DOI:
https://doi.org/10.1016/j.jval.2016.10.014

Title

Health technology assessment case studies: factors influencing divergent reimbursement recommendations in Australia, Canada, England and Scotland

Authors

Allen, N[1,2,]
Walker, SR[1,2]
Liberti, L[2]
Salek, MS[3,4]

Affiliations

1- School of Pharmacy and Pharmaceutical Sciences, Cardiff University
2- Centre for Innovation in Regulatory Science, Hatton Garden, London, UK.
3- School of Life & Medical Sciences, Department of Pharmacy, University of Hertfordshire, Hatfield, UK
4- Institute for Medicines Development, Cardiff, UK.

Address for Correspondence:
Professor Sam Salek
School of Life & Medical Sciences
University of Hertfordshire
College Lane
Hatfield, Herts
AL10 9AB
United Kingdom
E-mail: mssalek@gmail.com
Tel: +44 7763574022

Key points

What is already known about the topic

The scope and methodologies utilised to conduct health technology assessments can vary greatly between agencies, as affordability, social and political factors are unique to each coverage population.

What does the paper add to existing knowledge

The paper identifies and compares the national regulatory, HTA and reimbursement pathways for public healthcare in Australia, Canada, England and Scotland, and identifies the factors behind the differing national HTA recommendations of these four HTA agencies.

What insights does the paper provide for informing health care-related decision-making

The identified differences in recommendations could be considered to be due to an individual agency's approach to their perception of risk and of the comparator used in clinical efficacy and cost-effectiveness studies.

Abstract

Objectives: The study objectives were to evaluate the national regulatory, health technology assessment (HTA), and reimbursement pathways for public healthcare in Australia, Canada, England and Scotland, to compare initial Canadian national HTA recommendations with the initial decisions of the other HTA agencies and to identify factors for differing national HTA recommendations between the four HTA agencies.

Methods: Information from the public domain was used to develop a regulatory process map for each jurisdiction and to compare the HTA agencies' reimbursement recommendations. Case studies that received positive recommendations from all four agencies were compared with those that received a negative recommendation from one of the four agencies.

Results: All four countries have a national HTA agency. Their reimbursement recommendations are guided by both clinical efficacy and cost effectiveness, and the necessity for patient input. However, their activities vary due to different mandates, and their unique political, social and population needs. All have an implicit or explicit quality-adjusted life-years threshold. The seven divergent case studies demonstrate examples in which new medicine-indication pairs have been rejected due to uncertainties surrounding a range of factors including cost-effectiveness, comparator choice, clinical benefit, safety, trial design and submission timing.

Conclusion: The four HTA agencies selected for inclusion in this study share common factors, including a focus on clinical efficacy and cost effectiveness in their decision-making processes. The differences in recommendations could be considered to be due to an individual agency's approach to risk perception, and comparator choice used in clinical and cost-effectiveness studies.

Introduction

The growing availability of less expensive generics plus the rising costs for new medicines and limited healthcare budgets increases the need for the rationalised allocation of public resources [1,2]. As a result, most public health providers require manufacturers to demonstrate the benefits of their new drug technology over existing treatments prior to reimbursement approval. The evaluations of treatments to guide health policy and reimbursement decisions are usually performed by health technology assessment (HTA) agencies. Generally, HTA agencies will evaluate the therapeutic value and cost effectiveness of a health technology. However, the scope and methodologies utilised to conduct HTA can vary greatly among agencies, as affordability, social and political factors are unique to each coverage population [3].

This study focuses on the HTA environments in Australia, Canada, England and Scotland, as these four nations have an entwined history and share a common liberal, basic security welfare state ideology [4,5]. The study objectives were therefore to evaluate the national regulatory, HTA and reimbursement pathways for public healthcare in the four regions to compare initial Canadian national HTA recommendations from January 2009 to May 2013 with the initial HTA decisions to identify factors for these differing national HTA recommendations.

