinib had the potential to reduce hospital-time in an end-of-life setting. Given that utility values do not capture such concepts of quality of life, the committee asserted that the ICERs underestimated gefitinib's cost-effectiveness.

For all of the TKI appraisals, NICE considered this class of drug's novel mechanism of action. This particularly contributed to gefitinib's positive recommendation. While the EFGR-TK mutation testing needed for gefinitib's indication was on the one hand viewed as an immediate burden because this testing was not common-place at the time of approval, NICE also posited that approving gefitinib would help to encourage the roll-out of this needed testing within the NHS. While afatinib and erlotinib were accordingly labeled as more incremental innovation, the oral administration of all the TKIs was also viewed favorably.

SMC had similar considerations in its assessment of TKIs, although the innovation of gefitinib clearly failed to bring about a positive recommendation. The Scottish authorities did cite the ease of administration as an advantage of TKIs and factored in the need for additional testing. First-line NSCLC was also considered to not have a high unmet need in the case of afatinib.

As mentioned above, pCODR had difficult in making an explicit recommendation for afatinib due to the differing funding decisions of Canada's provinces. Weighing the met need in provinces funding erlotinib and gefitinib with patient values for treatment options, the committee was averse to making a blanket recommendation for afatinib and opted to recommend listing in settings where gefitinib was not a first-line therapy. The heterogeneity of comparators and funding schemes thus posed a unique obstacle for pCODR in its decision-making process.

Finally, PBAC principally considered, beyond the comparative and cost effectiveness of the TKIs, the maximization of patient choice for treatments. While PBAC also considered the usage and the financial impact of each drug, the body did not explicitly cite the contribution of either of these considerations to a positive or negative recommendation.

Discussion

One of the first outcomes of this study was the consideration that some agencies are more likely to approve new medicines that others. Yet, there is substantive agreement on the therapeutic and social value of nearly 2/3 of oncology drug-listing pairings. Similarity exists in that NICE, PBAC, pCODR, and SMC apply a mix of both scientific judgments and social values to determining the effectiveness and efficiency of medicines. What the foregoing has demonstrated is that, in many respects, the HTA bodies of Australia, Canada, England, and Scotland vary in in the methodologies used to assess medicines and, in particular, in the rigor of process, interpretation of evidence, and application of additional considerations.

Submission and recommendation timeframe

The major difference between all of the countries is in the timing of market access. The European countries' access to medicines roughly coincided with Australia's, while Canada was the clear laggard. In terms of the lag time between access and appraisal, pCODR's time-lag leadership is perhaps explained by the fact that the country has the least rigorous HTA approach—one that releases appraisals rapidly and that leads to the fewest definite "recommend" or "reject decisions."

Appraisal outcomes & agencies' overall approach to HTA

For drug-indication pairs, the rate of positive appraisals differs across all HTA bodies. This difference was tempered in substance, however, as 9 of 15 drug-listing pairs received positive indications across all reviewing agencies. That one-third of drug-listing pairs differ is not surprising given the differences in the methodological differences supporting each agency's recommendations.

NICE privileges—in the following order—comparative effectiveness, cost-effectiveness, and patient considerations (including quality of life and end-of-life factors). The last on this list can act as a modifier to considerations of clinical benefit, which allows for the justification of "poor" cost-effectiveness. The consideration of comparative clinical evidence before economic evidence

is also exemplified by the case of NICE recommending afatinib on the basis of its similar clinical benefit to other TKIs.

NICE's evaluation of the evidence demonstrated a great deal of rigor beyond the additional analyses conducted by the ERG. The committee readily rejects indirect comparisons because of uncertainties in the clinical trials or poor applicability to the English setting. NICE's desire for quality evidence is also demonstrated by its more frequent inclusion of evidence from phase II trials and systematic reviews.

SMC, on the other hand, weighs the effectiveness and efficiency cases for a drug about evenly, as partly evidenced by the fact that so many of its recommendations were conditional on patient access schemes. SMC is unique in the respect that it considered multiple (and many) secondary endpoints in its final analysis. In the TKI case study, the importance of cost-effectiveness in SMC's decision-making process was demonstrated by the rejection of gefitinib, which NICE and PBAC considered as innovative. SMC also factored in, to a considerable degree, unmet need.

The clear majority of pCODR's appraisals resulted in a conditional outcome, and the majority of these pegged conditionality to an improvement in cost-effectiveness. However, given the fact that pCODR exists "between" provinces, the ability for the committee to make a definitive statement on a drug's efficiency was circumscribed by the differences in provinces' reimbursement decisions. As such, pCODR's primary contribution is the assessment clinical benefit, which is exemplified by the fact that the rationales behind pCODR's decision often only highlight the drugs' impact on survival. The committee also weighed patient values, such as toxicity-effectiveness trade-offs, and unmet need heavily.

