London School of Economics and Political Science

The role of "Managed Entry Agreements" in managing the market entry of new, high-cost, cancer medicines.

The determinants and the impact of agreements implemented in Australia, England, Scotland and Sweden, as part of Health Technology Assessment processes.

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Declaration of Authorship

I certify that the thesis I have presented for examination for the Health Policy PhD degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it – see 'Statement of conjoint work').

I warrant that this authorisation does not, to the best of my belief, infringe the rights of any third party.

I declare that my thesis consists of 54,592 words, including footnotes, excluding references and appendices.

Statement of Conjoint Work

Part of the work presented in Chapters 4-6 of this thesis has been published or is currently under review in peer review academic journals, co-authored with Prof Panos Kanavos from London School of Economics (London, UK). For the published aspects of this work, I conceived the studies, designed the studies, collected the data, analysed the data, interpreted the findings and drafted the papers. I confirm that I am fully responsible for the entirety of the work presented in this doctoral thesis other than where I have cited the relevant work of others.

Chapter 4 has been published with Prof Panos Kanavos as co-author: Efthymiadou O., Kanavos P. (2021). Determinants of Managed Entry Agreements in the context of Health Technology Assessment: a comparative analysis of oncology therapies in four countries. *Int J Technol Assess Health Care.* 2021 Jan 29;37:e31. https://pubmed.ncbi.nlm.nih.gov/33509311/. I devised the study, wrote the manuscript, and am the guarantor. Panos Kanavos supervised the study, provided methodological guidance, and contributed to the published manuscript version.

Chapter 5 has been published and it is single-authored by myself as: Efthymiadou, O. Health technology assessment criteria as drivers of coverage with managed entry agreements: a case study of cancer medicines in four countries. *Eur J Health Econ* (2022). https://pubmed.ncbi.nlm.nih.gov/36219363/ I devised the study, wrote the manuscript, and am the guarantor.

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Other Relevant Work

During my PhD, I co-authored a number of publications, which, although highly relevant to the work presented here, did not directly contribute to the empirical chapters of my thesis. These are listed below:

Kamphuis B., Fontrier A.M., Efthymiadou O., Gill J., Salyga H. and Kanavos P. (2021) 'Access to medicines in Europe: Delays and challenges for access'. London School of Economics. https://www.lse.ac.uk/business/consulting/assets/documents/Access-to-medicines-in-Europe-Final-Report.pdf

Kanavos P., Fontrier A-M., Gill J., Efthymiadou O. (2020) Does external reference pricing deliver what it promises? Evidence on its impact at national level. Eur J Health Econ 21, 129-151. https://link.springer.com/article/10.1007/s10198-019-01116-4

Kanavos P., Tzouma V., Efthymiadou O., Mills M., Flannelly C. (2018). Accelerated Approval and Access Schemes: A mapping of policies across the globe and the impact of accelerated approval on the HTA of new oncology medicines. The London School of Economics and Political Science, London, UK. https://www.lse.ac.uk/business-and-consultancy/consulting/consulting-reports/accelerated-approval-and-access-schemes

Kanavos P., Fontrier A.M., Gill J., Efthymiadou O., Boekstein N. (2017). The Impact of External Reference Pricing within and across Countries. London School of Economics, London, UK. http://eprints.lse.ac.uk/84222/1/ERP%20Impact%20vF.pdf

Additionally, over the course of my PhD I had the opportunity to attend a number of international meetings and conferences to present the following work which was either directly related to work produced for my PhD thesis chapters or relevant to my broader PhD research topic.

- Efthymiadou O, Kanavos P. Determinants of managed entry agreements in the context of HTA; empirical evidence from oncology medicines in four countries. Poster presentation: ISPOR Europe 2019, Copenhagen, Denmark.

- Efthymiadou O., Mills M., Tzouma V., Kanavos P. Determinants of "Accelerated access" approval for new medicines; a global survey. Podium presentation: HTAi 2018 Annual Meeting, Vancouver, Canada.

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ABSTRACT

Background: Managed Entry Agreements (MEAs) are increasingly used in the reimbursement negotiations of new, high-cost medicines, especially in oncology, to address evidentiary uncertainties in Health Technology Assessment (HTA) decision-making, due to immature evidence on their clinical and cost-effectiveness. Despite the growing interest in MEAs, the decision-making factors that determine their uptake remain unclear, while empirical evidence about their role in enhancing access to medicines also remains scarce.

Objectives: The objectives of this thesis were three-fold: (i) to understand the extent to which the uptake of MEAs for cancer medicines differs across countries and why; (ii) to study the HTA variables that drive the uptake and different types of MEAs implemented across settings; and (iii) to evaluate the impact of implemented MEAs on improved availability of and timely access to cancer medicines.

Methods: Data from publicly available HTA reports of oncology medicines approved between 2009 and 2018 in Australia, England, Scotland, and Sweden were collected as follows: 1) Social value judgements (SVJs), 2) Clinical/Economic evidence submitted, 3) Interpretation of this evidence (i.e., uncertainties), and 4) Funding decision. The data were used to address the above objectives by deploying a variety of techniques including: (i) Cohen's k-scores to measure inter-rater agreement of countries on the uptake of MEAs as part of their funding decisions, (ii) a binary and multinomial logit model to analyse the role and weight of different HTA decision-making variables in determining the uptake and the type of MEA implemented respectively, and (iii) a binary logit model to capture the probability of a previously negative funding decision being reversed to positive following resubmission with a MEA and a gamma generalised linear model to capture the association between time to final funding decision and the presence of a MEA.

Results: Poor to moderate agreement existed between countries ($-0.29 < \kappa < 0.33$) on their MEA utilisation for cancer medicines. MEA uptake was influenced by (i) uncertainties around cost-effectiveness, (ii) uncertainties around the utilities included in the economic model and (iii) the SVJ of innovation. Outcomes-based MEAs were driven by uncertainties around generalisability to clinical practice, and clinical benefit/ evidence, whereas financial MEAs by the SVJs of innovation and societal impact of the technology appraised. Previously rejected

medicines were significantly more likely to receive a favourable funding decision following a resubmission with a MEA, although approval with an outcomes-based MEA significantly increased the timing to final funding decision.

Conclusions and policy implications: As MEAs are increasingly implemented across countries worldwide, the findings and policy implications arising from this thesis are critical in judging the true impact and sustainability of these agreements. First, identifying the aspects that shape the concept of "value" in decision-making under uncertainty can be used to optimise the respective MEA mechanisms used to address uncertainty, through informing transparent, "best-practice" guidelines for the design of more streamlined submission, negotiation and implementation processes for MEAs. Second, evaluation of whether previously implemented MEAs have met their objectives, is necessary in understanding how future agreements can be applied optimally to deliver the expected impact. If implemented appropriately, MEAs can play a key role in increased and faster access to new medicines. Future research can study the added value for patients and healthcare systems of the interventions approved with MEAs compared to other available interventions.

List of abbreviations

ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
AUS	Australia
C	Combination (agreement)
CAA	Commercial Access Agreement
CDF	Cancer Drugs Fund
CED	Coverage with Evidence Development
CEE	Central and Eastern Europe
CI	Confidence Interval
DALY(s)	Disability Adjusted Life-Year(s)
DH	Department of Health
DMT	Disease Modifying Therapy
DNL	Do Not List
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENGL	England
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
F	Financial (agreement)
FBA	Financial Based Agreement
GBD	Global Burden of Disease
GDP	Gross Domestic Product
HCV	Hepatitis C virus
HSDP	Highly Specialised Drugs Program
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
ICER	Incremental Cost Effectiveness Ratio
INN	International Non-proprietary Name
IRR	Independent Review Panel
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCE	The Belgian Health Care Knowledge Centre
L	List
LSDP	Life Saving Drugs Program
LWC	List with conditions
LWCMEA	List with conditions, including a MEA
MA	Marketing Authorisation
MAA	Managed Access Agreement
MCBS	Magnitude of Clinical Benefit Scale
MEA(s)	Managed Entry Agreement(s)
MES	Managed Entry Scheme (Australia)
MS	Multiple Sclerosis
MTA	Multiple Technology Appraisal
MYMI	Multi-Year Multi-Indication
NCD	Non-Communicable Disease
NHS	National Health System
NICE	National Institute for Health and Care Excellence
O	Outcomes-based (agreement)
OECD	Organization for Economic Co-operation and Development

OR	Odds Ratio
PASLU	Patient Access Scheme Liaison Unit
PBA	Performance Based Agreement
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PICOs	Population Intervention Comparator Outcomes
PVA(s)	Price Volume Agreement(s)
QALY	Quality Adjusted Life Year
QoL	Quality of Life
R&D	Research & Development
RCT	Randomised Controlled Trial
RRMS	Relapsing Remitting Multiple Sclerosis
RSA(s)	Risk Sharing Agreement(s)
RSS	Risk Sharing Scheme
SCOT	Scotland
SE	Sweden
SMC	Scottish Medicines Consortium
SPAs	Special Pricing Arrangements (Australia)
SPSS	Statistical Package for the Social Science
STA	Single Technology Appraisal
TGA	Therapeutic Goods Administration
TLV	Dental and Pharmaceutical Benefits Board in Sweden
UK	United Kingdom
US	United States of America
VBP	Value Based Pricing
W.A.I.T.	Waiting to Access Innovative Therapies
WHO	World Health Organisation
WTP	Willingness To Pay

1. Introduction and background

1.1 Pharmaceutical expenditure and the rising need for Health Technology Assessment

Healthcare spending has grown considerably across the globe in the last decade, with pharmaceutical expenditure accounting for nearly one fifth of all healthcare costs across the Organization for Economic Co-operation and Development (OECD) countries (WHO, 2015). Despite the growth of patented and new products, the proportion of total spending on pharmaceuticals across key markets globally has remained a relatively steady share of the total healthcare expenditure since 1995; primarily as a result of the genericization cycle, and the significant increase in the use of discounts and rebates in specialty products (IQVIA, 2021a). Nevertheless, the continuous introduction of innovative, high-cost medicines still poses threats and growing challenges for governments and health insurers in developing strategic funding mechanisms that can maintain or decrease pharmaceutical expenditure, while achieving efficient and fair resource allocation within their finite healthcare budgets (Maskineh & Nasser, 2018; Gronde et al., 2017; Angelis & Kanavos, 2017).

There is no concrete definition for a "high-cost" or "high-priced" medicine, while a common definition of what constitutes an "innovative medicine" is also currently lacking (WHO, 2015; Ferrario et al., 2017). Broadly, the concept of a "premium-priced" medicine is a function not only of its high price but also of its high level of use or volumes yielding a high overall cost for the treatment of a single patient, which is typically defined as greater than €10 000 per patient for a yearly therapy for the public payer (WHO, 2015). In terms of innovativeness, a medicine is characterised as innovative primarily based on the benefits it offers for patients and societies, including better therapeutic, clinical or Quality of Life (QoL) outcomes for patients and improved socioeconomic burden for societies (WHO, 2015).

Despite the innovativeness of many new medicines, their high prices raise affordability issues for governments and social health insurance systems with immediate implications for patient access. For example, sofosbuvir (Sovaldi®) for the treatment of the hepatitis C virus (HCV) is highly innovative as it completely prevents the need for a liver transplant but due to its high list price, exceeding $80,000 for a 12-week treatment, health plans in the US refused to make it available for all patients with HCV infections (Gronde et al., 2017).

With many targeted immunotherapies in the pipeline, rising demand for health services, ageing populations and technological advances, these funding challenges are expected to grow, while the immature evidence of newly introduced highly priced health technologies around their real

world clinical and cost effectiveness poses additional pressures for policy-makers on reimbursement decision-making (Dabbous et al., 2020; Angelis & Kanavos, 2017).

As pharmaceutical spending is primarily driven by high prices and/or high volumes, in order to tackle these challenges, insurers can either aim to lower prices or reduce utilisation. This has been reflected in measures and mechanisms to restrain spending by policy-makers, including the introduction of co-payments for prescribed pharmaceutical, profit margins controls for pharmaceuticals, reference pricing, and performance of health technology assessments (HTAs) (Vreman et al., 2020; Goncalves et al., 2018). Specifically, the use of HTA has grown significantly over the last couple of decades, across the globe and primarily in Europe, aiming to assess and appraise the value of new medical technologies as well as inform coverage decisions (Angelis & Kanavos, 2017). Despite different evidentiary requirements, assessment criteria and involvement of a diverse range of stakeholders in HTAs conducted across countries, the overarching goal of this mechanism is to assess improvements in efficacy and safety in relation to cost variables around cost-effectiveness and budget impact, which aim to secure efficiency and affordability, respectively, of the pharmaceutical product under assessment (Butcher, 2016).

1.2 Decision-making in the context of Health Technology Assessment

Traditionally the decision-making process in the context of HTA has been based on cost per outcome economic evaluation approaches such as, the cost per Quality Adjusted Life Year (QALY) method (Wouters et al., 2015). Despite its widespread adoption, the cost per QALY approach limits the opportunity to consider and incorporate other key value dimensions apart from cost and clinical outcomes into the decision-making process (Angelis et al., 2018).

In response to this limitation, HTA decision-making practices have recently shifted towards more holistic, value-based assessments that consider supplementary evidence and criteria that capture additional value dimensions, beyond that of cost-effectiveness. Literature has described a widely applicable classification of these additional value criteria which relate to the following key dimensions; burden of disease (i.e., the impact that the disease has, which depends mainly on the severity/rarity of the disease and the unmet medical need or availability of treatment alternatives present in the specific indication targeted by the medicine under evaluation), innovation (i.e., any innovation characteristics of the treatment, relating to its added clinical

novelty, therapeutic benefit, ease of use and comfort), QoL impact (i.e., the impact that a treatment has on patients' QoL), societal impact (i.e., the impact a treatment has on indirect costs and productivity losses from the patient and caregiver perspective), and other special value considerations such as end-of-life criteria (e.g., in England and Scotland where there is a specific value placed on life-extending medicines for end-of-life patients) and the human dignity and solidarity principles (e.g., Sweden) (Angelis et al., 2018). A detailed definition of all the social value considerations used in the analyses performed for the purposes of this thesis is defined in detail in Table 4.

Even though these dimensions are applicable across most HTA systems (Nicod & Kanavos, 2016), they are typically employed on an ad-hoc basis and not explicitly considered in the decision-making processes of the different HTA systems (Angelis et al., 2018). More importantly, the final selection of the criteria used to interpret and determine the value associated with a treatment under assessment, as well as the relative importance/weight of these criteria in the decision-making process is highly subjective across countries and remains equivocal. Additionally, HTA decision-making and subsequently, HTA recommendations are highly dependent on HTA agencies' requirements for the clinical and economic evidence submitted for assessment and on other criteria that may shape decision-makers' preferences on how to interpret this evidence. These may refer to preferences on healthcare system specific criteria, such as the preferred perspective to be adopted in the economic evaluation (e.g., societal, National Health System (NHS) or Personal Social Services (PSS) perspective), clinical evidence criteria such as the choice of comparators and their relevance to clinical practice in the setting of interest, preferred clinical study designs and preferred types of endpoints used to demonstrate clinically relevant and QoL outcomes (e.g., preference for clinically relevant as opposed to surrogate outcome measures, or preference for generic QoL endpoints over disease-specific endpoints), economic evidence criteria such as preferred types of costs and utilities to be included in the economic model and preferred Willingness To Pay (WTP) thresholds on cost-effectiveness. Finally, HTA decision-making also varies widely between settings based on how the respective HTA system operates, and on how HTA fits into the decision-making process and into the final coverage decisions, given the role/scope of the respective HTA system (e.g., advisory, regulatory, or coordinating) (Fontrier et al., 2021).

All these variations in the HTA decision-making processes and the way value and uncertainty is interpreted in the context of HTA across countries, often result in unexplained heterogeneity among the coverage decisions for medicines across settings, even for the same medicine-indication pair (Akehurst et al., 2017). Although some of this decision heterogeneity could be explained based on the different national healthcare budgets and priorities, it is not yet clear how all the different decision-making criteria and preferences interact with one another, and what their relative importance is in shaping HTA funding decision outcomes (Devlin & Parkin, 2004). As the drivers of this variation remain largely unexplained, this encourages inconsistencies in medicine's eligibility for coverage across settings and raises important implications around equitable and fair patient access to medicines at a global scale (Akehurst et al., 2017). Therefore, with the rising utilisation of HTA across healthcare systems globally, understanding the determinants of HTA funding decision outcomes arises in parallel as a necessity to establish a transparent shared understanding on what constitutes value in the context of HTA decision-making across countries.

1.3 Oncology care and medicine costs

The latest figures from the Global Burden of Disease (GBD) study, reveal that in 2017, there were approximately 25 million cancer cases and over 9 million cancer-related deaths worldwide (Fitzmaurice et al., 2019). Despite substantial efforts for cancer prevention and treatment in recent years, the cancer burden is projected to grow chiefly due to aging global populations and increased prevalence of lifestyle-related risk factors such as smoking and obesity (GBD Cancer Collaboration, 2013). This is reflected on recent evidence showing that although a decade ago cancer ranked sixth among the top causes of Disability Adjusted Life Years (DALYs) globally, in 2017, it has been ranked as the second leading cause of DALYs and global deaths, after cardiovascular disease (Fitzmaurice et al., 2019).

Additional to its high burden of disease, cancer also represents one of the costliest Non-Communicable Diseases (NCDs) for health systems globally. Oncology is the first among the top three therapeutic areas with the highest pharmaceutical sales in Europe, amounting up to about $30 billion, followed by autoimmune diseases ($13 billion) and diabetes ($S10 billion) (Greiner et al., 2021). Total cancer care related costs reached nearly €200 billion in Europe in 2018 (Hofmarcher et al., 2020), and $183 billion in the United States (US) in 2015 and this amount is estimated to grow by 34%, as newly diagnosed cancer patients will increase worldwide to 20–27 million by 2030 (ACS CAN, 2020; Godman et al., 2018; WHO, 2015).

Apart from pharmaceuticals' sales and direct medical costs, a significant proportion of the high cancer care figures described above is driven by informal caregiving costs, transportation costs and indirect costs from productivity losses incurred by people with cancer and their families (Hofmarcher et al., 2020; ACS CAN, 2020). Therefore, cancer presents with a substantial financial burden for patients and healthcare systems but also with significant intangible and socioeconomic costs, given that the increased financial strain is often associated with high levels of symptom and poor QoL burden exhibited by cancer patients (Lathan et al., 2016). This upward shift in the disease and financial burden of cancer makes an urgent call for the prioritisation of funding mechanisms that ensure access to universal health coverage and protect against the catastrophic costs directly associated with the cancer treatment per se and with the broader, long-term costs related to cancer diagnosis for a household (Fitzmaurice et al., 2019).