Methods

Information for regulatory approval and HTA reimbursement recommendations was collected from the public domain directly from the European Medicines Agency (EMA) [6], CADTH [7], Health Canada [8], the National Institute for Care and Health Excellence (NICE) in England [9], the Pharmaceutical Benefits Advisory Committee (PBAC) of the Pharmaceutical Benefits Scheme (PBS) in Australia [10,11], the Scottish Medicines Consortium (SMC) [12,13,14], and the Therapeutic Goods Administration (Australia) [15] websites. This information facilitated the development of a process map for each jurisdiction using a previously developed mapping methodology [16]. These maps enabled the identification and relationships between the HTA agencies and the body responsible for the final reimbursement decision. Regulatory approval dates were identified from the regulatory authorities' online databases [6, 8, 15].

The CADTH Common Drug Review (CDR) programme was selected as the primary agency for this study to complement a previous study evaluating the impact of CDR recommendations on provincial listing decisions [17]. A CDR listing recommendation issued from January 2009 to May 2013 was a criterion for a drug product's inclusion in this study. New indication submissions were also included if the initial submission met the inclusion criteria. The proprietary name, generic name, indication, and recommendation were recorded from the online CDR database [7]. The corresponding HTA agency recommendations for Australia, England and Scotland were identified by generic name and indication. Medicines marketed under a different brand name for the Australian or European market were

included, provided they were listed for the same indications as the initial CDR recommendation. Where an agency has reviewed indications separately or issued different recommendations per indication within a single review, this was recorded as a medicine-indication pair for all four agencies.

Statistical analysis

HTA recommendations classified in binomial or multinomial categories can be numerically coded to calculate the quantity of concordant recommendations for each medicine between jurisdictional pairs. Not all HTA agencies will have reviewed the same medicines. Thus, reporting the total number of concordant recommendations alone could be misleading and, therefore the percentage agreement was calculated between jurisdiction pairs to report the proportion of concordant recommendations. The 95% confidence interval was also calculated for each recommendation classification using the Wilson score method. This method was chosen because it is suitable for small n values and will not produce confidence intervals with negative or larger than 100% value [18].

Results

HTA Processes in Australia, Canada, England and Scotland

These four healthcare systems include a national HTA body to assess the added therapeutic value and cost-effectiveness of new medicines. However, there are key differences between the mandates and processes of these agencies that should be considered when comparing their HTA recommendations. For example, Canada is the only agency assessed in this study that has two national HTA programs: the pan-Canadian Oncology Drug Review (pCODR) for the assessment of oncology medicines and the CDR for the assessment of new medicines and indications (Figure 1). As this study was only looking at reviews from the CADTH CDR program, no oncology products were included in this research.

In the UK, the SMC reviews all new medicines to provide a reimbursement recommendation to NHS Scotland, but in England, NICE only reviews significant new medicines and indications that have a formal request for review from the Secretary of State for Health (Figure 2). Therefore, the number of medicines with a recommendations issued by NICE will be much lower compared to the other three agencies. However, from April 2016, NICE will review all new oncology medicines under the recent reforms to the Cancer Drugs Fund.

In Australia, the PBAC's primary role is to recommend whether new medicines should be subsidised. The Australian government determines the final listing decision, but can only consider medicines with a positive listing recommendation from the PBAC; This is very different from the UK and Canada. NHS England and commissioning groups must comply with positive recommendations by NICE and provide the medicines as advised by NICE within three months of the recommendation publication. Similarly, if the SMC provides a positive recommendation, Scottish NHS boards must provide the

recommended medicine or an SMC approved equivalent as soon as possible. In Canada, the recommendations issued by the CDR are not mandatory. The CDR was originally established to replace the independent review processes of 18 provincial, federal and territorial drug plans, but the final reimbursement decision remains the responsibility of the 18 individual drug plans. These drug plans are also responsible for negotiating a price directly with the manufacturer. Therefore, the CDR does not negotiate price with the manufacturer, but may issue a recommendation 'do not list at the submitted price' to indicate where a lower price may have resulted in a positive recommendation. In the UK, manufacturers can submit a proposal for a Patient Access Scheme to improve the cost-effectiveness of medicines and lead to a positive recommendation based on the conditions of the PAS.

These agencies also have varying approaches for incorporating patient input from accepting online comments from patients and citizens (PBAC) to sending E-Alerts to patient input groups for comments (CDR), including patients and lay persons at meetings (NICE) and hosting regular Public Involvement Network Advisory Group meetings and establishing a Patient and Clinician Engagement process (SMC).