Finally, the case studies above present a "mixed bag" of conclusions for PBAC. The rigorousness of PBAC's comparative assessment process is exemplified by its requirement of clear non-inferiority between comparators in order to conduct cost-minimization analyses. Paradoxically, however, PBAC declared several comparators as non-inferior, even when other agencies refused to do so because of a lack of evidence needed for indirect comparisons. While PBAC also sought to ensure that patients had treatment options—as evidenced in the TKI case

study, the review body restricted access to pazopanib because the manufacturer was unable to demonstrate clear non-inferiority compared to sunitinib.

With respect to considerations of cost in PBAC's decision-making process, the fact that the ICERs were not substantially different across all four categories of its appraisal outcomes suggests that perhaps cost was not an appreciable concern. On the contrary, the conditional recommendation of pazopanib, the frequent use of cost-minimization analyses, and the consideration of novel risk-sharing agreements demonstrate that PBAC has prioritized the efficient allocation of resources in its decision-making process. Finally, it is notable that, in the case studies above, PBAC was the only agency to explicitly consider a drug's superior safety in making its final recommendation.

Evidence-base & comparative effectiveness

Within a drug-listing pair, the chosen pharmaceutical comparators varied across the agencies. The TKI appraisal above is a case in point. It is also notable no other technologies commonly used in cancer treatment, including radiology or surgery, were considered, with the exception of 3 PBAC appraisals (bortezomib, cetuximab, and trastuzumab).

The three primary outcomes used across all oncology appraisals were PFS, OS, and HRQoL. Evidence primary originated from phase III trials, but NICE and PBAC were especially open to evidence beyond the 'pivotal' studies, including other RCTs, phase II trials, or lay people groups.

Two methodological hurdles confronted HTA bodies in the interpretation of evidence from clinical trials. First, studies relying on open-label trials required the use of statistical methods, such as RPSFT, to adjusted for patient cross-over upon disease progression with the comparator (usually a placebo). Second, many of the RCTs were placebo-controlled or were not applicable to clinical therapy choices in the appraising countries. HTA bodies were required to use indirect comparison methods, thereby introducing uncertainty into comparative effectiveness estimates.

Such uncertainty appeared to have an effect on HTA bodies' willingness to recommend medicines. Three of 4 of NICE's recommended drugs were based on RCTs that directly compared the appraised drug to the relevant medicines in English clinical setting. For medicines that were conditionally recommended or not recommended, 7 of 10 relied on indirect comparisons, while 5 of 10 utilized direct comparisons. For the SMC, 4 of 4 recommended medicines involved comparative effectiveness research that compared the appraised medicine to that relevant in the Scottish setting; 8 of 11 conditional or rejected medicines included a direct comparison. In Canada, the only recommended medicine in the drug-listing group involved an RCT featuring a direct comparison that was relevant to Canadian practice. For PBAC, 6 of 9 of the recommending drug-listing pairs relied on a direct comparison from RCTs, while deferred appraisals accounted for the 2 remaining direct comparisons considered by the Australians. An immediate interpretation of this evidences suggests that there is a clear need for clinical trials that compare new drugs to those already in clinical practice. Perhaps a more troubling implication is that recommendations are heavily influenced by the quality of the evidence, rather than by the actual quality of the drug.

Economic assessment

Cost-utility analyses were the most commonly used cost-effectiveness measures across all of the agencies. This study has demonstrated that the findings and role of cost-effectiveness analyses in appraisal decisions for oncology drugs can be variable and opaque. Indeed, ICERs are tools, not rules.

Within drug-listing pairs, ICERs differed across the appraisal bodies. Such differences would be expected given differences in economic modeling methodologies, data sources, comparators and clinical settings. Countries that are similar in the latter, England and Scotland still differed in their cost-effectiveness estimates when similar data sources were utilized and comparators considered. In the case of gefitinib cited above, versus platinum-based chemotherapy NICE reached ICERs below £50,000/QALY, while SMC projected ratios higher than £70,000/QALY. And in the case of ipilimumab, NICE and SMC accepted ICERs of £58,590/QALY and £36,118/ICER in the presence of patient access schemes. This difference still resulted despite

both bodies utilizing data from the same clinical trial (MDX010-20). While ultimately the difference in ICERs for ipilimumab was not reflected in different appraisal decisions, the geftininb case is concerning because NICE and SMC rendered positive and negative decisions, respectively, thereby translating into differential access for patients within the same country.