Despite the introduction of generic and second-in-class cancer agents, the prices of oncology medicines have not decreased over time (Leighl et al., 2021) leading to intense debate about the cost of cancer medicines, particularly when considered in association to the clinical benefits they offer. As such, the value, budget impact and cost-effectiveness of new cancer medicines is under intense scrutiny, raising significant differences in the uptake of/ access to new cancer medicines across different markets due to differences in the extent of assessments carried out for new cancer medicines, the timing of the assessments and differences in reimbursement and funding decision-making processes, including differences in cost–effectiveness and evidentiary requirement thresholds (WHO, 2015). Additional factors spiralling market access variations across countries, include divergent regulatory requirements, disparities in countries' purchasing power based on their respective gross domestic product (GDP) per capita, and differences in healthcare related spending, pricing of pharmaceuticals and utilisation rates (Vogler et al., 2017). Literature suggests that all these factors underscore a major challenge that remains in relation to accessing new, innovative therapies across countries, and across therapeutic areas, notably in oncology (Angelis et al., 2018). Even across EU member states, whereby collaborative, targeted efforts have been made to secure and expedite availability of and patient access to medicines, significant divergence exists in access to medicines metrics across countries, particularly in terms of time to market access. For example, the EU Transparency Directive mandates that pharmaceutical products should become available in the markets of EU member states within 180 days following pricing and reimbursement negotiations and decision-making (Kamphuis et al., 2021; EC 1998). However, observations

from the 2020 European Federation of Pharmaceutical Industries and Associations (EFPIA) Patients Waiting to Access Innovative Therapies (W.A.I.T.) Indicator survey specifically about oncology products, showcase that availability of newly approved cancer medicines varies significantly between EU countries, at least in the 12 month timeframe following regulatory approval at the EU level, as does their respective time to becoming available to patients (measured as the days between the date of regulatory approval and the date that patients can have factual access to these products within their respective countries) (IQVIA, 2021b).

In response to the above, the World Health Organisation (WHO), supported by several organisations including the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO), has conducted a comprehensive assessment of high-cost cancer medicines and provided recommendations on how to address high prices and their respective implications for patient access. Based on that, a key objective for healthcare systems is to promote uniform, global access to the WHO's list of essential cancer medicines, whereas ensuring that this list comprises all newer, high-value, transformative cancer medicines is also important to achieve better cancer outcomes for patients globally (Leighl et al., 2021). Furthermore, towards this goal, performing HTA is paramount particularly when results can be shared across settings, accounting for each country's system costs and thresholds for affordability. Additionally, the use of universal value frameworks established by professional cancer societies (e.g., the ESMO Magnitude of Clinical Benefit Scale (ESMO MCBS)) should remain a major focus for patients, physicians and policy-makers in assessing the added benefits of cancer therapies across jurisdictions and determining fair pricing (Goldstein et al., 2015; Leighl et al., 2021).

1.4 Managed Entry Agreements as part of Health Technology Assessment processes

The greatest challenge payers are facing is not the high prices of innovative medicines per se but the combination of innovative medicines with immature or early phase evidence yet high expected value, reaching the market often at high prices (Dabbous et al., 2020; Ermisch et al., 2016). As outlined in section 1.1, often the overall evidence submitted by manufacturers for HTA purposes is insufficient to accurately estimate the real-life budget impact, clinical and cost-effectiveness of a medicine, generating significant uncertainties regarding the clinical and cost effectiveness of new technologies at the point of decision-making. This increases pressure for manufacturers to demonstrate a new product's "value for money" but more importantly for

policy-makers to take decisions around the reimbursement of new, promising, high-cost therapies that present with significant uncertainties regarding their clinical effectiveness and/or utilization and budget impact in real practice.

While evidence arising from clinical trials always presents with some level of uncertainty, the challenges in decision-making for payers are primarily generated when multiple sources of uncertainty exist. Different types of uncertainty may include those related to clinical uncertainties (e.g., risk-benefit shift over the treatment course, long-term clinical benefit that is not captured in clinical trials), financial uncertainties (e.g. number of doses required per treatment, duration of treatment, need for treatment combinations, aggregate budget impact) and utilisation uncertainties (e.g. is the product eventually prescribed for eligible patient sub-groups where it was found to be "cost-effective"?) (Robinson et al., 2017; WHO 2015).

In response to these challenges, both manufacturers and payers have shown interest in solutions to reduce the uncertainty around the real-world value of medicines, while ensuring reimbursement for manufacturers and therefore achieving access for patients (Van de vooren et al., 2015). One of these mechanisms has been with the introduction of Managed Entry Agreements (MEAs). MEAs represent a "mutually beneficial" negotiation between manufacturers and payers/purchasers (such as insurance companies or government healthcare bodies) that enables access to/ reimbursement of a health technology with "uncertain" value, subject to specified conditions that link price and reimbursement levels to real-world performance or utilization of medical products (Klemp et al., 2011). Essentially, MEAs aim to offset the risk for payers of paying high reimbursement costs for treatments with uncertainties over their clinical and/ or health economic value and for pharmaceutical companies to avoid the risk of a rejection due to the above mentioned uncertainties (Ando, 2011); as such, these agreements are also often called Risk Sharing Agreements (RSAs) (Ferrario & Kanavos, 2015).

MEAs have been extensively implemented across a number of countries, namely, in Western Europe (e.g., Belgium, England & Wales, France, Italy, Scotland and Sweden) and Australia and particularly in oncology, while a growing number of other countries have begun to implement MEAs more recently (e.g., New Zealand, Poland, Romania and Serbia) (Dabbous et al., 2020; Pauwels et al., 2017; Ferrario et al., 2017). Despite the recognised potential of MEAs to facilitate patient access and optimise utilisation of pharmaceuticals in the real clinical

practice, they are not explicitly designed to address the actual high prices of pharmaceuticals or the rising pharmaceutical expenditure itself (KCE, 2017) Furthermore, their often complex administrative requirements and unsupported evidence about their effectiveness in meeting their objectives pose further questions about their use for the purposes of pricing and reimbursement decision-making in the context of HTA (EC, 2018) (see also section 1.5 – Issues with MEAs, and alternative access mechanisms).

1.5 Description and Taxonomy of Managed Entry Agreements

The Health Technology Assessment international (HTAi) Policy Forum in 2010 defined a MEA as "an arrangement between a manufacturer and payer/ provider that enables access to (coverage or reimbursement of) a health technology subject to specific conditions (WHO 2015; Klemp et al., 2011). Since then, several nuances in the definitions of MEAs have been observed in the literature and these continue to evolve as the use of MEAs increases across settings, although the concept of an agreement between two parties to mitigate the risks between high cost and uncertain clinical benefit remains the foundation of the various definitions given for MEAs (Vreman et al., 2020; Dabbous et al., 2020; Wenzl & Chapman, 2019). Countries have designed a variety of different MEAs and respective mechanisms in implementing them. Regardless of the mechanism involved in their implementation, these agreements typically aim to address three main objectives namely managing budget impact, achieving cost-effective resource allocation and monitoring appropriate utilisation (Ferrario & Kanavos, 2013). Defining different MEA taxonomies based on the respective mechanism(s) used for their implementation would have resulted in the existence of numerous MEA types, with subsequent challenges in referring to and classifying agreements entailing features of more than one mechanism used. Therefore, for simplicity, literature has proposed that the taxonomies used to classify MEAs should reflect the objectives countries are trying to achieve through MEAs (Klemp et al., 2011). The most common taxonomy used in the literature to classify MEAs into broader categories largely follows the taxonomy proposed in 2010 which distinguishes between non-health and health outcome-based schemes (Carlson et al. 2010). This taxonomy mainly distinguishes between financial based agreements (FBAs) and performance- or outcomes-based agreements (PBAs or OBAs), or agreements that have a combination of the two elements, all falling under the umbrella term of MEA. For the purposes of this thesis the terms PBA(s) and OBA(s) have been used interchangeably to refer to agreements that target health outcomes. Other studies have further classified FBAs and PBAs based on whether they

are applied at the population or individual level (Dabbous et al., 2020; Ferrario & Kanavos, 2013).

FBAs are primarily targeted at resolving budget impact and affordability issues raised by a new product, through sharing with the manufacturer the financial risks posed by their product entering the market. FBAs aim to contain the cost without taking into consideration health outcomes (Ferrario & Kanavos, 2013). Traditional FBAs implemented across countries include mechanisms that lower prices or contain expenditure such as simple discounts, free stock and free initiation treatments, and price-volume discounts or Price-Volume Agreements (PVAs) (Figure 2). It has been suggested that FBAs can be more effective if applied for chronic disease treatments received over a period of time rather than acute treatments as for example often the payer agrees to pay for a specified amount of the population over a given period of time and the remaining courses of treatment need to paid for by the manufacturer (Dabbous et al., 2020).

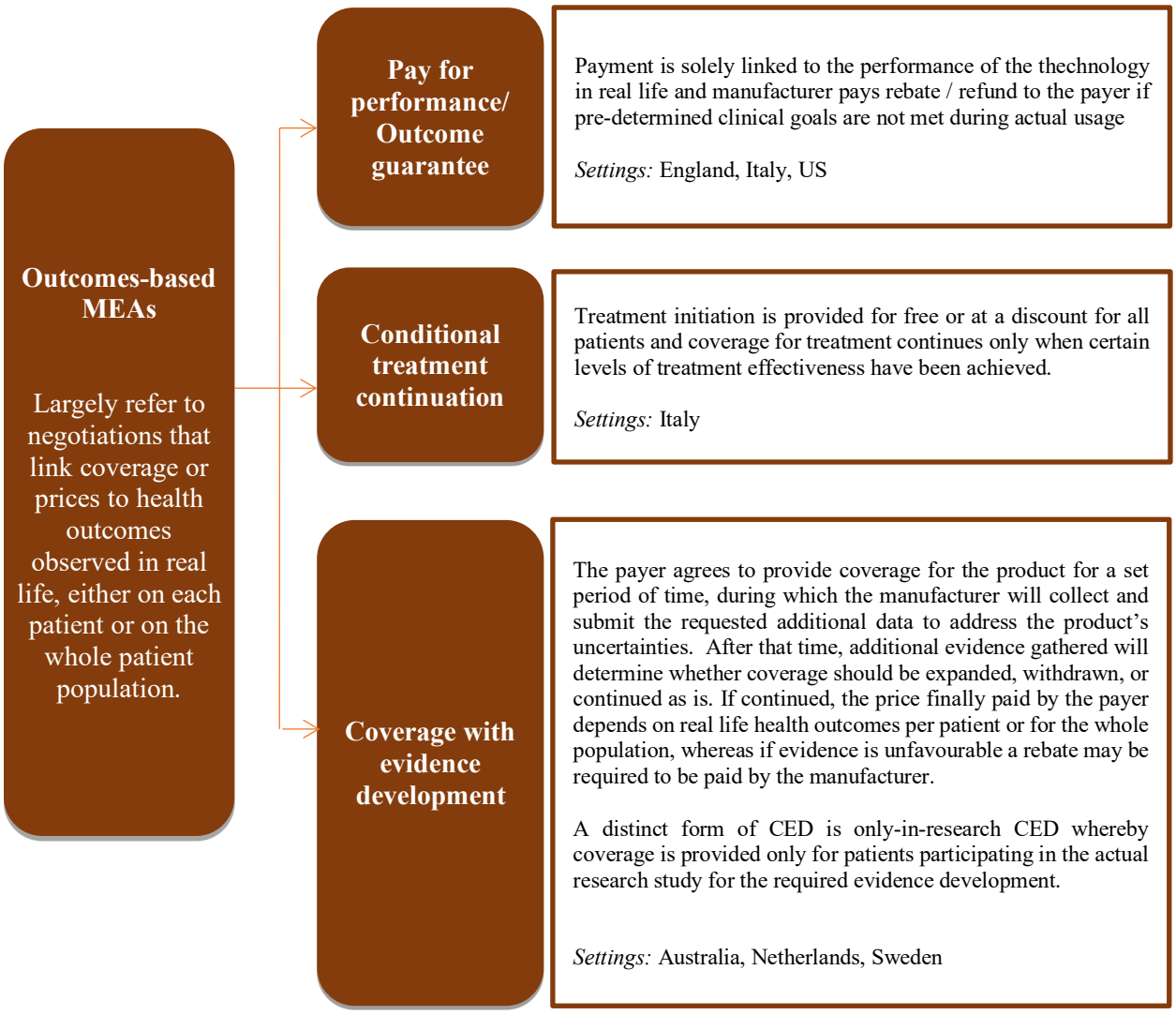
On the contrary, PBAs are focused on the performance of a product. Typically, when a new product is subject to an outcomes-based agreement, the evidence around its clinical effectiveness is not sufficient for payers to estimate the product's performance in the real clinical setting. Uncertainties often arise as the evidence generated from clinical trials does not capture patient relevant outcomes and/or does not clearly showcase clinical benefits and as such, for payers to consider reimbursement manufacturers are requested to assess such relevant endpoints in real life and provide the respective additional evidence. Therefore, payment is structured such that the therapy is paid for upfront with rebates from the manufacturers when expected treatment outcomes are not achieved or the therapy can be covered by payers only after favourable result have been demonstrated (Vreman et al., 2020). Finally, another form of PBA, often described as a distinct type of MEA in the literature, is Coverage with Evidence Development (CED), a mechanism whereby therapies with limited data at the time of approval are granted funding while the manufacturer generates the necessary evidence to address the existing uncertainties in clinical outcomes (Figure 1). Once presented with new, additional evidence, payers may re-evaluate and adjust the conditions of their reimbursement agreement – this may include requiring additional data collection, product price adjustments, or even reimbursement rate adjustments (Dabbous et al., 2020).

In general, FBAs are considered relatively simple to negotiate for payers and manufacturers, while their implementation has been associated with lower administrative and budgetary

burden for healthcare systems compared to PBAs. This is because FBAs do not involve data collection processes for outcomes or clinical benefit measurement. Nevertheless, FBAs inherently lack the opportunity to leverage evidence generated post-approval (Bouvy et al., 2018). On the contrary, successful implementation of PBAs may be administratively complex as it requires well-defined performance benchmarks and endpoints to be measured, clear alignment between the actual data collected and data required by payers for decision-making and an overall governance framework that ensures the transparency of the data collection processes throughout (Facey et al. 2021; Vreman et al., 2020). An additional challenge for PBAs arises in cases where data collection needs to be performed at the individual level, which is regarded as a time-consuming and burdensome activity for healthcare professionals involved in the process, while it often fails to capture key confounders, rendering the interpretation and the use of such data problematic (Dabbous et al., 2020). The complex nature of PBAs when compared to FBAs has been well documented in the literature and constitutes the main reason behind the popularity and increased implementation of FBA contracts across all countries implementing MEAs (see Chapter 3- section 3.1.2- Country selection and geographic scope) (Wenzl & Chapman, 2019; Ferrario & Kanavos, 2015, Ferrario & Kanavos, 2013, Adamski et al., 2010).

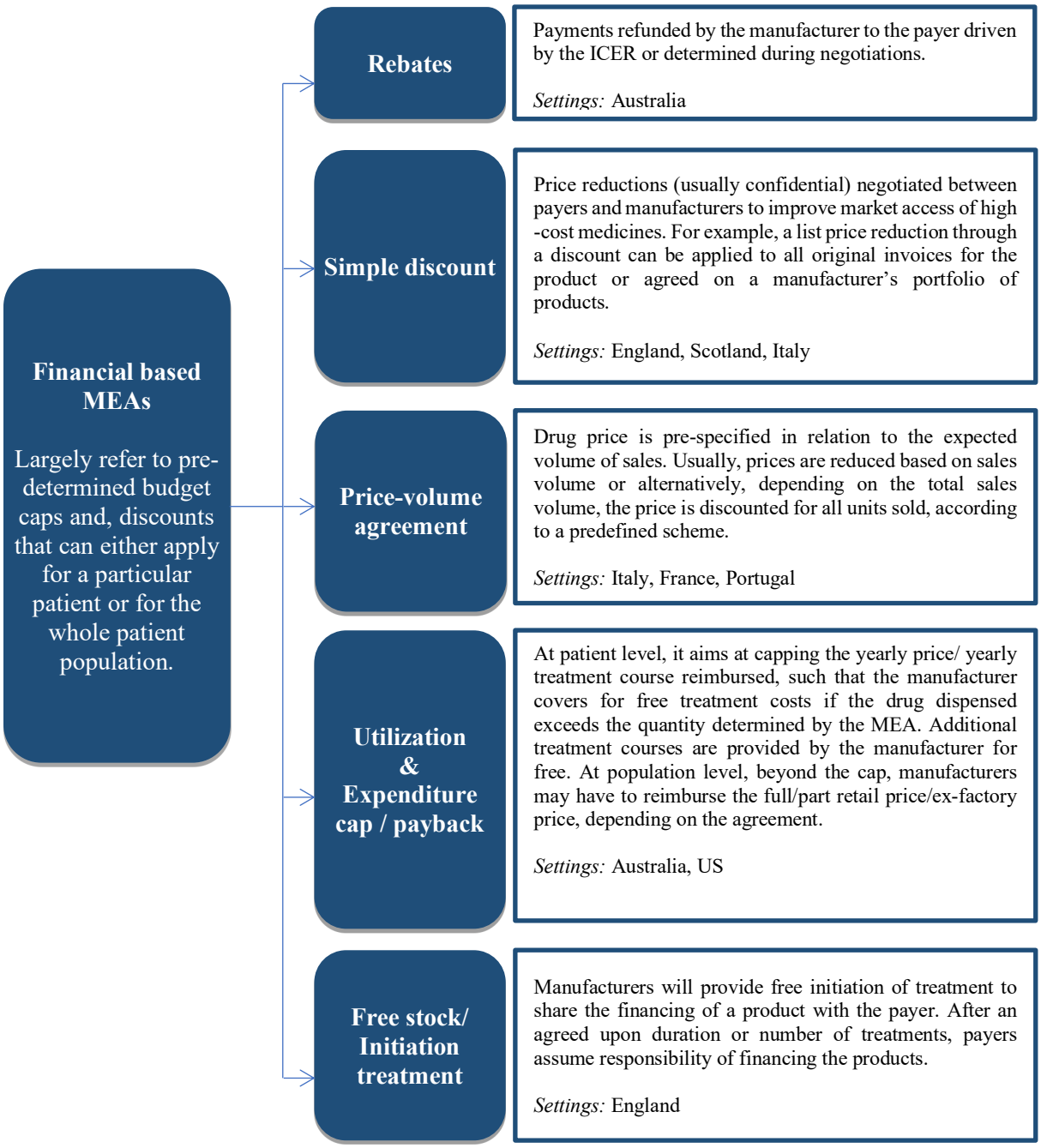
Figures 1 and *2*, present the definitions around the types and tools of MEAs whereas *Figure 3* presents a schematic taxonomy of MEAs and their tools based on the types of uncertainties they are trying to address and whether they are applied at the population or individual level. Finally, a schematic representation of other taxonomies of MEAs from the literature is presented in the Appendix (Appendix 1).

Figure 1. Outcomes-based MEAs and their respective implementation tools/ mechanisms.