HTA recommendations for new medicines-indication combinations for Australia, Canada, England and Scotland

Eighty-nine submissions for medicine-indication pairs met the inclusion criteria for an initial submission to CDR between January 2009 and May 2013. The most common therapeutic areas were the central nervous system (n=19), followed by the cardiovascular system (n=12) and endocrine system (n=11).

New indication submissions were also included if the initial submission met the inclusion criteria. Sixteen different HTA recommendation outcomes were recorded from across the four HTA agencies. These have been classified into three multinomial categories for comparison: recommended, recommended with restrictions and not recommended. CDR issues two distinct negative recommendation categories: 'Do not list' and 'Do not list at the submitted price'. The PBAC's 'authority required' recommendation is allocated to the universal recommended with restrictions category. Three different recommendations were identified from PBAC-published summary documents namely, unrestricted, rejected andauthority required restricted benefit.

The three HTA recommendation classification categories (recommended, recommended with restriction and not recommended) were coded for direct comparison between each of the four HTA agencies. The percentage agreement was calculated for each agency pair and all scored between 21% and 49%. The multinomial categories enable the inclusion of the restricted recommendations, but restrictions can vary by each medicine and agency remit, and this variation is difficult to align within a single restriction category. Therefore, a binomial classification wass also included to compare

recommendations as either positive (recommended, recommended with restriction) or negative (not recommended).

The PBAC issued the greatest number of 'recommendations with restrictions' (59%). However, when calculated using the binomial category classification, which combines the 'recommended' and 'recommended with restrictions' groups, PBAC issued the third most positive recommendations (62%) followed by the CDR (47%). NICE issued the greatest proportion of positive recommendations (93%), but also issued the lowest number of total recommendations (n=29), although it should be recognised that NICE does not review all new medicines and indications. SMC issued the second highest proportion of positive recommendations (75%) and also reviewed the second largest number of medicine-indication pairs (n=71). Greater concordance is expected for the binomial classification, as there are fewer categories for comparison. However, the percentage agreement for the binomial categories still suggests a sizeable proportion of issued discordant recommendations.

Of the eighty-nine medicine-indications evaluated in this study, only twenty-five were reviewed by all four HTA agencies (Figure 3). Seven of these medicines were granted a positive recommendation from all agencies and no medicines received a negative recommendation from all agencies. Thirty-four medicine-indications were reviewed by three agencies and twenty-one were reviewed by two HTA agencies. The smallest group includes medicines reviewed by CDR only (n=9) of which only two were granted a positive recommendation.

The group of medicines reviewed by all four HTA agencies was evaluated to select medicine-indication pairs for case studies. Seven medicine-indications pairs received all positive recommendations and 8 received a negative initial recommendation from one agency (Figures 4 and 5). Interestingly, no negative recommendations were issued for the medicine-indication pairs that were submitted to all four agencies in this study. The proportion of negative reimbursement recommendations decreased as the number of agencies that received a submission increased (Figure 6). This could be due to manufacturers being discouraged from seeking reimbursement for medicines that have already received negative reimbursement recommendations. This may suggest that fewer markets will receive a submission for reimbursement as the number of negative HTA recommendations increases. Fewer submissions reduce potential opportunities for positive reimbursement recommendations and subsequently result in reduced access to these medicines. It could be argued that this may prevent the funding of low value drugs, or prevent patients from receiving medications that may not allow them to achieve their desired outcome. If a manufacturer also anticipates that a medicine is unlikely to be reimbursed by HTA agencies with similar criteria, then the decision to not submit saves time, and resources for both the manufacturer and HTA agencies.

Evaluation of factors influencing discordant HTA recommendations for Australia, Canada, England and Scotland

The seven medicines that received a negative recommendation from one HTA agency and their market access timelines are shown in Figures 4 and 5. In the case study for ranibizumab two indications are reviewed, despite only one of these meeting the inclusion criteria, as both indications were reviewed in the same submission on most occasions. Each case study is accompanied by a timeline that outlines the sequence of regulatory approvals, and HTA recommendations.