The literature has identified that several of these agencies have thresholds that a drug must remain below in order to receive approval (£30,000/QALY in the case of NICE) (Kanavos 2013). The evidence did not allow for a robust estimation of thresholds for PBAC and pCODR. NICE and SMC appear to have cut-offs between all three categories of appraisal. Between recommended and LwC, this value is about £30,000/QALY; and between LwC and not recommended submissions, the grey area of rejection is in the £50,000/QALY-£60,000/QALY range. However, the cost-effectiveness estimates for the latter cut-off are worthy of deeper consideration because so many of NICE's and SMC's decisions to conditionally approve medicines were based on the availability of PAS's. All but one of the drug-listing pairings that received a conditional recommendation from NICE was offered under a PAS. For SMC, two-thirds of LwC medicines were offered under a PAS. The frequent use of PAS's to approve drugs is also concerning because of the aforementioned uncertainties in clinical evidence were common to LwC and rejected appraisals. Stated more succinctly, the analytic utility of cost-effectiveness thresholds for NICE and SMC is perhaps minimal given the fact that a positive recommendation appears to be secured through a PAS.

The frequency of conditional recommendation under PAS's for cancer drugs highlights a paradox of HTA. On the one hand, lowering the price on a clinical effective drug clearly improves the value of that medicine; as such, to the extent that HTA agencies can encourage price reductions, they have been fulfilling their mandate for ensuring efficiency in the allocation of resources. On the other hand, the weight that is given to PAS's might suggest that even drugs with uncertain clinical effectiveness may receive a positive listing. Efficiency is not simply about reducing prices; rather, HTA bodies must also consider how they can best encourage affordable innovation. It is therefore troubling that, for instance, some agencies (NICE) recognized the novelty of gefitinib, while others (SMC) did not and instead chose to fund drugs (afatinib and erlotinib) that demonstrated more incremental innovation.

Cost-minimization analyses were the second most common type of reported cost-effectiveness analysis, and they were used to evaluate the relative efficiency of clinically similar or non-inferior drugs. HTA authorities differed in how such analyses contributed to outcome of HTA appraisals. On the one hand, NICE passively utilized cost-minimization analyses to explore the cost differences between erlotinib and gefintib under patient access schemes. On the other, PBAC leveraged cost-minimization in a "winner-take-all" style, which is conceptually similar to tendering processes for generic medicines, in order to achieve lower prices across all TKIs.

Other considerations

From the case studies above, it was clear that three considerations—especially those that permitted the inclusion of social value judgments into the analysis of value—played at least a modest role in HTA authorities' decision-making.

1. **Adverse events**. All HTA bodies primarily gathered adverse event frequency from phase III RCTs (some phase II trials were also included). Agencies not only considered the rate of adverse events, but also drugs' toxicity profiles (the type of adverse events that patients experienced). pCODR was unique in that it sought to understand the clinical benefit versus toxicity trade-offs that patients were willing to make.

   The extent to which toxicity profiles influenced the decisions occurred primarily through considerations of choice. New medicines' adverse events were considered acceptable if they afforded new therapies to patients unable to tolerate existing options.

2. **Innovation**. Level of innovation, defined according to a comparison between existing therapies' and new drugs' mechanism of action, was explicitly considered in the case of TKIs on account of their novel mechanisms of action. With later market entrants (afatinib and erlotinib), the novelty of the TKI was no longer viewed as an advantage for NICE and PBAC. Innovation was also considered in appraisals of drugs that offered a novel mode of administration or that required additional testing.

3. **Unmet need and patient choice**. The former was determined via an assessment of existing treatment paradigms/clinical pathways and burden of illness information. Several of the drugs under review were for indications with high unmet need, while others submissions were for listings with well-established comparators. In indications with unmet need (BSC or placebo as a comparator), 5 out of 6 for NICE received positive appraisals, 8/10 for SMC, 6/7 for pCODR, and 5/9 for PBAC.

   Recalling the above cases of pazopanib and the TKIs, PBAC perhaps appears inconsistent in its stance towards unmet need. In the former, PBAC recommended restricted access to pazopanib on the basis that the need had already been met by sunitinib. However, where PBAC was especially aggressive, as mentioned above, was in ensuring that patients were afforded choice within a particular listing. Where these cases differed, however, was in PBAC's ability to determine clinical non-inferiority between the comparators.

These latter two considerations represent the agencies' broad scope of evidence consideration, which checks scientific judgments with social value considerations. The HTA bodies' consideration of social values reflects an understanding that, especially in cancer care, drugs should not only be effective and efficient, but also equitable in their distribution and access.

A final consideration referenced by all agencies was budgetary impact. Beyond appraisals that featured cost-minimization analyses, however, budgetary impact was never explicitly cited as a rationale for recommending/rejecting a drug.