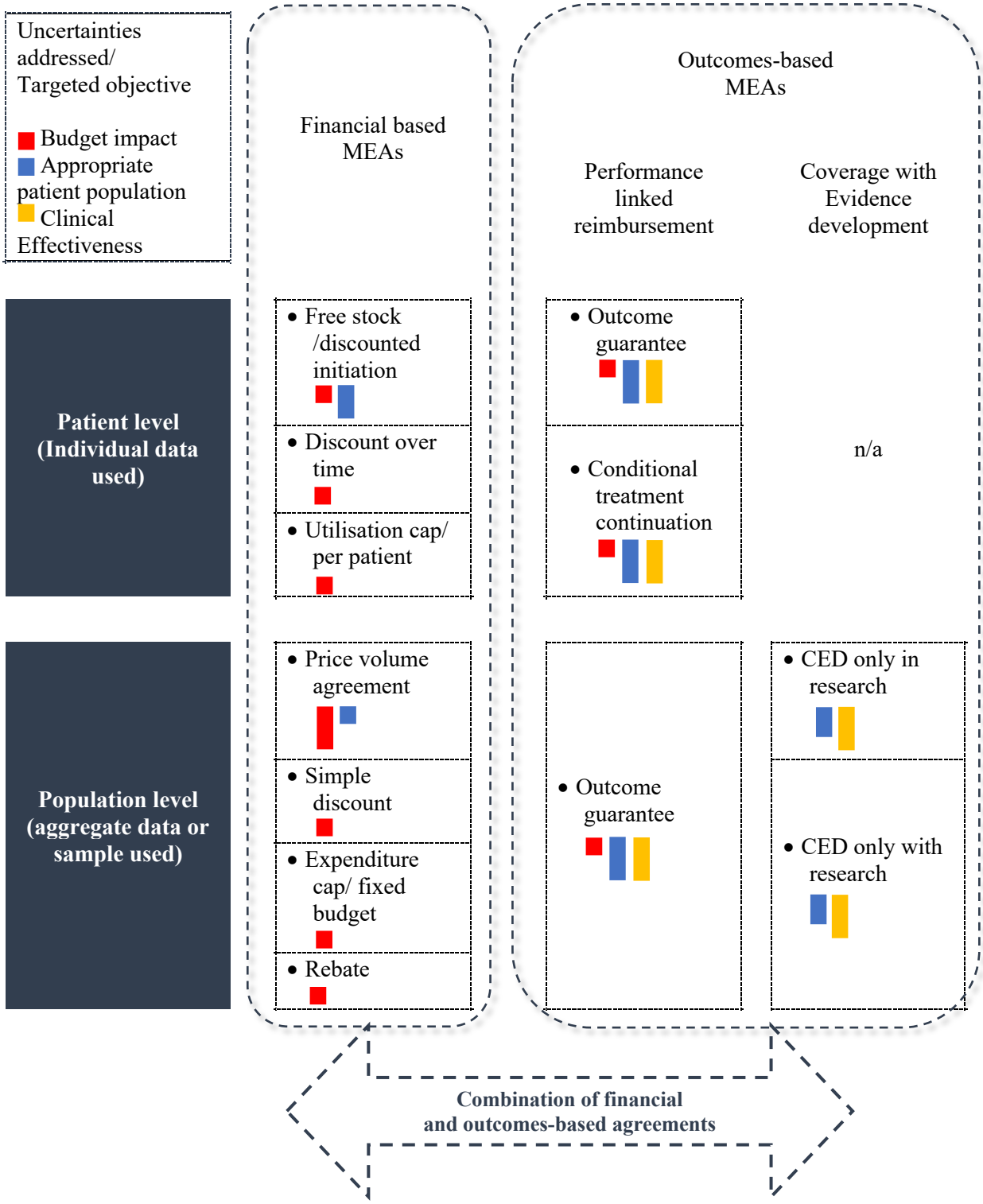
Source: The author based on definitions from the literature (Dabbous et al.,2020; KCE, 2017; Ferrario & Kanavos 2013, Ando, 2011).

Figure 2. Financial based MEAs and their respective implementation tools/ mechanisms.



Source: The author based on definitions from the literature (KCE, 2017; Ferrario & Kanavos 2013, Ando, 2011, Dabbous et al., 2020).

Figure 3. Taxonomy of the different types of MEAs, their tools and respective uncertainties they are trying to address.



Source: The author, drawn from Lucas (2017) and Ferrario & Kanavos (2013).

Note: The length of the coloured bars reflects a relative measure of the extent to which each MEA tool/mechanism targets the uncertainty/ objective denoted by the respective bar colour.

1.6 Issues with Managed Entry Agreements, and alternative access mechanisms

1.6.1 Managed Entry Agreements as a sustainable policy option

Achieving "normal" market entry for a new treatment, where regulatory approval is followed immediately by a coverage and funding decision, and, ultimately, by patient access is increasingly rare and this is highlighted by the growing number of MEAs used as part of the reimbursement decisions across major and emerging markets (Dabbous et al., 2020; Ando, 2011). Indeed, literature has largely agreed that under certain circumstances MEAs can facilitate the diffusion/ introduction of new high-cost technologies by addressing post-authorisation uncertainty and promoting patient access to innovative treatments (EC, 2018).

Nevertheless, not all countries that engage in HTA activities also employ "risk sharing" strategies in their reimbursement policies. In some markets (e.g., Australia, England, Scotland) and for certain therapeutic areas (e.g., cancer) risk-sharing is implemented to an extent that it forms an indispensable component of the HTA reimbursement decision-making, whereas in other markets (e.g., Germany) MEAs are not seen as an efficient reimbursement tool. For example, in Germany, sickness funds may refrain from using this type of agreements due to concerns that once the agreement expires and a number of patients have already started treatment, the manufacturer might either not be willing to continue providing the medicine as part of the agreement or the conditions of it will become less favourable compared to when the medicine was first introduced (Ferrario & Kanavos, 2013). This pattern is highly reflected by the on-going debate around the strengths and weaknesses of MEAs (EC, 2018; KCE 2017; Ferrario & Kanavos, 2013; Barros 2011).

More precisely, literature has focused particularly on two critical issues (sustainability and confidentiality) around the implementation of MEAs, potentially placing constraints for many countries seeking to understand the potential applicability of these agreements to their own context and for key stakeholders to understand their capacity in shaping reimbursement decisions, ultimately discouraging the widespread acceptance of MEAs as a pharmaceutical reimbursement policy tool (Garattini & Curto, 2016; Hollis, 2016; Klemp et al., 2011).

With regards to sustainability, MEAs present with a number of sustainability concerns; this is because (a) the long-term financial and administrative burden that is associated with their implementation has not yet been evaluated (Barros, 2011); and (b) despite the significant

number of agreements implemented to date in Europe and elsewhere, there is still little evidence to support their effectiveness in meeting key policy objectives (Gamba et al., 2020; KCE 2017; Garattini & Curto, 2016; Hollis 2016; Ferrario & Kanavos, 2013; Klemp et al., 2011). More importantly, it is still unclear whether these agreements contribute meaningfully in mitigating the uncertainties about the therapeutic benefit of new medicines, while potential cessation of funding which is associated with a MEA may raise access implications for patients over the long-term (Vitry et al., 2016). This is important when taking into consideration that even when a country implements MEAs there are still budget restrictions, which limit the volume of patients that can benefit from a new technology reimbursed with a MEA; this highlights that the existence of a MEA does not necessarily guarantee improved access (Ferrario et al., 2017).

With regards to confidentiality, MEAs operate largely on a confidential basis with no best practice guidelines in place and a lack of clarity around the definitions on what constitutes a MEA, what is perceived as "uncertainty" and the criteria used to select when—and, more importantly, how—these agreements are applied (Vreman et al., 2020; Ando, 2011) (i.e. the rationale for setting up the agreement, uncertainties to be addressed, outcomes to be monitored and the criteria for terminating the agreement (Klemp et al., 2011)). For example, in some countries (e.g., Belgium and France), the content of a negotiation is strictly confidential for the public, whereas elsewhere (e.g., Italy, England & Wales, Scotland and Sweden) the respective information is publicly available - although there is still confidentiality on the financial aspects of the agreement, which is crucial in understanding the characteristics of these agreements, irrespective of the country where they have been applied (Pauwels et al., 2017). Additionally, the confidential nature of these agreements also leads to inconsistencies whereby what is considered to be a MEA in one setting may not be perceived as such in another (WHO 2015); for example, conditional reimbursement is implemented both in Italy and Denmark, but only the former considers this as a MEA. Similarly, NICE in the UK imposes several reimbursement restrictions in terms of defining patient eligibility but does not consider such restrictions as a form of MEA (see Chapter 3- section 3.3.; Table 4, Table 5).

The lack of transparency among countries around the implementation of MEAs renders the classification of MEAs challenging as this requires a thorough understanding of their implementation mechanism(s), while it also hinders shared understanding of the ways in which decision-making is done for the initial and for continuation of funding (Vitry et al., 2016). The

need for a transparent methodological framework on MEAs implementation becomes more crucial when taking into consideration that even among countries where such agreements are implemented, each country has its own approach and implementation strategy for risk sharing, with different requirements for the potential need for MEAs (Vreman et al., 2020; WHO 2015; Allen et al., 2013). Indeed, since each country takes into account its own regulations/ socioeconomic context to form coverage decisions, leading to heterogeneity in HTA recommendations across countries (Pauwels et al., 2017; Nicod & Kanavos 2016; Maynou - Pujolras & Cairns, 2015), it follows that the strategies applied to implement MEAs are also highly specific to the setting specific HTA decision-making modalities in which they operate (Ferrario & Kanavos, 2013; Pauwels et al., 2017).

1.6.2 Special drug funds and special funding options

Given the weaknesses of MEAs, in combination to growing concerns that existing pricing arrangements may not be sufficient to address affordability challenges, other approaches in managing the access of high-cost pharmaceuticals while enhancing patient access are increasingly being discussed and implemented across numerous countries. One of the most common alternative approaches to innovative funding relates to establishing special funds and budgets for the financing of certain categories of medicines such as the fund for innovative, expensive and under patent medicines in Bosnia and Herzegovina, the New Medicines Fund in Scotland, and the Cancer Drugs Fund (CDF) in England (see chapter 3*,* section 3.1.2- Country selection and geographic scope) (Ferrario et al., 2017). While the use of special funds may enhance access, it raises equity considerations about the funding of treatments targeting other disease areas and/or patient groups that are not eligible for special funding.

Other approaches discussed in the literature focus on more flexible pricing and reimbursement frameworks that may include new models applied on a case-by-case basis, such as mortgages, refinancing, and the inclusion of the concepts and principles of amortization and depreciation, although these have not yet been consistently applied in the pharmaceutical industry.

These novel funding models can broadly refer to i) contracting/over-time models, ii) portfolio agreements and iv) re-insurance models. Contracting or over-time models (alternatively known as high-cost drug mortgages) typically refer to innovative financial agreements that allow purchasers to secure funding through spreading the costs of high-cost therapies, including

cancer and cell/gene therapies, over the time in which benefit is accrued (Garrison et al., 2019; Kanavos 2020). More comprehensive models that have been implemented in this category, involve multiple years with payments spread over time based on achievement of pre-specified performance criteria (Kanavos, 2020), such as Multi-Year Multi-Indication (MYMI) agreements that span multiple indications of the same molecule across multiple years bringing significant benefits for patient access, particularly in countries that would otherwise assess each indication: a process that is resource intensive and delays patient access (Wilsdon et al., 2019) (see also chapter 8- Areas for further research). Furthermore, portfolio agreements refer to a model whereby for each purchaser that wants to buy medicines, the manufacturer negotiates the overall number of treatments bought, allowing the supply of multiple treatments to individual purchasers. Finally, reinsurance and stop-loss policies whereby insurance providers purchase reinsurance or stop-loss from another insurance company, are discussed as a possible option for financing high-cost curative therapies by transferring the financial risk of these therapies to the reinsurance company which pools risk over a larger scale (Kanavos, 2020).

1.7 Definition and measurement of "access to medicines"

The concept of "access to medicines" is evolving and multifaceted. As such, different approaches to defining "access" have been discussed in the literature and elsewhere, depending on the specific aspects of access that each definition is focused on, as well as on the different context, perspective, and goals of the relevant healthcare system in question. Across the board, common metrics of access comprise, among others, affordability, availability, time to access, healthcare system adaptability/ preparedness to launch new, innovative therapies and its organisational capacity to prioritise highly effective therapies targeting significant unmet need. Based on the WHO approach, "access to medicines" is a function of availability and affordability of medicines, referring respectively to the extent to which new therapies can become available in the market for which they are intended and the extent to which medicines' prices are reflective of the purchasing capacity of both healthcare systems and patients (WHO, 2010). Other approaches to defining and measuring market access and availability focus primarily on the aspect of time to market access, instead of affordability. For example, the W.A.I.T indicator, measures specifically the level of medicines availability (i.e., the number of pharmaceutical products readily available for patients, typically measured by the date when a product is approved for listing in the positive list of a country) and the time to availability (i.e.,

the time -measured in days- following regulatory approval and until all post-regulatory approval procedures have been completed, to allow for access by patients (IQVIA, 2019).

Historically, relevant literature and sources of evidence on access to medicines, have focused on market access instead of patient access. However, discrepancies may arise between the two concepts and as such, when measuring "access to medicines" it is critical to define whether access is measured from the market or the patient perspective. Availability of pharmaceutical products in the market (i.e., market access) may not always reflect a respective level of access from the patient's side. Beyond market availability and healthcare system affordability, practical accessibility for patients (defined as "the phase that starts when the first patient is treated under a formal reimbursement scheme" (Vintura, 2020a) is also subject to post-marketing dimensions such as the rate at which clinical guidelines are updated to include novel medicines and hence, the ability to obtain a prescription for the medicine in question, the purchasing/procurement framework of medicines and whether it occurs at the national, regional or hospital level, and finally issues with logistics and supply of medicines related to the manufacturer, wholesaler and pharmacy (Kamphuis et al., 2021).

2. Literature review and research questions

2.1 Literature selection

A comprehensive literature review was conducted to collect information around: (i) conceptual and theoretical models, (ii) empirical results (iii) definitions and stakeholders' perceptions, and (iv) objectives of MEAs across the globe. The literature search was designed based on the Population Intervention Comparator Outcomes (PICOs) criteria for establishing a clinically relevant research question (Aslam and Emmanuel 2010) as follows:

	Population	**Intervention**	**Comparator**	**Outcomes**
PICOs criteria	Any institutional body or agent involved in pricing & reimbursement decision-making and negotiations	Managed access and funding negotiations/ activities/interventions	This could take different forms (e.g., MEAs *vs.* free-pricing, MEAs vs. External Reference Pricing)	Affordability Availability Timely Access

After a thorough review and testing of an extensive list of relevant search terms used in the literature to define and research MEAs (Antonanzas et al., 2020; Dabbous et al., 2020; Bouvy et al., 2018; Yu et al., 2018; Kanavos et al., 2017; Wilsdon & Barron, 2016; Carlson et al., 2015; Grrison et al., 2013; Ferrario & Kanavos, 2013; Klemp et al., 2011; Carlson et al., 2010), I retained the following key words or joint search terms as the most adequate combinations to enhance the sensitivity of the search:

"Conditional coverage" OR "conditional reimbursement" OR "list with conditions" OR "coverage with evidence" OR "rebate" OR "outcome(s) guarantee" OR "patient access scheme(s)" OR "discount(s)" OR "pay for performance" OR "payment by results" OR "price volume agreement(s)" OR "risk sharing" OR "manged entry" OR "managed access" AND "schemes" OR "agreements" OR "contracts" OR "negotiation(s)" AND "health technology assessment" OR "access" OR "reimbursement" OR "funding".

For the peer-reviewed literature MEDLINE - PubMed was searched, while Google and Google Scholar were used to retrieve information from the grey literature (namely, technical reports commissioned by the WHO, the European Commission and the OECD, as well as privately commissioned/consulting reports, conference abstracts and proceedings). The inclusion/exclusion criteria were that the sources identified focused on at least one of the four main themes of interest for the purposes of this thesis (i.e., conceptual and theoretical impact

assessment models, empirical results, definitions and stakeholders' perceptions, and policy objectives). Additionally, only schemes implemented for pharmaceutical products were of interest for the purposes of this research and therefore, any evidence on schemes related to medical devices and diagnostics was excluded. The search language was limited to English, although the search did not apply any time or geographic limit, and all study, newspaper article, report, or document containing information about existing MEA in the study countries was included. The search was first conducted in April 2017 and was updated in August 2021.

2.2 Literature on the determinants of Managed Entry Agreements

The search retrieved 935 references (from the peer-reviewed and grey literature), of which 752 were excluded because of duplicates and records with no abstracts or full text available, and 131 excluded based on the inclusion/exclusion criteria. The final number of articles and reports of relevance was 52.

Some, but not significant, research has been done on presenting the definitions of MEAs, the types of MEAs typically pursued by payers in different settings and the respective perceptions of "risks" and "uncertainties" that these agreements aim to address, and stakeholders' views on MEAs across settings (WHO, 2015; Ferrario & Kanavos, 2015; Ferrario & Kanavos, 2013; Adamski et al., 2010; Gandjour 2008). Even though literature has contributed significantly to our understanding of what is perceived to be a MEA across settings, it has also highlighted that there is still a need for a transparent methodological framework and best practice guidelines on MEAs across countries, which would provide a universal definition of what constitutes "risk" or "risk-sharing" and what is perceived as sufficient/insufficient evidence in the context of HTA decision-making.

Greater evidence exists in the literature on the types of the technologies where MEAs have been applied, the respective uncertainties and expected outcomes targeted by these agreements across settings and therapeutic areas (Dabbous et al., 2020; Antonanzas et al., 2020; Yu et al., 2018; Ferrario & Kanavos 2013; Carlson et al., 2010; Stafinski et al., 2010), within settings (Lu et al., 2015; Vitry & Roughead, 2014) and specifically within orphan medicinal products (Facey et al., 2021; Morel et al., 2013), whereas one study also explored the relationship between setting specific HTA governance & regulatory framework and the implementation of MEAs (Ferrario & Kanavos, 2015).

Overall, literature has demonstrated great variation on the types, tools and targeted objectives of MEAs implemented across settings. Nevertheless, there is no quantitative evidence to identify the determinants and methodological strategies, at the HTA decision-making level, that lie behind the uptake of these agreements, and more importantly, behind the variation observed among countries on the strategies followed for the implementation of MEAs. More specifically, the most comprehensive study on the implementation strategies of MEAs in Europe showcased that a common trend of MEAs across settings is that these are typically applied for highly priced, innovative medicines presenting with limited evidence about their long-term effectiveness in real clinical practice, and these were mainly antineoplastic and immunomodulating agents (38% of existing agreements), followed by alimentary tract/ metabolism medicines (Ferrario & Kanavos, 2013). However, it was highlighted that only in limited cases countries implemented a MEA for the same medicine-indication pair and even in these cases, there was still variation in the type/tool of the MEA in place (Ferrario & Kanavos, 2013). For example, among the same sample of medicines studied across countries, it was shown that Italy mostly engaged in outcomes-based agreements implemented through "conditional study continuation" and/or "pay for performance", Netherlands and Sweden also applied outcomes-based agreements but mainly through "CED" mechanisms, whereas England almost exclusively applied financial based agreements using "discounts". Ferrario & Kanavos (2015) also observed that overall countries are targeting three main objectives when implementing MEAs, namely management of budget impact, management of uncertainty relating to clinical and/or cost-effectiveness, and management of utilization to optimize performance in real clinical practice. Nevertheless, the type of objective targeted by agreements implemented across settings is often different even for the same pharmaceutical product, presenting with similar uncertainties. Both studies suggested that health system specific context, and perception of MEAs across settings might only partly determine such differences and thus, directed future research to also explore the relative role of other decision-making related criteria (such as the interpretation of the evidence submitted for HTA purposes and its respective uncertainties) which might explain more thoroughly the drivers of such variations (Ferrario & Kanavos, 2015; Ferrario & Kanavos, 2013).

Similarly, a study focusing on the experience with MEAs in a specific therapeutic area (i.e., orphan indications) confirmed that a variety of schemes were increasingly used by European payers to manage aspects of uncertainty (which might be of a clinical, utilisation, or budgetary nature) associated with the introduction of orphan medicinal products in the various healthcare

systems, although differences were observed in the type of agreements introduced (Morel et al., 2013). It was suggested that such differences were determined by differences in how different healthcare systems deal with 'uncertainties' in HTA decision-making, although this relationship was not explored further (Morel et al., 2013). Carlson et al., (2010) also concluded that the implemented schemes identified at an international level provided a picture as to what types of products might be candidates for outcomes-based schemes and suggested that factors such as disease areas with high unmet need, high cost, variable treatment duration, and their respective uncertainties around long-term benefits might play a significant role in implementing an agreement. However, there was no additional analysis conducted to explore the relative importance of each of the above determinants in relation to the studied MEAs.