***Case study 1**: Dabigatran (Pradaxa) for prevention of venous thromboembolism*

Dabigatran was first granted marketing authorisation by the EMA (March 2008) for the prevention of venous thromboembolism and was positively approved by the SMC and NICE within six months. The PBAC was the third HTA agency to issue a positive recommendation in November 2009. The CDR was the only HTA agency to issue a negative recommendation (January 2009) as non-inferiority was not demonstrated to enoxaparin in the only trial which used the Health Canada approved dose. Dabigatran use in this study was also associated with a statistically significant increase in a composite of deep vein thrombosis, non-fatal pulmonary embolism and all-cause death. The CDR noted that there were some potential cost-savings associated with dabigatran use versus enoxaparin, but did not consider these to be sufficient to off-set the increase in venous thromboembolism demonstrated in the trial.

The SMC, NICE and PBAC all included enoxaparin as a comparator and the SMC agreed that dabigatran was non-inferior to enoxaparin and NICE determined dabigatran was likely to have an equivalent clinical and cost effectiveness. The SMC, NICE and PBAC all noted cost-saving benefits of orally administering dabigatran compared to sub-cutaneous comparators as part of their recommendation rationale. For this case study, the CDR was the only agency to issue a negative recommendation despite other HTA agencies also expressing concerns over evidence supporting non-inferiority with comparator. The CDR was also the only HTA agency that did not explicitly refer to the cost-saving benefits of dabigatran's oral route of administration.

***Case study 2**: Fingolimod (Gilenya) for multiple sclerosis*

Fingolimod was the first oral medicine available for the treatment of active, relapsing multiple sclerosis and was granted marketing authorisation by the TGA, EMA and Health Canada within a two-month period in 2011. All four HTA agencies reviewed fingolimod and concluded that it produced a significant reduction in annualised relapsed rates and generally accepted that efficacy was comparable to Interferon beta-1a, which was the main comparator included in all submissions. The submission to the PBAC also nominated interferon beta-1b and natalizumab as secondary comparators, which the PBAC considered to be informative. However, NICE and SMC both noted concerns regarding the manufacturer's choice of interferon beta-1a as the only comparator, as the submissions should include comparators that reflect clinical practice. The marketing authorisation from the EMA specifies fingolimod is to be used by patients with high disease activity despite treatment with at least one disease-modifying therapy. Health Canada also specified that fingolimod is generally recommended for patients who have had an inadequate response or are intolerant to one or

more therapies for multiple sclerosis, but the TGA licensed indication was not restricted to patients who are intolerant or non-responders to current therapies.

The SMC was the only HTA agency to issue a negative listing recommendation, which was due to uncertainties regarding comparator choice for the initial submission in March 2012. The resubmission contained an additional comparator (natalizumab) and fingolimod was subsequently recommended for 'restricted use' by the SMC in September 2012. The need for additional comparators from the SMC could be due to the different label population. Fingolimod was issued a positive listing recommendation by all four HTA agencies within 14 months of first regulatory approval, despite the initial negative recommendation from SMC due to comparator choice. Fingolimod is an example of a high-cost medicine that achieved positive listing recommendations from HTA agencies that consider cost effectiveness and recognise innovative value.

Case study 3: *Golimumab (Simponi) for psoriatic arthritis*

Golimumab for the treatment of psoriatic arthritis, received a reimbursement recommendation from all four agencies within 12 months of the first recommendation issued by the CDR (March 2010). All four HTA agencies noted a lack of trials with direct comparators, but accepted that golimumab was clinically superior to placebo (CDR, NICE and SMC) and/or suggested similar efficacy to other tumour necrosis factor-alpha inhibitors (PBAC, NICE). The CDR, NICE, PBAC and SMC accepted adalimumab and/or etanercept as comparators, in addition, the CDR, NICE and SMC also included infliximab. Three agencies, CDR, NICE and PBAC, all recommended golimumab for reimbursement and the SMC issued a negative recommendation due to an insufficiently robust economic analysis. The CDR and PBAC both recommended golimumab on the basis of a cost-minimisation approach and the SMC eventually granted a positive listing recommendation for golimumab following a resubmission including a cost-minimisation analysis. Golimumab has also been reviewed for rheumatoid arthritis (Figure 4) and for ankylosing spondylitis. Both submissions for new indications received positive initial recommendations from the SMC. However, these were submitted after the initial golimumab submission for psoriatic arthritis and it could be concluded that the manufacturer's experience detailed in this case study provided useful insights for future submissions.