Implications & Further Questions

The findings of this study mirror those of other studies that have compared the outcomes and methodologies of HTA bodies across both all types of drugs, as well as oncology drugs. Chabot & Rochi (2014), Kanavos et al (2010), Nicod & Kanavos (2012), and van den Aardweg & Kanavos (2013) highlight appraisal outcome disparities across countries. With respect to

methodological approaches to the appraisal of the evidence, Kanavos et al (2010) found "considerable disparities in information required, interpretation of evidence, rigor of the appraisal process and state motivations for listing or not listing drugs" (4). The findings of this paper concur.

An analysis by Cairns (2006) concluded that NICE and SMC actual act as complementary agencies. Similar appraisal outcomes from different considerations of the evidence entailed that a positive recommendation from these two agencies confirmed the clinical and economic arguments for a given medicine. The findings of this paper are generally in agreement. While NICE and SMC certainly did not have perfect overlap in terms of appraisal outcomes, the similarity in outcomes is perhaps surprising given the relative differences in rigor, as well as evidence consideration and interpretation.

The findings of this study also align with those of Pomedli (2010), who compared HTA bodies' approaches to oncology indications. For NICE, SMC, and CDR, ICERs were generally predictive of a positive appraisal. However, other considerations, such as unmet need and patient choice, act as decision-modifiers that may allow a drug to "overcome" a relatively high ICER. Pomedli is uncertain, though, as to why "extenuating circumstances" did not outweigh high ICERs for pemetrexed and cetuximab in PBAC's appraisals (9). While the present study did not consider the former for that specific indication, it did consider the latter, which was rejected on the basis of uncertain clinical benefit. As explained above, evidence quality and certainty are primary considerations of PBAC. It is thus not surprising that cetuximab was rejected.

This analysis has generated several specific questions on the methodology behind health technology assessment. The quality and certainty of the clinical evidence seem to be determining factors in whether or not a drug is recommended across countries. Improving the evidence basis serves not only to improve the science of health technology assessment, but also the equitable access to drugs. Relatedly, the fact that one-third of the drug-listing pairs considered differed in appraisal outcomes entails that patients in societies with similar cancer burden of disease have inequitable access to medicines. There is thus a need for coordination between HTA bodies in order to ensure that all patients can benefit from those medicines that are truly beneficial.

A theme of the foregoing has been on the weight attached to financial considerations when approving clinically effective, but also uncertain, medicines. PBAC highlighted the role of non-financial based RSAs in splitting risk between manufacturer and payor in bringing new drugs to market. Yet, they were hardly considered in other agencies' appraisals. This paper has mentioned the potential impacts on innovation of HTA bodies' track record of appraisals. CADTH, NICE and SMC should consider these tools in the future.

Limitations of this study

This study has several limitations. First, the number of comparators was not large relative to the each agency's volume of appraisals. In order to ensure that comparisons made for the study were valid, appraisals that overlapped in terms of drug and indication, but not listing, played only a minor contribution to the analysis. Breadth was thus scarified for robustness. This, in turn, may have given some of the agencies short-shrift in terms of the conclusions relevant to specific HTA bodies. For instance, while one of the claims of this study was that the SMC is the least likely to recommend a drug, it is also true that the SMC has reviewed more drugs, by INN name, than any of the other agencies. The SMC may have such a low recommendation rate because, as shown in the example of TKIs, it is aggressive in comparing drugs within an indication.

Relatedly, this study only considered the most recent/final appraisals for a drug-indication pairing. It therefore excluded intermediate appraisals. PBAC and SMC both publish rapid appraisals, as opposed to NICE, which has tended to publish a final report upon completion of the entire appraisal process. Limiting the analyses to final recommendations may have prevented a more thorough analysis of the nuances of HTA review in Australia and Scotland. It also inflated the empirically justified lag time between market access and PBAC and SMC issuing an actual appraisal.

Third, the quality and thoroughness of the evidence varied between countries. For example, pCODR and PBAC were reluctant to report exact ICERs, which prevented optimal comparisons.

NICE was explicit in starting the main drivers of its decision, while SMC and pCODR were less complete in providing the relative contribution of individual factors to a final outcome.

Fourth, and less a weakness of the study so much as an important caveat, the four agencies in question have different mandates, thereby complicating the comparison of their outcomes and methodologies. NICE, a centralized body, clearly differs from pCODR's diffuse general advisory role.

Conclusion

Through an overview of cancer medicines and several case studies, this paper has demonstrated similarities and differences in outcomes and methodologies of the health technology assessment of cancer drugs across four countries. While the bodies are broadly similar in terms of the categories of evidence that they consider, agencies vary in the rigor of the appraisal process, as well as in their weighing and interpretation of the evidence. Future studies should compare not only the evolution of these four HTA bodies, but also other appraisal agencies. The rising burden of cancer will necessitate the right application of methods assessing efficacy, effectiveness and efficiency.

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