Another review of outcomes-based schemes implemented for two orphan drugs across countries in the European Union, Australia and Canada explored how different health systems had established and implemented both individual and population-based outcomes-based schemes. However, the aim of the study was to identify good practices followed across the countries for the implementation of outcomes-based schemes, in order to inform the development of a broader framework that could help support the application of these schemes for rare disease treatments (Facey et al., 2021). Therefore, the authors did not provide any conclusions as to the determinants of the different implementation strategies observed across countries.

Finally, a recent qualitative review of MEAs in Europe from 2000–2015 discussed the broader socioeconomic factors that contributed to the increased uptake of MEAs across countries (GaBi, 2018; Piatckiewicz et al., 2017). For example, it discussed factors such as the increased push and demands for Value Based Pricing (VBP) made by national healthcare payers during the early 2000s, the economic crisis, and its implications towards a greater push to contain costs and focus on cost-effectiveness. Similar to other findings reported in the literature as described above, the report also concluded that each country within the EU has adopted different strategies and developed different relationships with HTAs, which have led to noticeable differences in drug benefit evaluations, recommendations, and overall levels of access across the EU markets. Nevertheless, the authors did not discuss the determinants of the MEAs uptake and divergence between countries at the HTA decision-making level.

2.3 Literature on the outcomes of Managed Entry Agreements

Despite the increased interest and discussions around the implementation of MEAs, evidence about their impact on achieving their key objectives remains scarce and primarily descriptive. More precisely, several studies have attempted to estimate the financial impact of MEAs (Clopes et al., 2017; Fagnani et al., 2016, Barros, 2011, Gandjour, 2008; Zaric and Xie, 2009; Zaric and O'Brien, 2005) based on a theoretical economic model approach. Additionally, a number of studies have also provided descriptive considerations around the impact of MEAs on key healthcare system policy goals in the context of describing their strengths, risks and opportunities (Wenzl & Chapman, 2019; Kanavos et al., 2017, Ferrario & Kanavos, 2013). Other theoretical approaches to evaluating the impact of MEAs include studies reviewing their impact on patient access to innovation (Stafinski et al., 2010) and on the incentive to invest in Research and Development (R&D) (Cook et al., 2008; Levaggi et al., 2017).

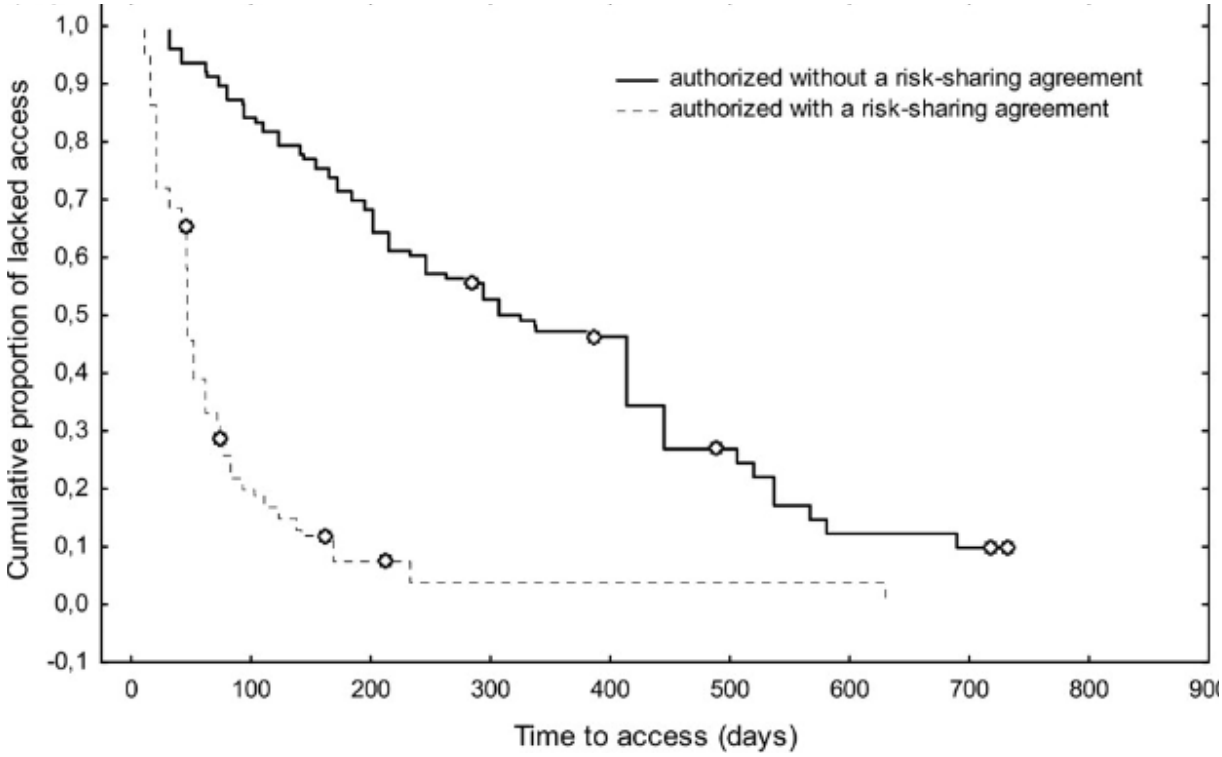
In terms of impact on improved access a descriptive analysis of 49 oncology indications in 13 countries/regions showed that in countries where cost-effectiveness is strictly applied, namely Canada, Australia, Scotland, England and New Zealand a high percentage of rejections has been observed due to the poor cost-effectiveness profile of the technologies, although many of these initially rejected medicines were eventually granted access following resubmission with a MEA mainly utilised to contain costs (Wilsdon et al., 2014; Cheema et al. (2012)).

Another study carried out a descriptive impact analysis of the risk sharing schemes on patients' access in South Korea. It was found that MEAs in South Korea significantly enhanced patients' access to new medicines and led to the alleviation of patients' out-of-pocket expenses. More specifically, as of the first half of 2019, out of 64 indications studied 52 indications (81.3%) were reimbursed, of which 39 (75%) were reimbursed with a MEA (primarily a financial based scheme), while the remaining 12 indications were not reimbursed or approved. Additionally, it was observed that after introduction of MEAs, the time gap between market approval and reimbursement was remarkably decreased. Medicines approved before MEAs took 1,167 days for reimbursement, whereas following the implementation of MEAs time to funding recommendation decision was reduced by about eight months (i.e., taking 924 days) (Lee et al., 2021).

Finally, a comprehensive review focusing on MEAs implemented in the Central and Eastern Europe (CEE) provided a theoretical/ qualitative analysis on the overall impact of MEAs on achieving sustainable outcomes (Ferrario et al., 2017). This study suggested that MEAs are unlikely to provide a sustainable solution to improving access to cost- effective medicines that bring a meaningful added value to patients, since it was observed that countries that implement MEA are still struggling in balancing patient access and budget impact (Ferrario et al., 2017). However, the above conclusions were only of observational nature since they were based on qualitative evidence from interviews with stakeholders.

An even more limited body of literature corresponds to empirical studies that assess the impact of MEAs (Gamba et al., 2020). A few studies based on statistical analyses provided quantitative evidence on the impact of implemented MEAs on reducing time to market access (Urbinati et al., 2017; Russo et al., 2010), on ensuring patient access (Maynou & Cairns 2017; Palace et al., 2015) and affecting list prices of pharmaceuticals (Gamba et al., 2020). More precisely, two studies conducted in Italy (Urbinati et al., 2017; Russo et al., 2010) provided quantitative evidence about the impact of MEAs implemented to date across the Italian regions on improving access to medicines. The former showcased that that the existence of a MEA can be a predictor of faster access to medicines only in cases of non-outcomes-based agreements (11.5 vs. 16.4 months for outcomes based), whereas the later demonstrated that overall, reimbursement with a MEA (regardless of type) was associated with faster patient access, characterized by a mean shortening of 256 days vs. a median of 342.7 days for the access of products reimbursed without an agreement *(Figure 4*). Urbinati et al. (2017) concluded that MEAs have become a key factor towards patient access in the Italian Market, although the authors concluded that MEAs still require better defined implementation procedures in order to achieve faster access to medicines. Similarly, Russo et al. (2010) suggested that it is still complicated to draw conclusions on the overall impact of MEAs across the different regions in Italy or even across countries due to opposing health system perspectives, different assessment/decision-making criteria, different market access/purchasing strategies and country specific market sizes.

Figure 4. Trendline of time to patient access (in days) for oncology medicines approved with vs. without a MEA across the Italian regions.



Source: Russo et al., 2010.

Additionally, again in support of non-outcomes-based agreements, an econometric analysis exploring the determinants of HTA decision outcomes across several European countries demonstrated that the existence of a financial MEA was associated with a higher probability of a favourable reimbursement decision (Maynou & Cairns, 2017). Another study evaluating the early results of the outcomes-based Multiple Sclerosis (MS) Risk-Sharing Scheme (RSS) in the UK (DoH, 2007) has demonstrated (based on observational data) that first line Disease Modifying Therapies (DMTs) for Relapsing Remitting Multiple Sclerosis (RRMS) covered under that scheme represent cost-effective options for the management of relapsing-remitting MS, although the final 10 year analysis would still be required to ensure whether these benefits can be sustainable or not (Palace et al., 2015). In continuation to this, the final 10 year analysis of the scheme concluded that Glatiramer Acetate provided under the RSS had a beneficial effect on long-term disability and was a cost-effective treatment for RRMS (Giovannoni et al., 2019).

Another quantitative impact assessment study that was conducted across a number of countries focused on the impact of MEAs on list prices, through a comparison of prices before and after any deductions due to the agreement (Gamba et al., 2020). Using a theoretical model, the above study showed that under most price setting regimes, the introduction of a MEA led to a higher list price. More precisely, the empirical analysis conducted in this study, which was based on a case study of 156 medicine indication pairs in six countries, estimated that the increase in price due to the MEA was nearly 6%. Therefore, a relevant policy implication in terms of the overall impact of MEAs was that payers may overestimate the financial gains that can be achieved through this tool (Gamba et al., 2020). Finally, a report produced by The Belgian Health Care Knowledge Centre (KCE)[1] (KCE, 2017) provided a theoretical evaluation on the outcomes of Belgian managed entry schemes that were terminated at the time of analysis and concluded that clinical uncertainties would not necessarily be addressed following the completion of a scheme, as once a product had already been reimbursed for some years, re-evaluation of its clinical effectiveness was not feasible. However, the report highlighted that due to data unavailability on the discussions and monitoring requirements shaping these agreements the outcomes on reducing uncertainty still remained unclear. Similarly, the impact assessment on budgets also remained ambiguous; despite the promising financial compensation figures presented by the Belgian National Institute for Health and Disability Insurance in 2015 (i.e., a compensation of more than a quarter of the turnover for all technologies under MEAs), the authors suggested that these financial gains should be interpreted with caution as it is unclear whether these technologies corresponded to an equally meaningful added value for patients. The same report also provided an overview of MEA outcomes reported in other European countries and it was again highlighted that despite potential savings noted in Netherlands and France robust conclusions could not yet be drawn because due to confidentiality of the negotiations it was unknown whether the discounted price of the reimbursed products was already higher than that of their alternatives. Furthermore, for outcomes-based agreements it was concluded that in Switzerland and France since no public data on any of the monitoring registries was available, the impact on patient outcomes could not be estimated, whereas evaluation of CED in Sweden showed that even though it has

[1] The KCE is a semi-governmental institution whose mission is to advice policy-makers about the possibilities to obtain an efficient allocation of scarce healthcare resources that optimizes the quality and accessibility of healthcare.

generated helpful evidence regarding costs and appropriate use of high-cost medicines, it offered limited value for managing uncertainty around clinical effectiveness.

2.4 Gaps in the literature

Overall, the body of evidence on the implementation strategies and impact of MEAs' implemented to date is weak. According to the literature review as described above, the author identified a number of key gaps in the MEA relevant research and areas of limited understanding around the implementation of MEAs that still need to be researched further before these agreements become an established funding mechanism in the reimbursement policies across settings. More precisely these gaps and/or areas of interest for further research are the following:

1. The lack of transparency not only on the perception/definition of a MEAs among stakeholders (Vitry & Roughhead, 2014; Ferrario & Kanavos, 2013; Morel et al., 2013; Gandjour, 2008) but more importantly, also on the HTA related determinants driving the rationale for their use and their variation across settings (Ferrario & Kanavos 2015; Carlson et al., 2010; Adamski et al., 2010). More importantly, the study of MEAs and how they interact with the HTA process in different markets has been very limited and largely descriptive to date. As described above, the current MEA literature provides a thorough description about the growing use of MEAs, focusing mainly on understanding the strengths, and weaknesses of implementing these schemes, identifying the types of MEAs implemented across countries and developing taxonomies for categorising such schemes. Nevertheless, discussions and conclusions about the application of MEAs in the HTA context are scarce.

2. The significant lack of empirical evidence and monitoring on the impact of agreements applied across and within settings. Literature is particularly scarce on structured post-implementation evaluations of MEAs that assess their impact on critical healthcare system objectives goals such as managing budget impact, enhancing timely patient access to medicines and rewarding meaningful industry innovation (EC, 2018; KCE, 2017; Ferrario & Kanavos, 2015; Garrison et al., 2013; Kemp et al., 2011). In response to that, further questions arise about the ability of MEAs to achieve their targeted

objectives and hence, their sustainability and effectiveness within the current healthcare systems (Dabbous et al., 2020)

3. Finally, there is scarce evidence on the overall welfare effect of these schemes, which would account for the impact of MEAs on factors such as the burden arising from the heavy infrastructure and financial/ administrative prerequisites to implement these schemes and the challenges arising from inadequate and non-integrated information systems in monitoring the outcomes of these agreements (Barros 2011; Adamski et al., 2010; Carlson et al., 2010).

2.5 Research objectives

The use of MEAs has gained a substantial role in the funding negotiation practices followed across countries globally and particularly in Europe. Nevertheless, to date there have been no best practice guidelines and/or a "gold standard" in the implementation of MEAs. Despite the recognised advantages in the adoption of MEAs, this gap in MEAs research represents one of the key barriers that need to be overcome, so that the implementation of MEAs is carried out in full (Goncalves et al., 2018).

Based on the above literature gaps and suggestions for further research, the objective of this thesis was to increase the body of evidence in order to address the first two points through three individual research articles. Considering potential limitations with regards to availability of relevant public data, addressing the third point described above was beyond the scope of this thesis. Subsequently, this PhD thesis investigates two different, but intricately linked research questions relating to the determinants and the outcomes behind the implementation of MEAs. More specifically, this research had two objectives: first, to draw a clear picture on the definition and the HTA related drivers of MEAs across settings and second to evaluate the impact that concluded agreements had on key health policy goals in a pre-defined set of countries. Therefore, the proposed research will focus on two broader research questions centred around a) the determinants and b) the impact of MEAs, as described in the following box (Box 1).

Box 1. Summary of broader research questions addressed in this thesis.

A. *What is the setting specific HTA context and variables that determine:*

i) the uptake and differences In MEA implementation practices across settings and

ii) the type of MEAs implemented across settings?

B. *What is the impact of currently implemented MEAs on key health system policy goals?*

Each of the broader research question corresponds to a distinct sub-set of interlinked research topics/hypotheses that were addressed through three different research articles as described below (Boxes 2-4). The first article provided an understanding on how setting specific HTAs influence the uptake of MEAs. The key objective of this research article was to provide an analytical framework which maps key HTA decision-making factors and uncertainties that drive the implementation of these agreements for oncology products across settings, and ultimately showcases why new antineoplastic and immunomodulatory therapies presenting with similar uncertainties across countries have been dealt with different "risk sharing" strategies across countries (Box 2).

Box 2. Research article I - Research hypothesis and objective.

Research hypothesis

HTA system-specific considerations (i.e., health system, HTA perspective etc.) as well as HTA decision- making criteria determine the uptake of MEAs across settings.

Research objective

- Conduct a descriptive, primary analysis of the HTA appraisals for oncology medicines approved in Australia, England, Scotland and Sweden between 2009 and 2018, to understand; i) the extent to which MEAs implemented for these medicines across the study countries differ and ii) identify key trends on the decision-making uncertainties and other clinical/economic considerations raised by each HTA body as contributing factors towards the implementation of a MEA among the study sample of medicine-indication pairs.

Subsequently, building on findings from research article I, the second research article provided an in depth, econometric analysis of the HTA decision-making factors and uncertainties that drive not only the implementation of MEAs across settings but also the type of MEAs implemented. More specifically, it explored by means of statistical evaluation if there are any associations between certain HTA-related variables and a) the existence and b) the type of MEAs applied for oncology products across different healthcare systems and if so, identify the relative importance of such associations (Box 3).

Finally, the third research article addressed the final broader research question of this thesis which focuses on the impact of implemented agreements. Specifically, this article tested the hypothesis that MEAs can promote availability of and timely patient access to medicines aiming to enhance the body of literature that provides concrete evidence and conclusions on the impact of MEAs (Box 4).

Box 3. Research article II - Research hypothesis and objective.

Research hypothesis

HTA system specific variables and decision-making criteria determine:

i) The existence and

ii) The type of MEAs across settings

Research objective

- Explore if there is any statistical association between HTA-specific endpoints (e.g., clinically meaningful endpoints, ICER etc.) and other social value and HTA system-specific considerations (e.g., severity of targeted disease, availability of alternatives, "end-of-life" treatments etc.) and: i) the existence and ii) the type of MEAs applied across settings for oncology products and if so, identify the relative importance of these associations.

Box 4. Research article III - Research hypothesis and objectives.

Research hypothesis

MEAs can promote availability of and timely access to new, high-cost medicines.

Research objective

- Conduct an econometric analysis of MEAs applied in Australia, England, Scotland and Sweden for new cancer medicines between 2009 and 2018 in order to understand if they managed to achieve their targeted objectives, namely if they contributed to enhanced availability and more timely access to medicines.

2.6 Contribution of this thesis

The rapidly growing number of high-cost medicines entering the pharmaceutical market poses challenges around the affordability and long-term financing of these technologies. More importantly, this highlights the need for a methodological guidance on how healthcare decision-makers can optimise the entry of new pharmaceuticals, such that they ensure financial sustainability of healthcare systems but also encourage the development of new, cost-effective treatments to address areas of unmet clinical need (WHO, 2015). Towards that goal, significant focus has been placed on the role and application of MEAs in managing the entry of new, highly priced pharmaceuticals in the market. Even though literature has recognised the potential of MEAs to improve patient access and optimise market availability of such technologies, considerable debate and lack of pragmatic evidence remains in the literature around their long-term outcomes (EC, 2018; KCE, 2017; Ferrario et al., 2017).

Given the growing trend towards risk sharing based reimbursement, the above concerns pending around the implementation of MEAs necessitate that key stakeholders are provided with quantitative evidence about the role of MEAs in reimbursement decisions. More importantly, this can also support countries that do not yet implement MEA practices as part of their funding negotiations to understand the applicability and sustainability of these schemes to their own market. Essentially, literature has recognised that due to the confidential context in which these agreements operate, a shared understanding of the factors that drive the use of MEAs across countries is necessary to develop a transparent methodological framework that facilitates MEAs negotiations and implementation; this is not only necessary but should

actually be considered as an essential part of the global launch plan for new medicines (WHO, 2015; Ando, 2011).