Case study 4: *Prasugrel (Effient) for acute coronary syndrome*

The first HTA recommendation for prasugrel for was a restricted recommendation from the PBAC, followed by a restricted recommendation from SMC, and a 'recommended' recommendation from NICE. The CDR issued the last HTA recommendation for prasugrel in February 2011, which was a negative 'do not list' recommendation due to uncertainty over the applicability of the trial design to Canadian clinical practice for timing of administration of the comparator (clopidogrel). Concerns were also raised over safety due to trial results indicating a statistically significant increase in major bleeding events for prasugrel over clopidogrel. In June 2012, the CDR issued another 'do not list' recommendation in response to the manufacturer's resubmission, which included a lower price. However, the comparator (clopidogrel) had since become available as a generic. The resubmission

was based on a lower price but no new randomised controlled trials met CDR requirements for the CDR systematic review and the manufacturer's economic evaluation was limited due to CDR concerns over generalisability to the Canadian population. However, the resubmission recommendation also stated that a positive listing could be achieved at a lower price for prasugrel. This case study provides an example of discordant HTA recommendations as a result of differing HTA agency mandates in regards to the ability to negotiate price.

Case studies 5a and 5b: *Ranibizumab (Lucentis) for macular oedema*

Case study 5 has been split into two parts as NICE and SMC issued different HTA recommendations for the two sub populations included in the licensed indication: macular oedema secondary to branch retinal vein occlusion (BRVO) or secondary to central retinal vein occlusion (CRVO). The four HTA agencies all accepted laser photocoagulation as the comparator for macular oedema secondary to BRVO. However, macular oedema, secondary to CRVO does not respond to laser photocoagulation and three HTA agencies (CDR, PBAC and SMC) accepted 'observation' as the main comparator and NICE accepted 'best supportive care'. Ranibizumab received positive recommendations from the CDR, SMC and NICE for both BRVO and CRVO indications. However, the SMC recommendation for ranibizumab for the treatment of CRVO was initially negative, but a resubmission with a patient access scheme has since resulted in a positive recommendation. All three of these HTA agencies issued more restrictive recommendations for ranibizumab to treat BRVO, as this indication has other potential treatment options and patients can spontaneously improve, unlike CRVO.

The submission to PBAC was deferred due to ongoing concerns for comparator choice. PBAC and NICE both considered bevacizumab to be an appropriate comparator choice, despite no marketing authorisation to treat CRVO and no intravitreal formulation available. However, the PBAC does not consider reference to TGA-approved indications to be grounds for excluding a comparator where there are existing pharmaceutical analogues listed and NICE also allows unlicensed medicines to be considered if they are part of established clinical practice. This case study highlights how varying agency approaches for the inclusion of an off-label comparator can result in different reimbursement recommendations.

Case Study 6: *Telaprevir for Hepatitis C infection (genotype 1), chronic (treatment experienced)*

Telaprevir (Incivek) is licensed for the treatment of Hepatitis C infection (genotype 1) with compensated liver disease. This case study focuses on the treatment experienced population as this was the indication originally included in the submission to the PBAC in November 2011. However, the PBAC rejected the original submission as information from the TGA was not available at the time of the review as the TGA did not approve market authorisation until March 2012. The manufacturer's resubmission to the PBAC in March 2012 also included a request to review telaprevir for the treatment of naïve patients and the PBAC approved both indications for 'authority required' listing to be only available in specialised treatment centres.

The SMC was the second HTA agency to review telaprevir for patients with chronic hepatitis C and published two separate recommendations for treatment naïve and treatment experienced patients in December 2011. Both indications were determined to have a statistically significant clinical benefit and cost effectiveness compared to peginterferon alpha and ribavirin. However, the incremental cost effectiveness ratio (ICER) for telaprevir/peginterferon alpha and ribavirin for treatment experienced patients that were null responders was calculated to be as high as £73,600 per QALY, but this was sensitive to many variables (e.g. age) and cost effectiveness was accepted. Overall, telaprevir for hepatitis C infection in treatment experience patients achieved positive recommendations from the four HTA agencies. The initial negative recommendation from the PBAC was due to the timing of the submission as the TGA final product information was not available at the time of the meeting. Australia has offered a parallel review process since 2011 that allows manufacturers to submit to the PBAC and TGA at the same time. However, manufacturers are advised to wait until the fifth month of the TGA registration process as the PBAC review process is shorter and a medicine cannot be listed in the Pharmaceutical Benefits Scheme prior to listing in the Australian Register of Therapeutic Goods. The process in Australia is different to the other agencies included in this study as the CDR will only accept submissions up to 90 days prior to an expected Notice of Compliance and the SMC will accepts submissions following a positive opinion from the EMA Committee for Medicinal Products for Human Use (CHMP) or approval from the Medicine and Healthcare products Regulatory Agency (MHRA), but will not usually start a review until marketing authorisation is granted.