Therefore, the main contribution of this thesis is that it will go beyond the mere descriptive and theoretical analyses that have described the experience with MEAs to date. The econometric analyses conducted in this research allowed the author to draw concrete conclusions and enhance transparency around the drivers and the outcomes of MEAs at the international level. More importantly, the combined findings of this thesis are particularly useful in shaping a comprehensive empirical framework for HTA stakeholders and decision-makers which provides guidance on how to apply MEAs in order to optimize decisions under uncertainty about the market entry of new, high-cost medicines.

3. Methodology

As outlined above, this thesis is centred around three, individual but intricately linked pieces of research, which comprise both qualitative and quantitative methodological aspects, and their respective findings have provided the contents for three peer reviewed articles. Each chapter has its own methodological components as described in the respective sections. However, the sample of medicine-indication pairs studied in the three articles is the same and therefore, a common, overarching methodology for the sample selection and data collection is shared between the three different research articles of this thesis. The common processes followed for sample selection, data collection and management, as well as an outline of the data analysis methods used for each research article are presented below.

3.1 Sample selection

3.1.1 Selection of therapeutic area

The therapeutic area studied in this thesis was oncology. Oncology was selected among other therapeutic areas as it represents an area of significant and increasing financial burden for healthcare systems, while also being characterised by the continuous introduction of innovative technologies with high level of uncertainty, which reflects the main interest of MEAs.

As described in the introduction, oncology is the first among the top three therapeutic areas representing the highest pharmaceutical spend across Europe, while pharmaceutical spend growth is also forecast to be the highest in oncology (Greiner et al., 2020). The rising costs of novel cancer therapies not only raise issues for the budgets of healthcare systems per se but also around the sustainable financing of these therapies with immediate implications for patient access. Therefore, oncology was selected as the study therapeutic area for this thesis as it is also an area that specifically presents with significant issues around patient access, which is the subject matter of this thesis.

More precisely, the key differentiation of oncology from other therapeutic areas which explains why cancer medicines are more likely to face issues around funding and subsequently around patient access relates to their higher cost per QALY profile compared to the QALY profile exhibited by medicines targeting other therapeutic areas. For example, between the three highest therapy areas for pharmaceutical spend, namely oncology, diabetes and autoimmune diseases, it was found that in terms of their health economic value, diabetes therapies had a QALY benefit nearly 30 times higher than those for oncology and three times higher than those

for autoimmune diseases (Greiner et al., 2020). Additionally, while similar evidentiary requirements exist for the regulatory and funding approval of cancer and non-cancer medicines, the evaluation of cancer medicines often entails additional challenges which make it difficult for these medicines to demonstrate their long-term, health economic "value" relative to alternatives. Despite the implementation of oncology specific value frameworks such as the European Society for Medical Oncology Magnitude of Clinical Benefit Scale which evaluates clinical efficacy, the American Society of Clinical Oncology value framework which specifically also considers cost, among other outcomes and a Canadian value framework which also includes considerations of unmet need, and disease severity as part of the decision-making process, it is still challenging for cancer medicines to justify their prices in relation to the value they offer in terms of outcomes (Leighl et al., 2021). As described in more detail in Chapter 1, section 1.2, these challenges primarily arise due to the immature and/or poor quality of clinical evidence arising from clinical trials of cancer medicines compared to medicines for other therapeutic categories (Ciani et al., 2014).

Furthermore, another distinct feature of oncology compared to other therapeutic areas is the rapid innovations characterising this therapeutic area, which often translate in improved, long-term mortality prospects. In terms of funding recommendations, this is important because improved mortality as opposed to morbidity often ranks high in the factors that shape decision-making both for payers and the society, leading to prioritisation of oncology over other therapeutic areas based on societal preferences (Greiner et al., 2020).

Additionally, the therapeutic areas of oncology (including rare cancers), Multiple Sclerosis (MS) and Hepatitis C are typically among the primary therapeutic classes where MEAs are applied (Ferrario & Kanavos, 2013), although most of the MEAs that have been implemented so far correspond to oncology products (Goncalves et al.,2018; Ferrario & Kanavos, 2013; Espin et al., 2011). Since the objective of this thesis was to examine the role of MEAs as a reimbursement mechanism towards improved access to medicines, oncology was selected as the therapeutic area that presents both with issues around access to medicines and with a sufficient sample of implemented MEAs. Therefore, as the study sample comprised cancer medicines only, using the anatomic therapeutic chemical (ATC) search function for European Public Assessment Reports (EPAR) available from the website of the European Medicines Agency (EMA), all antineoplastic (ATC-L01/L02) agents authorised in the European Union (EU) between 2009 and 2018 were identified. Similarly, through the Therapeutic Goods

Administration (TGA) website, the Australian Register of Therapeutic Goods (ATRG) database was searched to find all antineoplastic (ATC-L01/L02) medicines that were registered to be lawfully supplied in Australia during the timeframe of interest. Medicines that were withdrawn post-approval, suspended, or refused were not included.

To create a homogenous sample, generics and biosimilars were excluded. Additionally, although the subject matter of this study was cancer, I did not include immunostimulant medicines (ATC-L03) because only some of these are indicated for cancer treatment.[2] Finally, this analysis covered only medicines reimbursed at the national level and for which publicly available reports were available from the respective HTA bodies on National Competent Authorities (NCAs). Therefore, medicines for which reimbursement was negotiated at the hospital level were excluded from this study.

The final list included 53 different molecules (i.e., different brand names) of which 15 (28%) had multiple cancer indications and therefore, corresponding to 74 distinct medicine-indication pairs studied in total across the four countries, yielding a working sample of n=296 observations (medicine indication pairs studied analysis is provided as Appendix – see Appendix 2).

3.1.2 Country selection and geographic scope

The geographic scope of the study included Australia (AUS), England (ENG), Scotland (SCOT) and Sweden (SE). These countries were selected for inclusion in the study because they all use HTA to guide their coverage decisions and they all largely implement MEAs. The HTA committees in England, Scotland and Sweden can advise to varying extents on the type of MEA that can be implemented, whereas in Sweden it can also propose MEAs (Ferrario & Kanavos, 2015). In Australia, PBAC can also play a role in defining clauses in the agreement and in influencing the Australian Government's decisions on all types of MEAs (Robinson et al., 2017). Furthermore, these countries were selected because they have publicly available HTA reports, and a publicly available list of MEAs, whereby the level of information provided is sufficient to gather information for the required analyses. More importantly, these countries were selected because they consider different factors in their decision-making process around

[2] In the ATC-L04, one antineoplastic agent was identified and included for analysis.

pricing and reimbursement of pharmaceuticals and therefore, reflect diversity in their HTA reimbursement decisions and the respective HTA determinants of access (Nicod & Kanavos, 2016) (Table 1).

Table 1. Study countries, their HTA agencies and respective perspective taken into HTA decision- making.

Study country	HTA body	HTA perspective	HTA Website searched
England	NICE: National Institute for Health and Care Excellence	Clinical and cost-effectiveness, national health and personal social services perspective	https://www.nice.org.uk
Scotland	SMC: Scottish Medicines Consortium	Clinical and cost-effectiveness, national health and personal social services perspective	https://www.scottishmedicines.org.uk
Sweden	TLV: Dental and Pharmaceutical Benefits Board	Clinical and cost-effectiveness, societal perspective	https://www.tlv.se/in-english.html
Australia	PBAC: Pharmaceutical Benefits Advisory Committee	Clinical and cost-effectiveness, national health system and societal perspective	https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings

Note: The health economic evaluation takes either a societal perspective – taking into account indirect costs of treatment and illnesses (as in Sweden) – or a health system perspective, in which only direct costs to the healthcare system are considered (as in England and Scotland). Some countries employ a mix of societal and health system perspectives (WHO 2015).

The different modalities in the pricing and reimbursement processes, including processes for the implementation of MEAs, followed across the study countries are presented below:

Australia

In Australia, the Pharmaceutical Benefits Scheme (PBS) is the public pharmaceutical insurance system. PBAC is an independent HTA body that appraises the evidence submitted by manufacturers on the medicines' health benefits and estimated financial implications for the

government and accordingly, makes recommendations for the inclusion of medicines in the positive PBS list based on their clinical and cost effectiveness profile (Robinson et al., 2017; Vitry & Roughhead, 2014). Funding recommendation decisions can fall under three broader categories, namely PBAC can decide to i) recommend the medicine to be listed on the PBS or the circumstances through which a medicine is already listed to be changed, ii) not to recommend the medicine to be listed on the PBS or the circumstances through which a medicine is already listed be changed and iii) defer a decision pending the provision of specific additional information that would be relevant and important to its decision (PBAC, 2003). However, a PBAC decision to not recommend listing of a medicine does not represent a final PBAC opinion about this medicine and is subject to review whenever a new submission is lodged (PBAC, 2003).

Often, the evidence submitted by manufacturers may not be sufficient for PBAC to reach a confident decision about the clinical benefit and financial implications of a medicine (Robinson et al., 2017). As such, MEAs have been employed increasingly in Australia since 2003 as an integral part of the funding decision-making process, aiming to address the uncertainties arising from this equivocal evidence. In general, the majority of agreements implemented in Australia refer to two types of arrangements, namely, special pricing arrangements (SPAs) and risk sharing arrangements. SPAs have a published and a real, confidential price, whereby the refund by manufacturers should follow the difference between the two prices. Risk-sharing arrangements aim to address various potential risks associated with the reimbursement of new technologies with evidentiary uncertainties, including risks around cost-effectiveness, overall cost to the PBS, overall health gain requiring data collection and monitoring, and overall utilization related to the number of patients (Lee et al., 2021).

These two arrangements mainly manage financial-related risks and therefore correspond to financial based contracts including price or volume rebates, refund with subsidization or expenditure cap or combinations of these (Tuffaha & Scuffham, 2018). However, since 2011 outcomes oriented Managed Entry Schemes (MES) have also been implemented in Australia to share the risks related to uncertainties around clinical efficacy (Lee et al., 2021). MES aim to ensure continuation of funding subject to subsequent provision of favourable efficacy data at the population level (Vitry et al., 2016). Under MES, an initial price of the medicine is established and evidence from clinical trials must be submitted to the PBAC within a specified timeframe. By reviewing resubmitted data, the PBAC can propose a final recommendation for

the PBS listing and the medicine price will be reset at this future time. (Lee et al., 2021). Prior approval to continue funding is based on the information provided by the prescribers about the patients' outcomes while on the medicine and these arrangements are referred to as "continuation rules" in PBS restrictions (Robinson et al., 2017). Finally, although not a form of risk sharing, the life-saving drugs program (LSDP) was established in Australia since 1995 as an alternative funding option for specific essential medicines to treat patients with rare and life-threatening diseases (DH Australia, 2021).

England

In England and Wales, NICE is responsible for assessing the clinical and cost-effectiveness profile of medicines and other healthcare technologies. After reviewing the clinical and economic evidence submitted by manufacturers, NICE makes a recommendation about the use of a medicine or technology which can fall under four broad categories including: i) Recommended (i.e., the technology can be used as per its licensed indication) ii) Optimised (i.e., the technology is recommended for more restricted patient group than the one prescribed by the marketing authorisation, iii) Recommended for use only in research (i.e., the technology can be used only as part of a research study continuation) and iv) Not recommended (Ferrario & Kanavos, 2013). NICE typically uses the incremental cost-effectiveness ratio (ICER) threshold of £20,000 to £30,000 per QALY gained to reach a recommendation decision, although NICE appraisals suggest that various other factors are taken into consideration and a medicine can be recommended even if the ICER exceeds that threshold. More precisely, NICE will specifically take account of other factors, such as the level of certainty around the ICER, the innovation a new technology offers (i.e., in terms of mechanism of action or therapeutic advancement), other quality-of-life benefits that might have not been captured by the ICER, and the potential "life-extensive" nature of the treatment under assessment (Fontrier et al., 2021; Charokopou et al., 2015). Even though NICE recommendations per se do not necessarily correspond to a reimbursement decision for a medicine, NHS England is still legally obliged to provide funding for technologies recommended by NICE and in cases where a technology is not recommended by NICE this can still be provided subject to local NHS decisions about funding (Fontrier et al., 2021; Ferrario & Kanavos, 2013). In order to facilitate patient access to medicines which would have otherwise been rejected by NICE due to their non-favourable cost-effectiveness profile or due to uncertainties about their clinical benefit and costs, alternative funding arrangements have been implemented in England throughout the years.

The first arrangement that has been described as a form of MEA in England was implemented in 2002. This refers to an outcomes-based scheme, namely the Multiple Sclerosis Risk Sharing Scheme, as described earlier (see also section 2.2- Literature on outcomes), which monitored the long-term cost-effectiveness of a number of DMDs for RRMS by collecting data from over 5,000 patients for more than a decade (MS Trust, 2018). Nevertheless, since that scheme there has generally been little emphasis in England on implementing schemes that aim to generate additional evidence mainly because outcomes-based schemes have been deemed administratively burdensome for the NHS, the industry and the clinicians and health staff involved in the collection of additional data (Wenzl & Chapman, 2019). The option of outcomes-based agreements still exists but these are applied in limited cases (Ferrario & Kanavos, 2013). Therefore, NICE has since focused primarily on implementing financial based Patient Access Schemes (PAS) as a form of MEA. The PAS option was first described in 2009 in the context of VBP under the pharmaceutical price regulation scheme (PPRS) in England, which primarily outlined the principles for the development and implementation of PAS.

According to the PPRS, PAS in England are mainly targeted at bringing the cost-effectiveness of a medicine to an acceptable level for a favourable funding recommendation by NICE, and this is typically achieved by lowering the medicine cost. As such, PAS are usually implemented as two broader categories, namely a simple discount scheme and a complex scheme. The simple discount scheme involves a fixed pricing agreement that is lower than the list price of the treatment or a percentage discount from the list price, while complex schemes involve all other types including rebates, provision of upfront free stock, and outcomes-based dose capping without requiring additional monitoring such as an outcome-guarantee agreement (NICE PASLU).

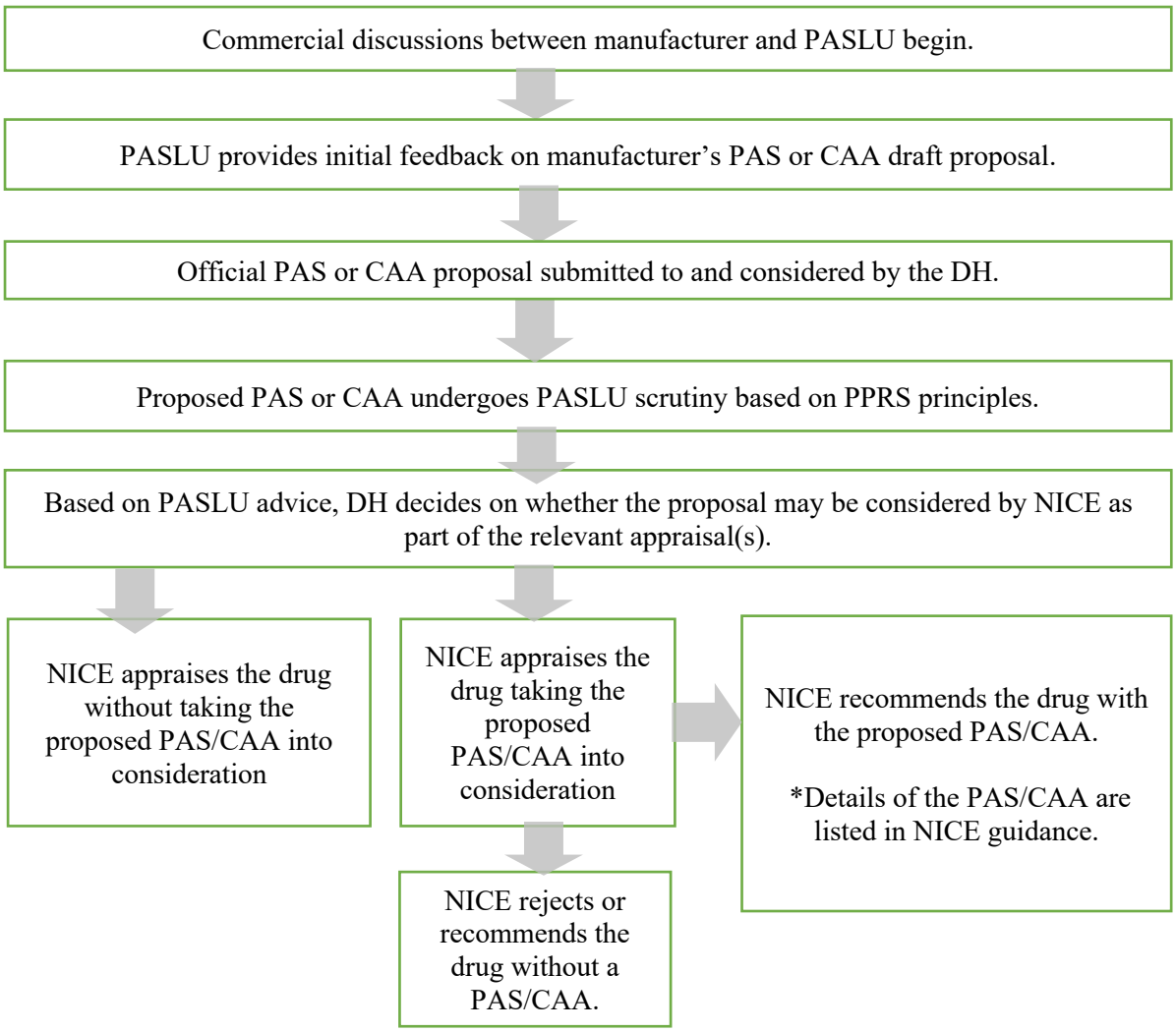
Additionally, for oncology medicines, in cases where a PAS is not approved, and NICE does not recommend the technology due to its non-favourable cost effectiveness profile, this can still be funded through a manged access fund, namely the CDF. More precisely, in 2011 the CDF was established to provide access to cancer medicines with unfavourable cost-effectiveness profile and hence, not recommended by the NICE. However, following equity controversies and criticism about inefficient resource allocation to medicines which might prove cost-ineffective, the CDF was reformed in 2016. Under the new CDF, if a promising cancer medicine presents with evidentiary or cost-effectiveness uncertainties it is recommended for “observation in the CDF”. This offers more time to collect evidence about

the efficacy of the medicine in practice, allowing for evidentiary gaps to be filled while interim funding and access is provided through the CDF, and until permanent funding can be achieved (Vintura 2020b; Vogler et al., 2018).

Even though traditionally the CDF has not been classified or treated as a MEA per se in the literature but instead as an alternative access fund, following its recent reform, both the literature and the relevant NICE guidance have described CDF a part of a managed access agreement which operates under the concept of population-level coverage with an evidence development (CED) (Wenzl & Chapman, 2019; NICE, 2021, NICE, 2018). More specifically, NICE states that when the appraisal committee decides to recommend a technology for use within the CDF, the company will be invited to propose a Commercial Access Agreement (CAA), or vary an existing agreement (NICE, 2018). This forms the CDF Managed Access Agreement (MAA), which is agreed between the company and NHS England and consists of two key components: i) Data Collection Arrangement – this sets out the outcomes that need to be collected in order to resolve the key areas of clinical uncertainty and ii) CDF Commercial Access Agreement (CAA) – this determines the cost of the medicine during the managed access period (NICE, 2021). Therefore, for the purposes of this thesis any NICE recommendation decisions falling under the new CDF will be treated as listed with a MEA.

The development and submission of a PAS or CAA by a manufacturer follows a designated, standalone procedure. More precisely, following the introduction of the PPRS, NICE was mandated by the Department of Health to establish the Patient Access Scheme Liaison Unit (PASLU) with its main purpose being to provide initial feedback to manufacturers about their draft proposals and subsequently, provide advice to the Department about the official PAS/CAA proposals submitted by manufacturers. Ultimately, a manufacturer suggested PAS or CAA can only be considered for the NICE appraisal process subject to approval from the Department of Health. The lifetime of the relevant guidance from the NICE also determines the duration of the MEA, but the exact agreement needs to be clear and conditions on MEA's termination need to be specified. In case of new indications or changes in the scheme type, a new MEA submission is required (Pauwels et al., 2017). The PASLU process is not part of the appraisal process. Changes could be made to a PAS proposal after NHS England has referred it to NICE, however, these must be discussed and agreed with NHS England (NICE, 2018). Figure 5 illustrates the pathway followed in England for PAS/CAA submission, approval and implementation; this process applies to all PAS proposals.

Figure 5. Simplified, schematic representation of the PAS or CAA development and approval process in England.



Key: CAA: Commercial Access Agreement, DH: Department of Health, PAS: Patient Access Scheme, PASLU: Patient Access Scheme Liaison Unit, PPRS: Pharmaceutical Price Regulation Scheme.

Source: The author based on Ferrario & Kanavos (2013) and NICE (2018).

Scotland

In Scotland, the SMC was established to advise NHS Scotland on whether a newly licensed technology should be funded based on its value for money profile from the NHS Scotland perspective. More precisely, as soon as possible following the launch of a product, SMC evaluates its clinical and cost related evidence as provided by the manufacturer and provides accordingly a central recommendation decision about the reimbursement of this product.

Similar to England, in Scotland, reimbursement is also predominantly based on the overarching principle of cost-effectiveness. SMC recommendation decisions can be categorised in four broader categories including: i) Acceptable for Use in NHS Scotland, ii) Acceptable for Restricted Use in NHS Scotland, whereby restrictions may relate to use within a specified patient population and/or use by specified prescribers, iii) Not recommended for use in NHS Scotland following a full appraisal, iv) Not recommended for use due to a non-submission (NHSAAA, 2012). A negative decision by SMC (i.e., the third category as described above) warrants re-submission and re-assessment of the set price for successful reimbursement (Charokopou et al., 2013).

Although the relationship between the SMC assessments and reimbursement decisions is not explicit, SMC recommendations are used as a guide to local health boards to define their drug formulary which determines the medicines that are reimbursed. As such, following completion of the SMC assessment process, its advice for NHS Scotland is published and the final formulary inclusion decision is made by the local health boards using this advice. NHS local boards will consider all advice produced by SMC but can still decide to exclude such medicines from their own local formulary, such as in cases where the medicine does not represent sufficient added benefit compared to existing medicines on the formulary for the same indication (Charokopou et al., 2015). Of course, only medicines approved by the SMC can be included in the local formularies and subsequently, once local health boards also recommend the medicines that should be used in their area, clinicians can then decide what to prescribe (Wilsdon et al., 2014).

To facilitate reimbursement decision-making and access to medicines, MEAs in the form of PAS are applied in Scotland too, whereby companies can propose a PAS to improve the cost effectiveness of a medicine (SMC, 2019). The Patient Access Scheme Assessment Group (PASAG) reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation and operates separately from SMC to maintain the integrity of the assessment process (Pauwels et al., 2017). There are two types of PAS in Scotland: simple discount schemes and complex schemes. Simple discount schemes are the preferred scheme type in NHS Scotland as they do not impose any significant additional burden to the NHS or pharmaceutical companies. Complex schemes include all other types of PAS such as: rebates (when medicine is supplied via secondary / tertiary care or homecare), stock supplied at zero cost, dose / spend capping, outcome-based schemes (based on patients' response to treatment). Experience with

complex schemes has been that they can introduce significant complexity and burden for the NHS Scotland and pharmaceutical companies and their perceived financial benefits may not be fully realised in practice. As such, MEAs in Scotland primarily refer to financial based PAS, while outcomes-based schemes tend to be accepted only in exceptional circumstances (SMC guidance). Finally, in terms of duration, PAS in Scotland are by rule applied for 5 years, unless there is a price decrease. After 5 years, the company can indicate to continue or stop the MEA however the product should continue to be available at the price agreed within the MEA or a lower list price (Pauwels et al., 2017).

Sweden

The Swedish healthcare payer system is highly decentralized, with 21 self-governed County Councils, each with its own administrative set up for management of medicines' procurement, use and cost control. The Swedish Dental and Pharmaceutical Benefits Agency (TLV) is the NCA responsible for assessing the cost-effectiveness of all new out-patients medicines introduced in the Swedish healthcare market and providing recommendations about the inclusion of medicines in the national reimbursement scheme. However, the Councils are the actual payers of the reimbursed medicines, and the degree and rate of a medicine's local uptake may vary between regions. County councils have different budget-planning mechanisms and varying interpretations of TLV assessments. Therefore, the New Therapies (NT) Council is a group of experts that supports the Swedish county councils on questions concerning new pharmaceutical therapies. The NT Council is commissioned to make recommendations to the county councils on the use of new pharmaceutical therapies, with the aim of enabling equal treatment for patients throughout the different regions of the country (Janusinfo, 2018).

For the purposes of this research, I took into consideration only the recommendations produced at the national level (i.e., at the TLV level) and as such, refer to TLV as the Swedish HTA agency. Firstly, TLV is the competent authority in Sweden responsible for pricing and reimbursement and as such, it also performs HTA. Additionally, a number of previous studies that have also explored cross-country differences in HTA recommendation decisions (e.g., Nicod & Kanavos 2016; Nicod & Kanavos, 2016b) TLV have also classified TLV as the Swedish HTA agency/body. Therefore, referring to and treating TLV as the Swedish HTA agency for the purposes of this analysis is in line with the literature.

TLV uses three main principles in its decision-making, including the principle of human value, the unmet need and solidarity principle and the cost-effectiveness principle (Fontrier et al., 2021). After reviewing the available evidence based on the above principles it makes one of the following three recommendations: i) Unconditional reimbursement (no restrictions on indications or patient eligibility), ii) Conditional reimbursement (with restrictions on indications or patient eligibility), and iii) Exclusion from reimbursement (Ferrario & Kanavos, 2013), typically for products with uncertain or high ICER (Jaroslawski & Toumi, 2011a).

Conditional reimbursement refers to three main situations: a) Reimbursement is recommended only when a medicine is used in specific indications, and/or for a specific level of severity of a particular condition, and/or for specific patient subgroups, but the manufacturer is not required to submit additional evidence about the medicine; b) Similar to the previous decision, although in this case the manufacturer is also requested to collect and provide additional data about the medicine in question; c) There are no restrictions around the indications, and/or level of disease severity, and/or patient population eligibility but there is a requirement for the manufacturer to submit additional data (Ferrario & Kanavos, 2013).

The nature of uncertainties addressed by MEAs applied in Sweden varies. The main goal of the agreements is to address uncertainties around cost-effectiveness and utilisation in real-life, including appropriate prescribing, although some agreements also look at long term clinical outcomes, including those on morbidity and mortality. As such, MEAs in Sweden typically fall under the second and third categories of the conditional reimbursement described above, whereby in addition to coverage being limited to a specific sub-population of patients, TLV may also request the manufacturer to collect additional data based on clinical practice and to re-submit the cost-effectiveness model. These agreements usually reflect coverage with evidence development contracts which allow an initial period of conditional coverage until the manufacturer submits favourable additional evidence to obtain unconditional coverage.

3.2 Data sources

Data collection was based on secondary sources to gather information on all medicine-indication pairs subject to a MEA between 2009 and 2018 in the four study countries. First, the websites of EMA and TGA were searched to obtain general information around the marketing authorisation characteristics of cancer medicines (approved between 2009 and 2018 in Europe and in Australia respectively). Additionally, ClinicalTrials.gov was searched to collect data

related to the design of the studies corresponding to the medicine-indication pairs in question. ClinicalTrials.gov is an international database for trial identification and their characteristics of privately and publicly funded clinical studies conducted around the world (ClinicalTrials.gov).

Publicly available sources such as HTA appraisals and reimbursement decisions from the websites of the respective NCAs or HTA bodies, namely PBAC, NICE, SMC and TLV were also searched to gather information around the HTA characteristics of the medicine-indication pairs studied, such as HTA recommendation decision dates, the outcome of these decisions and factors considered in the HTA decision-making process (see section 3.4.1- Description of variables). The search on NCAs' websites was conducted in local languages (English and Swedish) where possible to increase accuracy and comprehensiveness of the extraction and google translate was used to translate Swedish reports.

The analyses performed for the purposes of this thesis were based only on publicly available HTA reports or summaries of HTA reports. For chapters 4 and 5 only the final recommendation decisions were analysed. Therefore, the determinants were studied only based on data arising from the reports of the final recommendation decisions available from each HTA body, whether these corresponded to "full submission" reports (i.e., submissions for the first time) or resubmission reports following previous rejection. Appraisals that were labelled as "abbreviated submission" or "IRP guidance (Independent Review Panel)" were not taken into consideration for this analysis because they do not provide all the necessary information needed on the submitted evidence. To the best of the author's knowledge information arising from publicly available reports was sufficient to capture all the relevant information needed, including information on MEAs implemented, for the medicine indication pairs of the study sample. The author is not aware of any cases (among the study medicine-indication pairs) whereby a MEA was implemented, without this being accounted for in a publicly available, updated, final recommendation report for a specific product. Finally, for chapter 6, publicly available HTA reports corresponding to previous submissions (where available) were also searched to extract data on the timelines and outcomes of the previous decisions. Time was measured from the date of the very first funding recommendation decision available for each medicine-indication pair.

3.3 Conceptual framework

Based on the relevant literature on analysing HTA recommendation decisions and dealing with uncertainty in HTA decision-making a conceptual framework was developed to describe the main principles behind the nature of data that would need to be collected for the purposes of the analyses in this thesis and subsequently, facilitate and guide the respective data collection process (Morrell et al., 2018; Nicod et al., 2017; Nicod & Kanavos, 2016; Charokopou et al., 2015; Maynou & Cairns, 2015; Dakin et al., 2015; Cerri et al., 2014; Dakin et al., 2006; Devlin & Parkin, 2004) . The relevant literature has demonstrated that the quantity and quality of clinical evidence, including the type of study (e.g., Randomised Controlled Trial (RCT), observational study etc.) used in the submitted evidence, as well as the study design and characteristics (e.g., sample size, statistical significance and relevance of study endpoints) play a cardinal role in shaping HTA decision-making (Dakin et al., 2006). Additionally, beyond the ICER consideration, other economic considerations such as the modelling methodology itself and the evidence on cost may play a role (Devlin et al., 2004). Ultimately, it has been argued that it is the uncertainty around the evidence, primarily that on clinical effectiveness that has the highest contribution towards payers' decisions about coverage (Nicod, 2017; Dakin et al., 2006). Literature has also demonstrated that in addition to the clinical and economic base, HTA decision-making and the flexibility applied therein may be influenced by the nature of the disease for which the technology is indicated, including its rarity, severity and burden for the society, as well as characteristics of the intervention per se such as its route of administration and the unmet need it covers in terms of treatment alternatives (Nicod & Kanavos, 2016; Nicod & Kanavos, 2016b; Charokopou et al., 2015; Cerri et al., 2014; Harris et al., 2008; Dakin et al., 2006).

Based on the above observations, the conceptual framework used to guide the data collection conducted for this thesis operates under the overarching hypothesis that HTA funding decisions (whether positive, negative or restricted) are primarily shaped by the HTA decision-making process itself, including the evidence appraised therein (whether clinical, economic or otherwise), the way this evidence is interpreted/assessed by the decision-makers, and the broader socio-economic and political context in which the decision-making is taking place (Cerri et al., 2014). Essentially, this working framework divides the HTA decision-making process and relevant variables of interest in four buckets where it is hypothesised that a combination of variables within buckets (A), (B) and (C), determine the observed outcome in

bucket (D) as follows; **(A) Clinical and economic evidence appraised** (e.g., trial characteristics, comparators, Incremental Cost Effectiveness Ratio (ICER) and economic model specifications); **(B) Interpretation/assessment of this evidence** (i.e., clinical and economic evidence related uncertainties raised); **(C) Societal and system-specific context in which decision-making operates**; (i.e., dimensions of value that a technology adds in the society/setting of interest, such as the unmet need it targets in terms of therapeutic treatment availability, the societal benefit it offers in terms of improved patient QoL and functional ability outcomes etc.) and system-specific processes for decision-making (e.g., the use of a single or multiple technology appraisal in England); and **(D) Funding decision outcome**, which can be favourable, favourable with restrictions, favourable with restrictions that include a MEA as part of this restriction and non-favourable (Table 2; Figure 6).

The conceptual framework was used to build a common dataset applicable for the analyses conducted in all research articles. However, due to its importance and novelty in the classification of restricted funding outcomes it has been presented as a distinct part of research article I, and therefore, more details, as well as a schematic representation of the framework have been included in the respective chapter (***see chapter 4, section 4.2.2; Figure 6***).

A specific feature of this thesis is that it classifies funding with a MEA as a distinct funding decision outcome under bucket (D) (Table 2). Therefore, according to the hypothesis of the framework, the uptake of MEAs should be determined by variables within buckets (A), (B) and (C) based on the following equation (1):

$$\boldsymbol{MEA_{ij} = \alpha_0 + \beta_1 SC_{ij} + \beta_2 MC_{ij} + \beta_3 SU_{ij} + \beta_4 MU_{ij} + \beta_5 V_{ij} + e_i} \quad \textbf{(1)}$$

Where:

- MEA_{ij} is the decision to fund with a MEA in setting *i* and medicine-indication pair *j,*
- SC_{ij}, denotes a vector capturing study and respective clinical evidence characteristics
- MC_{ij} denotes a vector capturing model and respective economic evidence characteristics

- SU_{ij}, represents an uncertainty component around the study and respective clinical evidence
- MU_{ij} represents an uncertainty component around the model and respective economic evidence
- V_{ij} reflects a vector capturing value (societal and characteristics of the product)
- $\beta_1,\beta_2,\ldots,\beta_5$ are unknown vectors of regression coefficients

And

- e_i is a random error component

3.4 Data collection

3.4.1 Description of variables

As explained above, a significant proportion of the molecules included in this study sample had more than one oncology related indication and these molecules/brand names had separate HTA appraisals and respective funding recommendations for each of their clinical indication. Therefore, data for this study was collected for each available indication of each medicine (i.e., at the medicine indication pair level).

General characteristics for each medicine indication pair in question were collected from the EMA and TGA websites. More specifically the variables collected here included: molecule and brand name, manufacturer or marketing authorisation holder, indication(s) under review, EMA and TGA marketing authorisation date, scheme of marketing authorisation approval and orphan designation (Table 6). Information was extracted on the date of marketing authorisation in Europe and Australia for the first indication and, if applicable, the date of authorisation of additional cancer indications (only authorisation of indications for different types of cancer), not extension of indications within already approved cancers (e.g., new early breast cancer, previously only metastatic cancer)). For the second part of the data collection, the websites of NCAs were searched to collect data specific to the HTA appraisal and funding decision (Sweden) or recommendation for use (Australia, England, Scotland) of each medicine-indication pair. First, I extracted information on the date and outcome of the final recommendation or reimbursement decision available for each indication of a medicine from the websites of NCAs (the dates collected reflect the dates when the summary HTA appraisal

and recommendation reports were published). For the purposes of chapter 6, I also extracted information on previous funding or recommendation decisions (if any), including date and funding decision outcome. In terms of the funding decision, it is important to highlight here that it was preferred to treat the final decision outcome as a four category outcome variable, namely "Listed", "Listed with restrictions (excluding a MEA)", "Listed with restrictions, including a MEA" and "Do not list" (Table 2), instead of the three outcome variable traditionally used in the HTA literature (i.e., listed, restricted, rejected) as it better reflects the multiple coverage options available when studying restricted HTA decisions. Importantly, this granularity between the two different levels of restricted outcomes (i.e., with vs. without a MEA) has implications for the econometric modelling of the funding decisions, given that often, the weight placed on the different types of evidence appraised, or the criteria applied to assess this evidence may vary between these different types of restrictions (Dakin et al., 2006).

Table 2. Classification of HTA funding recommendation decision, as used for the purposes of this thesis.

Type of funding decision	
L	List (i.e., positive funding recommendation decision, with no restrictions/conditions for approval)
LWC	List with restrictions but which are not perceived by the HTA body as MEAs (i.e., clinical restrictions as to treatment eligible sub-population)
LWCMEA	Listed with restriction(s) including, among other restrictions (if any), a restriction perceived by the HTA body as MEA
DNL	Do not list (i.e., negative funding recommendation decision)

Furthermore, for the purposes of this thesis the definition of a restriction was based on the concept that only where a recommendation is made for a technology to be used in a population identical to its EMA/TGA licensed indication, it is considered as 'Listed'. Alternatively, when the recommendation with one of the following conditions in relation to the technology, is considered to be "Listed With Restriction(s)": (i) it should be used in a sub-population of its licensed indication; (ii) it should be used in a second line or higher line of therapy; (iii) it required monitoring; (iv) it should be used at the lowest acquisition cost; or (v) it required prescription by a specialist (Raftery, 2006). Table 3 summarises the different types of restrictions that are typically applied as part of the funding decision outcomes across the study

countries. Additionally, based on the framework of the working hypothesis (see section 3.3) three other broad categories of variables were collected relating to: i) the clinical evidence submitted by manufacturers, ii) the interpretation of this evidence by HTA decision-makers and iii) the social value judgments considered by HTA decision-makers. More precisely, variables under the evidence submitted included, among others, trial design and duration, study population and subgroup data, comparators, treatment outcomes and safety. Those under uncertainties included both clinical and economic while variables relating to additional qualitative considerations included among others, considerations around innovation, unmet need, and disease severity (Table 4). All dimensions of uncertainties and SVJs were applicable to all medicine-indication pairs studied and each dimension was either raised or not raised and considered or not considered respectively in the decision-making process. Moreover, variables on MEAs, including type of MEA, start/end date, tools used to implement MEA, their objective and targeted uncertainties were also collected for each medicine-indication pair (Table 4). The classification used to assign categories in the typology and tools of MEAs was based on previous studies describing the methods used to implement MEAs and has been described extensively in chapter 1; section 1.3 (Toumi et al, 2017; Robinson et al., 2017; Ferrario & Kanavos, 2013; Garrison et al., 2013; Walker et al., 2012; Toumi & Jaroslawski, 2011; Jaroslawski & Toumi, 2011b; Carlson et al., 2010) (Figures 1-3). The full dataset used for the purposes of this thesis included 97 variables, of which 26 were used for the analyses conducted for this thesis. A detailed list of all the variables collected under each broader category described above, a respective description/definition (where applicable) and possible sets of values (where applicable) of each variable is presented in Table 4.

Data collection was performed between June and December 2018, and the data collection process and the sample used for this analysis comprises part of a larger sample of drugs studied for a different, broader research initiative on HTA (IMPACT-HTA project funded through Horizon 2020). Nevertheless, the aims of that research initiative are not related to this thesis, and neither is the conceptual framework used for data analysis. This thesis did not receive any funding related to the above-mentioned research initiative. The only common elements between the two studies relate to the overarching principles followed for data collection, as well as the classification and validation of dimensions studied. A team of researchers involved in the IMPACT-HTA including the thesis author, identified all potential variables of interest and these were then validated through a series of consultations between the researchers and HTA experts.