Case Study 7: *Ticagrelor (Brilinta/Brillique) for acute coronary syndrome*

Ticagrelor, sold as Brillique in Europe and Brillinta in Canada and Australia, received the first positive HTA recommendation from the SMC in May 2011. In July 2011, the PBAC issued an 'authority-required' recommendation and a 'recommended' recommendation from NICE in October 2011. All three HTA reviews accepted ticagrelor as clinically superior to clopidogrel, but uncertainties were raised over comparative safety (PBAC). NICE decided the potential benefits of ticagrelor outweighed the risks, and SMC found the increase in adverse events was not significant. The PBAC, NICE and SMC reviews all accepted the increased cost per ICER to clopidogrel to be below the implicit or explicit thresholds. The CDR issued a 'do not list' recommendation as a regional analysis did not provide evidence that ticagrelor would provide significant benefits over clopidogrel for the North American population and the CDR could therefore not justify the increased cost of ticagrelor. However, as with prasugrel, the CDR recommendation summary also stated that a positive recommendation would be more likely if the price was reduced. Once again, this is a divergent recommendation issued by CDR, as price negotiation is not part of the CDRs remit.

Discussion

This study describes a comparison of HTA in Canada, Australia, England and Scotland. These four jurisdictions were selected due to transparency and availability of data, including online summaries with rationale for reimbursement recommendations. The comparisons of the full HTA

recommendations dataset provides a useful overview of recommendations for non-cancer medicines issued over a period of more than three years.

Australia, Canada, England and Scotland all provide universal healthcare which is funded by taxation and shares a long history of Heath Technology Assessment. Currently, all four countries have a national HTA agency and reimbursement recommendations that are guided by both clinical efficacy and cost effectiveness and have a framework that includes patient input. These agencies share common factors, such as considering clinical efficacy and cost-effectiveness of new medicines and have an implicit or explicit QALY threshold. However, their activities vary due to different mandates as well as unique political, social and population needs. The divergent case studies presented in this research demonstrate examples of the rejection of new medicines due to uncertainties surrounding a range of factors including cost effectiveness, comparator choice, clinical benefit, safety, trial design and submission timing. In two of the case studies with divergent recommendations (Case studies 1, 5a and 5b), the rationale for the negative recommendation was also considered by the other three agencies yet they issued a positive recommendation. Therefore, the differences in recommendations could be considered due to agencies approaches to risk perception. When one or more of these agencies issues a negative recommendation it is possible that the manufacturer may decide against further submissions to those agencies that consider similar factors. Case study 6 provides an example of a negative recommendation due to poor submission timing as the PBAC required a resubmission to allow consideration of final product information from the TGA. This example was a result of the PBAC's parallel submission process that enables manufacturers to submit to the PBAC at the same time as the TGA. However, parallel review processes can provide benefits by speeding up the review process and patient access to medicines. In Canada, the introduction of a parallel review process cleared the backlog of CDR applications and removed the requirement for a separate priority review process [19].

The HTA recommendations for the 89 medicine-indication pairs have identified substantial variation between the first recommendations issued by CDR, PBAC, NICE and SMC as, unlike studies by Clement and colleages [20] and Nicod and Kanavos [21], this investigation excluded resubmissions providing insights into how successful the initial submissions are for these four established and transparent HTA agencies. However, for the case study examples Information on resubmissions recommendations has been included, as this can help identify the impact of the updates for the resubmissions. These case studies included trials that did not appropriately follow clinical practice for the country of submission (case study 4) or which had uncertainties surrounding comparator choice (Case studies 2, 5a and 5b). These findings support those by Spinner et al. [22] and demonstrate that factors such as comparator choice and varying clinical evidence influence an agency's decision, although this research did not focus on clinical evidence, but has identified other factors for divergent decisions. This includes an agency's ability to negotiate price or product listing agreements (Case studies 4 and 7) which adds further evidence to the existing body of knowledge for understanding the

impact of changes to healthcare systems which is also supported by the findings of Clement et al.[20] and Nicod and Kanavos [21].