Table 3. Taxonomy of applicable restrictions per study country.

	Clinical restrictions	Administrative restrictions	Economic restrictions
Australia (PBAC)	Population restriction Dosing restriction	Section 100 - Highly Specialised Drugs Program (HSDP) Authority required (streamlined/telephone) Life Saving Drugs Program (LSDP) Safety Net early supply rule	Cost-minimisation Risk Sharing Agreement (RSA) Managed Entry Scheme (MES)
England (NICE)	Population restriction Dosing restriction	Cancer Drugs Fund	Patient access schemes Commercial Access Agreement
Scotland (SMC)	Population restriction	Not applicable	Patient access schemes
Sweden (TLV)	Population restriction	Additional data required	Risk Sharing arrangement Coverage with Evidence Development

Note:

- **Population restriction:** funding is restricted only to a specific sub-population within the population defined in the licensed indication.
- **Section 100 - HSDP:** defines restrictions on how specialised medicines for chronic conditions can be prescribed and supplied, due to their clinical use and other special features. In most cases, restrictions require that medical practitioners undertake specific training or are affiliated with a specialised hospital unit to prescribe these medicines.
- **Authority-required:** restriction whereby a medicine (or proposed prescription in relation to a medicine) listed in the Australian Pharmaceutical Benefits Scheme (PBS) requires prior approval from the Australian Government Department of Human Services (or the Australian Government Department of Veterans' Affairs) before being prescribing. In some cases, the application for prior approval must be made in writing.
- **Authority required (streamlined):** restriction whereby a medicine listed in the PBS requires a four-digit authority code to be written on the authority prescription.
- **Specialist restriction:** medicine can only be prescribed by a specialist doctor.
- **Cost minimisation:** funding provided only if the agreed price is cost-neutral, or cost-saving compared to the current standard of care.
- **RSA:** a funding arrangement between the supplier of a PBS-listed medicine and the Australian Government that adequately monitors identified risks (or undesired events such as cost ineffective use or greater than expected use) and manages them by appropriate mechanisms for sharing the impact of these risks between the supplier and the government should they arise.
- **MES:** schemes that allow for PBAC to recommend PBS coverage at a price justified by the existing evidence, pending submission of more conclusive evidence of cost-effectiveness to support listing of the medicine at a higher price.
- **Safety Net early supply rule:** the Safety Net early supply rule means that for some PBS medicines a repeat supply of the same medicine within less than a specified interval will fall outside the Safety Net.
- **LSDP:** the Australian Government provides fully subsidised access for eligible patients with rare and life-threatening diseases to essential medicines through the LSDP. To access medicines funded under the LSDP, treating physicians must apply for access on behalf of their patient. Once approved, the medicines are delivered to a nominated pharmacy (usually a hospital) for dispensing to the patient.

Table 4. List of all the variables collected for each medicine-indication pair of the study sample.

Variable and respective set of values (where applicable)	Source/Website
REGULATORY & HTA CHARECTERISTICS	
Molecule name	EMA/TGA
Brand name	
Manufacturer	
Disease area (ATC code)	
Indication(s) under review (as per EMA/TGA)	
EMA and TGA marketing authorisation date	
Scheme of approval 1=Standard 2=Conditional Marketing Authorisation 3=Authorisation under exceptional circumstances 4=Accelerated assessment	
Orphan designation 0=No 1=Yes	
HTA funding decision date	NICE, PBAC, SMC, TLV
Submission is a re-evaluation or update 0=No 1=Yes	
Recommendation decision 1=List 2=List with criteria 3=List with criteria, including MEA 4=Do not list Not submitted 5=Not submitted 6=Deferred (Australia)	
Clinical restrictions based on HTA agency recommendation	
Administrative restrictions based on HTA agency recommendation	
Economic restrictions based on HTA agency recommendation	
HTA report reference	
Source/Weblink	
MANAGED ENTRY AGREEMENTS	
MEA in place 0=No 1=Yes	NICE, PBAC, SMC, TLV
MEA type 1=Financial based 2=Outcomes based 3=Combination	
Start/End year of MEA *n.b.*: End date not always available/ ongoing scheme	
Tool(s) used to implement MEA (e.g., discount, free stock, CED, rebate etc.)	
Uncertainties leading to MEA (where available)	
Objective/Rationale (e.g., to address budget impact, reduce uncertainty around cost-effectiveness or utilisation in real life, ensure compliance to the restricted reimbursement)	

CLINICAL EVIDENCE

Trial name	
Pivotal trial 0=No 1=Yes	
Study Type 1= Interventional study 2= Observational study 3= Indirect comparison	
Type of observational study 1=Case-crossover 2=Cross-sectional 3=Case-control 4=Retrospective cohort 5=Prospective cohort 6=n/a	
Allocation 1=Randomized 2=Non-randomized 3=n/a	
Trial Identifier (NCT number)	
Intervention model 1=Single group assignment 2=Parallel assignment 3=Cross-over assignment 4=Factorial assignment	
Used to inform economic model 0=No 1=Yes	
Trial Phase 1=Phase III 2= Phase II 3=Phase IIa 4= Phase IIb 5=multi-stage 6=Phase IV 7=Phase I 8=n/a *n.b.:* "n/a" is used to describe trials without FDA-defined phases, including trials of devices or behavioural interventions.	ClinicalTrials.gov
Arm 1=Single Arm Trial 2=Double Arm Trial 3=Multi-Arm Trial	
Masking 1=Single blind 2=Double blind 3=Open label or unblinded	
Sample size in the trial	
Length of trial	
Length of the follow-up (months)	
Number of comparators 1=One 2=More than one	

Type of comparator 1=Active 2=Placebo 3=No intervention (for non-comparative) 4=Sham	
Name of comparator(s)	
Type of analysis 1=Modified intention to treat (randomized) 2=Intention to treat (randomized) 3=Full Analysis Set (non-randomized)	
PRIMARY OUTCOMES	
Primary endpoint(s)	
Type of primary endpoint 1=Surrogate Endpoint 2=Clinical Endpoint 3=Surrogate &Clinical 4=n/a	
Results of the primary endpoint	
SECONDARY OUTCOMES	
Actual Secondary Endpoint(s)	
Results of secondary endpoints	
HRQoL Measurement tool	
Results of HRQoL	
SAFETY PROFILE	
All Adverse Events of trial (%)	
Serious Adverse Events (%)	
Withdrawal Rates due to adverse events (%)	
Death (%)	NICE, PBAC, SMC, TLV
SECONDARY EVIDENCE INCLUDED	
Secondary trial(s)	
Used to inform what? 1=Safety 2=Clinical effectiveness 3=Economic model	
SUBGROUPS	
Is there a sub-group analysis performed that stemmed to a restriction? 0=No 1=Yes	
If yes: name of the subgroup & subgroup analysis results	

ECONOMIC EVIDENCE

Type of economic analysis 1=Cost of illness 2=Cost minimisation 3=Cost effectiveness 4=Cost consequence 5=Cost utility 6=Cost benefit	
Model Structure (e.g., partitioned model, Markov etc.)	
Model perspective	
Model horizon	
Comparator(s)	
ICER Submitted by the manufacturer	
ICER accepted by payer	
Cost savings	

	n.b.: Only applicable for cost-minimization and other cost analysis not for cost-utility	
	Final cost (cost-comparison) *n.b.:* Only applicable for cost-minimization and other cost analysis not for cost-utility	
	Submission price	
	Secondary evidence included (only if used in the economic case)	
	†Budget impact performed 0=No 1=Yes	

CLINICAL UNCERTAINTIES

Clinical benefit 0=Not raised 1=Raised	Limited or poor clinical benefit stemming from the clinical evidence; 1) Modest or low clinical benefit from trial 2) The response of the treatment varied from study to study 3) The response of the treatment is effective only in a subpopulation 4) The response of the treatment is not statistically significant compared with the comparator	NICE, PBAC, SMC, TLV
Clinical evidence 0=Not raised 1=Raised	1) Lack of comparative clinical data 2) Lack of long-term evidence 3) Lack of safety data	
Study design 0=Not raised 1=Raised	1) Limitation in trial design leading to confounding in the clinical benefit 2) Study blinding unsuitable 3) Sample size (too small) 4) Use of surrogate endpoints vs clinical endpoints	
Clinical comparator 0=Not raised 1=Raised	1) Comparator not marketed in the country 2) Comparator not suitable because not used in the clinical practice 3) Comparator is not the standard of care in the country 4) Placebo-controlled trial	
Generalizability of population 0=Not raised 1=Raised	1) Trial population is not generalizable to the country population due to ethnicity/ baseline characteristics and prevalence 2) The trial population is not included/underrepresented the population of the indication under review 3) Only a subgroup of the trial is considered suitable for the indication	
Clinical practice 0=Not raised 1=Raised	1) Differences in the pathway of routine clinical practice of the country 2) Differences in the administration/dose in comparison with standard of care 3) Treatment criteria (e.g., baseline of the patients for starting the treatment) differ between the study and clinical practice 4) A pharmaceutical is thought to have limited use in the study country. (e.g., clinical pathways of PBAC)	
Indirect comparison 0=Not raised 1=Raised	1) Indirect comparison not well designed 2) Population across different studies non comparable 3) Statistical analysis performed not suitable (e.g., butcher vs Bayesian model)	
Adverse events 0=Not raised 1=Raised	1) Substantial number of patients discontinuing the therapy due to adverse events 2) Significantly higher number of safety issues in comparison with current treatment used. 3) There are notable adverse events that would lead to specific monitoring	

ECONOMIC UNCERTAINTIES		
Modelling 0=Not raised 1=Raised	1) Modelling used is not suitable 2) The use of curves is not appropriate 3) Extrapolation's method is not appropriate 4) Misrepresentation of the population under review or of some specific subgroup 5) Computational errors	NICE, PBAC, SMC, TLV
Model type 0=Not raised 1=Raised	1) The economic model used in the analysis is not suitable/ not appropriate	
Economic comparator 0=Not raised 1=Raised	1) Comparator used in the model is not marketed in the country of interest 2) Comparator used in the model is not used in clinical practice of the relevant country of interest 3) Comparator used in the model is not the standard of care in the country of interest	
Cost 0=Not raised 1=Raised	1) Some costs included in the model are too low or too high 2) Model does not include specific cost that would lead to over/under- estimation of the cost-effectiveness such as administration cost or wastage	
Utilities 0=Not raised 1=Raised	1) Utility values used in the model are not suitable leading to over-or under-estimation of the ICER 2) Utility source is unsuitable, or the measure was inappropriate	
Cost-effectiveness 0=Not raised 1=Raised	1) ICER over the threshold 2) ICER too high even after sensitivity analysis or re-evaluation carried out by manufacturer/HTA body/ external reviewers	
Sensitivity analysis 0=Not raised 1=Raised	Any issues around the sensitivity analysis performed by the manufacturer or by the HTA body experts	
Clinical evidence 0=Not raised 1=Raised	1) The clinical evidence used in the economic model is not suitable due to limitations in sample size, poor trial design etc. 2) There is a lack of evidence following the nature progression of the disease (e.g., lack of long-term evidence) 3) Concerns about the study design of the indirect comparison used to populate the clinical input of the model	
SOCIAL VALUE JUDGEMENTS		
Rarity 0=Not considered 1=Considered	Cases when the rarity of the disease or the orphan status of the medicine were recognised.	NICE, PBAC, SMC, TLV
Severity 0=Not considered 1=Considered	Disease severity and its impact on the patients and their caregivers	
Unmet need 0=Not considered 1=Considered	Unmet need for new treatments was recognised	
Innovation 0=Not considered 1=Considered	The treatment represents a therapeutic advancement in the disease area of question, or it has an innovative mechanism of action.	
Short life expectancy 0=Not considered 1=Considered	Targeted disease has a poor prognosis with a short life expectancy	

Administration advantage 0=Not considered 1=Considered	Refers to the route and the frequency of administration of the treatment
Impact on society 0=Not considered 1=Considered	The broader impact a treatment has on the society; refers to the "wider societal impact" arising from a person's ability to be part of society as a result of the treatment compared with their capacity to engage with society without the treatment or with an alternative treatment.
Impact on QoL 0=Not considered 1=Considered	Treatment has a significant impact on the length and quality of life.
Ethic/equality 0=Not considered 1=Considered	Possible inequalities arising from the reimbursement of the treatment including those associated with gender, age, race, disability and/or socioeconomic status and the need to subscribe to solidarity and human dignity
Special demographic populations 0=Not considered 1=Considered	Some features of the population are considered such as age, pregnant women.
Safety profile 0=Not considered 1=Considered	The safety profile of current treatments is heavily affecting patients who would prefer to have more options with a different Safety profile (It is not limiting to a better safety profile
Emotional burden 0=Not considered 1=Considered	Emotional burden created by the disease to patients or families.
Functional burden 0=Not considered 1=Considered	Burden on the ability of the patients and their families/caregivers to carry out work and daily activities
Special considerations 0=Not considered 1=Considered	Set of additional value considerations explicitly considered by specific HTA agencies in their decision-making (e.g., Human dignity principle in Sweden or the end-of-life criteria in England/ Scotland)

Note: ATC: Anatomical Therapeutic Chemical classification, EMA: European Medicines Agency, FDA: Food and Drug Administration, HTA: Health Technology Assessment, HRQoL: Health Related Quality of Life, ICER: Incremental Cost Effectiveness Ratio, NCT: National Clinical Trial number, PBAC: Pharmaceutical Benefits Advisory Committee, QoL: Quality of Life, NICE, SMC: Scottish Medicines Consortium, TGA: Therapeutic Goods Administration, TLV: The Dental and Pharmaceutical Benefits Agency.

Key: † Since budget impact is only considered by PBAC, a budget impact specific uncertainty was not studied due to lack of comparability across countries. Nevertheless, any budget impact related issues that might have been raised by PBAC were reflected in the "cost" and "modelling" related uncertainties (e.g., if certain costs in the economic evidence submitted were over or underestimated).

Data on the above variables per medicine-indication pair in all study countries were extracted from publicly available HTA appraisals published in the respective HTA bodies' websites, namely PBAC (AUS), NICE (ENG), TLV (SE) and SMC (SCOT). A database stratified by HTA agency was built to describe and classify MEAs across the respective HTA bodies and ultimately, facilitate data analyses.

In the data collection process, it was found that even though redacted information existed throughout the HTA reports studied, this only related to specific prices, and/or trial results, figures and specific values which were not needed and/or collected for the analyses conducted for this thesis Therefore, I confirm that all variables included in the analyses performed for this thesis were available in the HTA reports of all medicine-indication pairs studied in this thesis and the level of text available was sufficient for the data collector to understand if a specific uncertainty/ SVJ was raised/considered respectively, and if a MEA is in place for a specific medicine-indication pair and if so, what is its respective type and objective.

3.5 Data management and analysis

All the data extracted was inserted in a database in Excel®, which was stored securely under an LSE verified shared folder accessible by the team of the involved researchers only. The data collected was stratified by HTA agency and was homogenised/coded accordingly (where needed) for analysis. It is important to highlight here that even though decisions in Sweden relate to reimbursement and in Australia, England and Scotland refer to recommendation for use within the national health system, for the sake of simplicity the term used in this thesis to describe/code the outcomes of decisions is "reimbursement", "funding" or "coverage".

For the purposes of this thesis, both qualitative and quantitative approaches were applied to analyse the collected data. The specific methodologies and analytical frameworks used for the data analyses conducted in each research article are presented in more detail below, as well as in the respective chapters of the thesis.

3.5.1 Data analysis: Research article I

The first research article of the thesis explored the extent to which the uptake of MEAs for cancer medicines differs across countries, and if so, provide key trends on the variables that might shape the uptake of MEAs. To address the above objective Cohen's k-scores were used

to measure inter-rater agreement of countries on whether they consider a MEA as part of their restricted funding decisions or not, and Pearson's chi squared (χ^2) test of independence, along with descriptive statistics were used to provide key trends on the variables that play at least some role in determining whether a cancer medicine will be funded with restrictions that include a MEA or not across the study countries. Therefore, as L and DNL funding outcomes, by definition, do not involve the implementation of a MEA, for the purposes of this analysis I only took into consideration medicine indication pairs with a restricted recommendation decision (i.e., LWC or LWCMEA) (Table 2).

For the first part of the research hypothesis, Cohen's kappa score (κ) was employed as an inter-rater reliability measure for cross-country agreement on whether restricted HTA outcomes across agencies comprised a form of MEA as a restriction (or not).

The Cohen's κ coefficient is a statistic which measures inter-rater agreement for qualitative (categorical) outcome variables, and takes values ranging from 0 to 1, reflecting a respective inter-rater agreement ranging from poor ($\kappa = 0$) to perfect ($\kappa = 1$), with negative values of κ corresponding to cases where inter-rater agreement can be even less than that expected by chance. The measure is described by the following equation (2):

$$\kappa = \frac{\Pr(a) - \Pr(e)}{1 - \Pr(e)} \qquad \textbf{(2)}$$

where κ is the inter-rater coefficient, Pr (a) is the actual observed agreement, Pr (e) is the proportion of cases whereby agreement would be expected to occur by chance, and 1−Pr(e) is the highest agreement that would be feasible to observe beyond chance, given the marginal distributions, while the statistical significance of the test follows the χ^2 distribution.

The Cohen's kappa coefficient has been chosen as the preferred inter-rater reliability measure, first because it has been used in comparable analyses to measure congruence/divergence between agencies in their HTA coverage recommendations, and second, because it allows for comparison of observed inter-rater agreement with agreement that would be expected by chance (Maynou & Cairns, 2020; Nicod & Kanavos, 2016). A key limitation of the Cohen's kappa score relevant to our sample is that in cases where the study sample size of medicine-indications is different across countries (which is the case in this analysis), the test may provide an underestimated measure of the factual congruence observed in the dataset (Flight et al.,

2015). However, in order to mitigate this risk scores were generated with only the mutual medicine-indication pairs that were both commonly assessed and restricted (LWC or LWCMEA) among all study countries (i.e., 15 molecules commonly assessed between England, Scotland, Australia and Sweden and 34 molecules commonly assessed and restricted between England, Scotland and Australia (see chapter 4 – Table 7).

For the second part of the research question, variables under HTA assessment and appraisal were analysed by means of descriptive statistics, including percentages and crosstabulations. Uncertainties and SVJs were treated and coded as binary variables based on whether they have been raised and considered (or not) respectively in the decision-making process. As such, bivariate analyses were performed, using Pearson's chi squared (χ^2) test of independence to test for statistical significance in the variables that shape differences in the restricted outcome (LWC or LWCMEA) between agencies. This analysis was essentially performed to provide an initial hypothesis/ perspective about the most influential HTA decision-making determinants of MEAs, as a guidance for the analyses conducted in the subsequent research articles.

The SPSS® (v.24.0) was used to perform statistical tests and measure inter-rater agreement, and Excel® 2013 to generate descriptive statistics.

3.5.2 Data analysis: Research article II

In the second research article, the key variables identified in the previous article were analysed further to also understand their level of impact/ importance on divergencies between the conditional/ restricted HTA recommendation decisions and the type of MEA in place across countries. More precisely, the second research article aimed to study the HTA variables that drive the uptake, as well as the different types of MEAs implemented across settings. To address the above objectives, first, a number of binary logit models were employed to capture the range of probabilities for a medicine indication pair to be restricted with or without a MEA, based on a set of HTA explanatory variables, and second, for medicine indication pairs restricted with a MEA, a multinomial logit model was used to capture the probability of the MEA, being Financial (F), Outcomes (O) based or Combination (C)) based on a set of HTA decision-making variables. For the purposes of the first econometric model, the restricted HTA outcomes were coded as a binary variable (i.e., LWC vs. LWCMEA), while for the second

model, the type of MEA was coded as a multinomial variable (i.e., F, O or C), based on the taxonomies described in the literature (Figures 1-3).