This study utilised information collected from the public domain to compare HTA recommendations and identify the rationale behind the decisions in the 7 case studies. This is a limitation that could be overcome for future studies by working directly with HTA agencies which might provide further insights. This study also builds upon previous research that focused on the CDR, which resulted in the inclusion criteria being limited to only CDR reviewed products [17]. This resulted in the exclusion of oncology products as these are reviewed by the pan-Canadian Oncology Drug Review (pCODR), which was transferred to CADTH in April 2014 to explore potential for alignment with the CADTH's CDR programme [23]. Future research would benefit from the inclusion of oncology products to evaluate the rationale behind discordant recommendations as the systems to assess oncology products continue to evolve. This will be particularly useful for research focusing on the UK as the NICE Board has approved a new Technology Appraisal process for the new Cancer Drugs Fund (CDF) which operates from April 2016. NICE will now appraise all new cancer medicines and will hold the initial appraisal committee meeting before the CHMP opinion is published to enable publication of NICE guidance within 90 days of marketing authorisation [24]. Future studies could also investigate the hypothetical possibility that greater agreement may exist between HTA agencies if the medicine evaluated is from a class which already has prior approval and where guidelines indicate that a full cost-effectiveness analysis is unlikely to be required. For example, the PBAC utilises overt cost minimisation in such circumstances.

The discordant recommendations are a result of varying factors including variations in the HTA agencies practices. Unlike regulatory authorities, the HTA environment is still very fragmented and it is arguably more difficult to align. For example, Drummond [25] argues that to create a pan-European HTA agency there are three critical areas that require harmonisation: economic evaluation guidelines; decision-making processes and societal willingness-to-pay. However, there are initiatives underway to help gain greater alignment amongst certain aspects of the HTA process between HTA agencies and also with regulators. The European Union supports cooperation on HTA through support of the EUnetHTA Joint Action projects, which developed tools and supported cross border collaboration, and by establishing a permanent HTA network in Europe. European HTA agencies have also been working with the EMA to pilot joint parallel scientific advice as evidence needs of multiple stakeholders can often be addressed in a single trial design or development programme. The recently published EMA report on this pilot program indicates positive results and provides recommendations for a final sustainable model of parallel regulatory HTA advice [26]. On a global level, the sixty-seventh World Health Assembly resolution urges member states to strengthen the link between HTA, regulation and management [27].

Overall, this study illustrates how multiple factors can impact HTA decision-making and result in discordant recommendations. This emphasises the challenging environment that manufacturers need to navigate and the results of this study have also shown that as the proportion of negative recommendations increases for a new medicine so the number of markets that receive a dossier decreases. As HTA agencies continue to evolve their processes, the proportion and rationale for discordant recommendations may also change.

References

[1] Pammolli F, Magazzini L. Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 2011;10:428-38.

[2] Stuckler D, Basu S, McKee M. Budget crises, health, and social welfare programmes. BMJ 2010;340:C3311.

[3] Allen N, Pichler F, Wang T, et al. Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. Health Policy 2013;113:305-312.

[4] Eikemo TA, Bambra C. The welfare state: a glossary for public health. J Epidemiol Community Health 2008;62:3-6.

[5] Arts W, Gelissen J. Three worlds of welfare capitalism or more? A state-of-the-art report. J Eur Soc Policy 2002;12:137-158.

[6] European Medicines Agency (EMA). European public assessment reports. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 [Accessed 2 March 2015].

[7] CADTH. Reports. Available from: https://www.cadth.ca/cdr/reports [Accessed 10 April 2015].

[8] Health Canada. Notice of Compliance (NOC) Database. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/index-eng.php [Accessed 2 March 2 2015].

[9] National Institute for Health and Care Excellence (NICE). Guidance List. Available from: https://www.nice.org.uk/guidance/published?type=ta [Accessed 3 February 2015].

[10] Pharmaceutical Benefits Scheme (PBS). Fact Sheet: Streamlined Authorities. Available from: http://www.pbs.gov.au/info/publication/factsheets/shared/fact-sheet-streamlined-authorities [Accessed 5 December 2014].

[11] Pharmaceutical Benefits Scheme (PBS). Public Summary Documents by Product. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product [Accessed 3 March 2015].

12 Scottish medicines Consortium. PAPIG. Available from: http://www.scottishmedicines.org.uk/Public_Involvement/PAPIG/PAPIG [Accessed 3 July 2013].

[13] Scottish Medicines Consortium. What we do. Available from: http://www.scottishmedicines.org.uk/About_SMC/What_we_do/index [Accessed 3 July 2013].

[14] Scottish Medicines Consortium (SMC). SMC Advice Directory. Available from: https://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory [Accessed 3 February 2015].

[15] Therapeutic Goods Administration (TGA). Australian Register of Therapeutic Goods. Available from: https://www.tga.gov.au/australian-register-therapeutic-goods [Accessed 2 March 2015].

[16] Allen N, Pichler F, Salek M, McAuslane N. Assessing performance & decision making by comparing key milestones from approval to reimbursement in eleven countries. MPharm, Cardiff University, 2010.

[17] Allen N, Liberti L, Salek MS. Benchmarking Canadian HTA Agency and Provincial Payer Decision-Making [Online] Available from: https://www.cadth.ca/cadth-symposium-archives/2014/poster-abstracts [Accessed 12 December 2015]

[18] Brown LD, Cai TT, DasGupta A, et al. Interval estimation for a binomial proportion - Comment - Rejoinder. Statistical Science 2001;16:101-133.

[19] Wooding S, Cochrane G, Taylor J, Kamenetzky A, Sousa S, Parks S. Insights on earlier adoption of medical innovations: An international review of emerging and effective practice in improving access to medicines and medical technologies [Online] Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/444921/RAND_final.pdf [Accessed 27 May 2016]

[20] Clement FM, Harris A, Li JJ, et al. Using Effectiveness and Cost-effectiveness to Make Drug Coverage Decisions A Comparison of Britain, Australia, and Canada. JAMA 2009;302:1437-1443.

[21] Nicod E, Kanavos P. Commonalities and differences in HTA outcomes: A comparative analysis of five countries and implications for coverage decisions. Health Policy 2012;108:167-177.

[22] Spinner DS, Birt J, Walter JW, et al. Do different clinical evidence bases lead to discordant health-technology assessment decisions? An in-depth case series across three jurisdictions. Clinicoecon Outcomes Res 2012;5:69-85.

[23] CADTH. Invitation to the Stakeholder Information Session on the Transfer of pCODR to CADTH. Available from: https://www.cadth.ca/sites/default/files/pcodr/Communications/pcodr-communication-29.pdf [Accessed 12 December 2015]

[24] NICE. PMG19 Addendum A - Final amendments to the NICE technology appraisal processes and methods guides to support the proposed new Cancer Drugs Fund arrangements [Online]. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/process-and-methods-guide-addendum.pdf [Accessed 22 May 2016]

[25] Drummond MF. Will there ever be a European drug pricing and reimbursement agency? The European Journal of Health Economics. 2003;4: 67-69.

[26] European Medicines Agency. Report of the pilot on parallel regulatory-health technology assessment scientific advice [Online] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/03/WC500203945.pdf [[Accessed 27 May 2016]

[27] World Health Organisation. WHA67.23 - Health Intervention and Technology Assessment in Support of Universal Health Coverage.WHA Resolution; Sixty-seventh World Health Assembly [Online]. Available from: http://apps.who.int/medicinedocs/documents/s21463en/s21463en.pdf [Accessed 27 May 2016]

Figure Legends

Figure1: Process maps for Australia and Canada (Common Drug Review)

Figure 2: Process maps for England and Scotland

Figure 3: Positive HTA recommendations for medicine-indication pairs

**0 positive recommendations represents the proportion of medicines that received all negative recommendations*

Figure 4: Market access timelines for case studies 1 to 4

Figure 5: Market access timelines for case studies 5a to 7

BRVO: Branch Retinal Vein Occlusion, CRVO: Central Retinal Vein Occlusion

Figure 6: Proportion of medicines that received negative recommendations