As explained in the respective chapter (see chapter 5, section 5.2.3- Data analysis) the relationships that this research article explored could only be described as probabilities rather than as a panel data design or modelled as a linear combination of explanatory variables (Maynou & Cairns, 2015; Dakin et al., 2015) and as such, a statistical model was designed to estimate the probability of a scheme being concluded and subsequently its type, based on the identified HTA variables of significance. Furthermore, as the dependent variables are categorical, non-linear, logit models were chosen (as opposed to probit), namely a binary and a multinomial logit model.

First, the binary logistic regression was used to model the probability (P) of a technology being restricted with MEA ($y_i = 1$) based on a set of explanatory variables (x_i), under the following equation (3):

$$P(y_i = 1 \mid x_i) = \frac{exp(x_i\beta)}{1+exp(x_i\beta)} \quad \textbf{(3)}$$

Where:

- y is a binary response variable with:

  - $y_i = 1$ if there is at least one restriction <u>in the form of a MEA</u> for the medicine indication pair in question
  - $y_i = 0$ if there is one or more restriction(s) for the medicine indication pair in question but <u>NOT in the form of a MEA</u>

- $x = (x_1, x_2, ..., x_k)$ is a set of HTA explanatory variables hypothesised to influence HTA decision-making (based on the conceptual framework described in section 3.3), whereby:

  - x_i is the observed value/outcome of the respective HTA explanatory variables tested

and

- β is a vector of parameters to be estimated and presented as odds ratios (e.g., a one-unit change in the jth variable, x_j, is associated with the odds ratio, $exp(\beta_j)$ (Dakin et al., 2015).

Finally, in order to examine which HTA decision-making variables determine the type of MEA in place, multinomial logistic regression was employed to model the probability (*Pr*) of an implemented MEA taking one of the three outcomes "F", "O" or "C" given the set of HTA determinants defined from the previous model, whereby each outcome is considered to be qualitatively different, and no ranking is assumed between the outcomes. The multinomial logit model estimates the effect of independent variables on the natural log of the odds of the outcome (e.g., the decision to fund with one of three MEA types) being outcome F or O as opposed to the referent outcome C, (or being outcome O, or C as opposed to F, or outcome F or C, as opposed to O – depending on which outcome is used as the reference case each time) (Dakin et al., 2005) and is described by the following equation (4);

$$ln\ \frac{\Pr(Y_i=k-1)}{\Pr(Y_i=k)} = \beta_{k-1} \cdot \boldsymbol{X}_i \qquad \textbf{(4)}$$

Where:

- k is the multinomial dependent variable, which can take one of three values: F, O, C
- β_k is the set of regression coefficients associated with outcome k
- i denotes medicine-indication pair in question

and

- x_i is a matrix of explanatory variables associated with observation/ medicine-indication pair i

The SPSS® (v.24.0) was used to perform the econometric models and Excel® 2013 to generate descriptive statistics where relevant.

3.5.3 Data analysis: Research article III

The objective of this research article was to evaluate the impact of implemented MEAs on improved availability of and timely access to cancer medicines. To address this objective, first a number of binary logit models were performed to capture the range of probabilities for a previously negative funding decision being reversed to positive following resubmission with a MEA (as a proxy for their impact on enhancing availability of medicines) and second, a number of gamma generalised linear models were employed to capture the association between time to final funding decision and the presence of a MEA (as a proxy for their impact on market access delays). Therefore, the dataset used for the purposes of this analysis included only medicine-

indication pairs with a resubmission after a preceding HTA rejection and those with a resubmission following completion/expiry of a MEA scheme.

For the first part of the analysis, as the dependent variable was binary and categorical, a non-linear, logit model was chosen, namely a binary logit, to model the probability (P) of a previously rejected technology receiving a favourable funding decision after resubmission ($y_i = 1$) (as opposed to remaining rejected), based on a set of explanatory variables (x_i), under the following equation (5):

$$P(y_i = 1 \mid x_i) = \frac{exp(x_i\beta)}{1+exp(x_i\beta)} \quad \textbf{(5)}$$

Where:

- y is a binary response variable with:
    - $y_i = 1$ if the resubmission resulted in a positive recommendation decision
    - $y_i = 0$ if the resubmission resulted in a negative recommendation decision

- $x = (x_1, x_2, ..., x_k)$ is a set of HTA explanatory variables hypothesised to influence HTA decision-making (based on the conceptual framework described in section 3.3), and a distinct explanatory variable on presence of a MEA (or not) as part of the resubmission whereby:

    - x_i is the observed value/outcome of the respective explanatory variables tested

and

- β is a vector of parameters to be estimated and presented as odds ratios (e.g., a one-unit change in the jth variable, x_j, is associated with the odds ratio, $exp(\beta_j)$ (Dakin et al., 2015).

For the second part of the analysis, the dependent variable (i.e., average time to final funding decision) was continuous, and assumed to follow an exponential (i.e., *gamma)* distribution (Appendix 2; Appendix Figure 5). Students *t*-tests were initially performed to understand if there is an association between the average timings to final recommendation decision and any of the HTA explanatory variables, including the variable of a resubmission with vs. without a MEA.

Subsequently, to model the relationship between the timing to final recommendation decision and various HTA decision-making explanatory variables (including the existence of a current and/or expired MEA and if so, its type) a generalised linear model (based on a log-link function) was built. This model was employed as the best fit of a regression model for a non-Gaussian distribution, which is described by the following equation (6):

$$g(\mu_i) = \boldsymbol{X}_i^{\mathbf{T}}\boldsymbol{\beta} = \beta_0 + \sum_{j=1}^{P} x_{ij}\beta_j \qquad (\mathbf{6})$$

Where:

- $\mu_i = \mathbb{E}(Y_i)$ is the expected value of the response Y_i given the predictors
- $g(\cdot)$ is a smooth and monotonic link function that connects μ_i to the predictors
- $\mathbf{X}_i^T = (x_{i0}, x_{i1}, \ldots, x_{ip})$ is the i-th observation's known predictor vector with $X_{i0} = 1$

and

- $\boldsymbol{\beta}=(\beta_0,\beta_1,\ldots,\beta p)^{\mathrm{T}}$ is the unknown vector of regression coefficients.

A log-link function was applied in the above to exponentiate the linear predictors as follows:

$$ln(\mu) = \beta_0 + \beta_1 X \Rightarrow \mu = \exp(\beta_0 + \beta_1 X)$$

Where:

- μ=predicted value of Y given X,
- $\exp(\beta_0)$ is the effect on the mean of μ when X=0

and

- $\exp(\beta_1)$ is the multiplicative effect on the mean of Y for a one-unit increase in X.

The SPSS® (v.24.0) was used to perform the econometric models and statistical tests, and Excel® 2013 to generate descriptive statistics, where relevant.

3.6 Study sample characteristics

296 medicine-indication pairs were studied across all countries of which 79% (n=235) were assessed and had a funding recommendation decision (i.e., L, LWC, LWCMEA, DNL). The remaining 61 medicine-indication pairs did not have a funding recommendation either because

their respective manufacturer submission was “Not assessed” (47.5%, n=29) by the HTA body, there was “No submission” (19.7%, n=12) or they were assessed only on the basis of a health economic report (relevant for TLV only) (32.8%, n=20). Therefore, the study sample comprised 235 funding recommendation decisions, across ENG (n=68, 29%) AUS (n=64, 27.2%), SCOT (n=61, 26%) and SE (n=42, 17.8%). Of these, 88% (n=207) of submissions received a favourable recommendation decision (with or without restrictions), while 12% (n=28) were rejected across all countries. Overall, among all the medicine-indication pairs assessed within each HTA agency, the highest proportion of favourable recommendation decisions was observed for SCOT (n=58, 95%), followed by ENG (n=61, 89.7%), SE (n=37, 88%) and AUS (n=51, 79.7%) (Table 5). From the medicine-indication pairs that received a favourable funding decision (n=207), the vast majority achieved so with a MEA (78.7%, n=163), 11.1% (n=23) with other restrictions not in the form of MEA, while 10.2% (n=21) achieved a positive reimbursement without any restrictions. Overall, among all the positive funding decisions within each study country, those that were based on a MEA were proportionally the highest in England (95%, n=58), followed by Scotland (87.9%, n=51), Australia (74.5%, n=38) and Sweden (40.5%, n=16). Financial based schemes were the most common type of agreement used in England, Scotland and Australia. More precisely, in England, 93% (n=54) of all MEAs were financial based, 96% (n=49) in Scotland, 76.3% (n=29) in Australia and only 27% (n=4) in Sweden. Outcomes based schemes were mostly implemented in Sweden (47%, n=7). In England only two agreements were based on outcomes, one agreement in Australia and none in Scotland. Combination schemes with both financial and outcomes-based aspects were primarily used in Australia (21%, n=8), although they were also observed in Sweden (26%, n=5), Scotland (4%, n=2) and England (3.5%, n=2). Finally, it is important to note that in England the four medicine-indication pairs that were reimbursed with an outcome or combination-based agreement (as described above) correspond to subsidization by the CDF. More specifically, two medicine-indication pairs were approved subject to a CED scheme under the CDF and two were based on CED under the CDF, as well as a CDF CAA to lower the cost of the medicine during the managed access period.

Table 5 presents an overview of the main descriptive statistics of the study sample, including number of assessments/ non-assessments per study country, number of approved indications (with or without MEA) per study country and types of MEA (where applicable) and their number of applied indications across the study countries.

Table 5. Study sample characteristics, including number of assessments/ non-assessments per study country, number of approved indications (with or without MEA) per study country, and types of MEAs (where applicable) and their number of applied indications.

All oncology medicine-indication pairs approved by EMA/TGA between 2007-2018 (n, %)

	England (NICE) (n=74)	Australia (PBAC) (n=74)	Scotland (SMC) (n=74)	Sweden (TLV) (n=74)	All sample (n=296)
List (L)	2 (2.7%)	1 (1.3%)	4 (5.4%)	14 (19%)	21 (7%)
List with restrictions (LWC/LWCMEA)	59 (79.7%)	50 (67.6%)	54 (73%)	23 (31%)	186 (63%)
Do not List (DNL)	7 (9.5%)	13 (17.6%)	3 (4%)	5 (6.8%)	28 (9.5%)
Not assessed	4 (5.4%)	10 (13.5%)	1 (1.4%)	12 (16.2%)	27 (9.1%)
Not submitted	2 (2.7%)	0%	12 (16.2%)	0%	14 (4.7%)
Economic report	n/a	n/a	n/a	20 (27%)	20 (6.7%)

Oncology medicine-indication pairs assessed by the study HTA agencies (n, %)

	England (NICE) (n=68)	Australia (PBAC) (n=64)	Scotland (SMC) (n=61)	Sweden (TLV) (n=42)	All sample (n=235)
L	2 (3%)	1 (1.5%)	4 (6.5%)	14 (33.4%)	21 (8.9%)
List with restrictions (LWC)	1 (1.4%)	12 (18.8%)	3 (4.9%)	7 (16.6%)	23 (9.8%)
LWC incl. MEA (LWCMEA)	58 (85.3%)	38 (59.3%)	51 (83.6%)	16 (38%)	163 (69.3%)
Of which:					
• **FBA (n, %)**	• 54 (93%)	• 29 (76.3%)	• 49 (96%)	• 4 (27%)	• 136 (83.4%)
• **PBA (n, %)**	• 2 (3.5%)	• 1 (2.6%)	• 0%	• 7 (47%)	• 10 (6.2%)
• **FBA & PBA (n, %)**	• 2 (3.5%)	• 8 (21%)	• 2 (4%)	• 5 (26%)	• 17 (10.4%)
DNL	7 (10.3%)	13 (20.3%)	3 (5%)	5 (12%)	28 (12%)

Key: n/a= not applicable for the HTA agency of interest

Note: FBA; Financial Based Agreement, PBA: Performance Based Agreement, EMA: European Medicines Agency; TGA: Therapeutic Goods Administration.

4. Research article I. Determinants of Managed Entry Agreements in the context of Health Technology Assessment: a comparative analysis of cancer therapies in four countries.

"The willingness to consider possibility requires a tolerance of uncertainty" - Rachel Naomi Remen

Box 5. Research article I - Highlights

- There is a poor level of agreement between countries on whether new oncology therapies with evidentiary uncertainties will be funded with a MEA or not, to mitigate these uncertainties.

- Diverging MEA outcomes are influenced heavily by economic evidence uncertainties, highlighting agency-specific preferences on cost-effectiveness thresholds and evidentiary requirements for economic modelling.

- The SVJs of innovation and burden of disease are paramount in allowing greater flexibility towards funding with restrictions (with or without MEA) but those around Impact of the technology on QoL, Societal impact and Emotional/ functional burden are influential specifically towards funding with a MEA.

- As additional dimensions of value seem to determine MEA outcomes it is essential to understand the extent to which MEAs can be used as complementary to VBP, through negotiations that enable weight adjustment of cost-effectiveness thresholds based on the therapeutic innovation, and/or wider societal benefits a new technology can offer.

ABSTRACT

Background: Managed Entry Agreements (MEAs) are increasingly used to address uncertainties arising in the Health Technology Assessment (HTA) process due to immature evidence of new, high-cost medicines on their real-world performance and cost-effectiveness. Literature remains inconclusive on the HTA decision-making factors that influence MEAs' utilisation. We aimed to assess if the uptake of MEAs differs between countries and if so, to understand which HTA decision-making criteria play a role in determining such differences. **Methods:** All oncology medicines approved since 2009 in Australia, England, Scotland and Sweden were studied. Four categories of variables were collected from publicly available HTA reports of the above medicines: 1) Social value judgements (SVJs), 2) Clinical/Economic evidence submitted, 3) Interpretation of this evidence, and 4) Funding decision. Conditional/restricted decisions were coded as Listed With Criteria (LWC) other than a MEA or LWC including a MEA (LWCMEA). Cohen's k-scores measured inter-rater agreement of countries on their LWCMEA outcomes and Pearson's chi square tests explored the association between HTA variables and LWCMEA outcomes. **Results:** 74 medicine-indication pairs were found resulting in n=296 observations. 8% (n=23) were LWC and 55% (n=163) were LWCMEA. Poor to moderate agreement existed between countries ($-0.29 < \kappa < 0.33$) on LWCMEA outcomes. Cross-country differences within the LWCMEA sample were partly driven by economic uncertainties and largely driven by SVJs considered across agencies. **Conclusions:** A set of HTA related variables driving MEAs uptake across countries was identified. These findings can be useful in future research aimed at informing country-specific, "best-practice" guidelines for successful MEA implementation.

Keywords: risk sharing; managed entry agreements; patient access schemes; HTA decision-making; HTA determinants.

4.1 Background and study objectives

Over the last decade, the continuous market entry of new therapies, which are either high volume – for treating many patients (i.e. anti-diabetic agents) or high cost – for a single treatment course (i.e. oncology therapies) has escalated pharmaceutical spending (Permanand and Bak Pedersen., 2015.[3] It was recently reported that pharmaceutical spending accounts for almost 20% of the total health expenditure in OECD countries and since funding from governments and social insurance schemes plays the largest role in pharmaceutical purchasing, this rise bears significant implications for health systems' budgets (OECD 2019).

The growing healthcare expenditure poses pressures for pharmaceutical manufacturers to demonstrate real-world value for money beyond that of safety and efficacy and simultaneously for national healthcare payers to engage in strategic pricing and reimbursement policies that ensure patients' access to new therapies while optimising budget impact (McCabe et al., 2009; Taylor et al, 2004). Although most new products are assessed as part of Health Technology Assessment (HTA) processes in many countries, the data available on the cost-effectiveness of high-cost therapies, particularly in oncology, are severely lacking at the time of product launch (Garrison et al., 2013). Uncertainties arise due to the often immature evidence available from controlled trials on the real world clinical outcomes of newly launched pharmaceuticals, meaning that the benefits of a new product cannot be fully estimated at drug launch; uncertainties may be present around treatment eligibility of patient sub-groups, generalizability of trial results to clinical practice, the use of surrogate outcome measures instead of "hard" endpoints and subsequent transferability of surrogate[4] outcomes used in trials to real-world studies (Ferrario & Kanavos, 2013). As these challenges can lead to delayed reimbursement decisions and patient access, manufacturers and payers are seeking ways to collaboratively

[3] This chapter has been published as: Efthymiadou O., Kanavos P. (2021). Determinants of Managed Entry Agreements in the context of Health Technology Assessment: a comparative analysis of oncology therapies in four countries. Int J Technol Assess Health Care. 2021 Jan 29;37:e31. https://pubmed.ncbi.nlm.nih.gov/33509311/

[4] A "**Surrogate" endpoint** is defined as a biomarker or physiological measure, laboratory test result, imaging result, or another replacement endpoint that is thought to capture the causal pathway through which the disease process affects the patient-cantered outcome (Ciani et al., 2021). It is measured in place of a clinically meaningful/ definitive endpoint and usually tracks the progress or extent of the disease. Scientists might choose a surrogate endpoint when it is not feasible to use a clinical one due to cost, time, or difficulty of measurement. However, it is challenging to determine whether the use of a surrogate endpoint is valid (i.e., is it strongly associated with the definitive outcome?). On the contrary, **"Hard/ Clinical" endpoints** are well defined in the study protocol, definitive in terms of disease process, and don't need to be validated further (PennState University, 2018).

manage the market entry of new pharmaceutical products and mitigate risks related to premature evidence (Wilsdon & Barron, 2016; Carlson et al., 2010); one way to achieve this has been through the introduction of contractual arrangements between the two parties, referred to as Managed Entry Agreements (MEAs) or Risk Sharing Agreements (RSAs).

MEAs are used in many countries worldwide and primarily in Europe, in accordance with country-specific governance and preferences around evidence requirements and evaluation for new medicines (Pritchett et al., 2015). Cross-country differences in HTA assessment requirements have led to a well-documented disparity in the respective risk-sharing practices followed by countries (Ferrario & Kanavos, 2013). A review of MEAs in the EU showcased that only for two drug-indication pairs in the whole sample, a MEA was applied in all six study countries and even between these there was variation in the type of MEAs applied (Pauwels et al., 2017).

Despite the growing interest of healthcare systems and manufacturers in the use of MEAs over the past decade, there is still a knowledge gap in the drivers of this variation, partially due to a lack of transparency in the negotiation from both parties (Piatkiewicz et al., 2017).

Even though literature has concluded that countries indeed differ in their MEA implementation practices, with MEAs being highly specific to the HTA decision-making context in which they operate, the current body of relevant literature arises mainly from secondary evidence and remains largely descriptive in nature (Ferrario & Kanavos, 2015; Morel et al., 2013; Carlson et al., 2010; Adamski et al. 2010). Therefore, we aimed to (a) make a methodological contribution to existing research on determining whether the uptake of MEAs differs between countries and (b) if so, to understand whether specific HTA decision-making uncertainties and considerations play some role in determining such differences.

4.2 Methods

4.2.3 Sample selection

A retrospective analysis of HTA appraisals on all oncology drugs (i.e., all L01 molecules, based on the Anatomical Therapeutic Chemical classification) which obtained regulatory approval by the European Medicines Agency (EMA) and by the Therapeutic Goods Administration

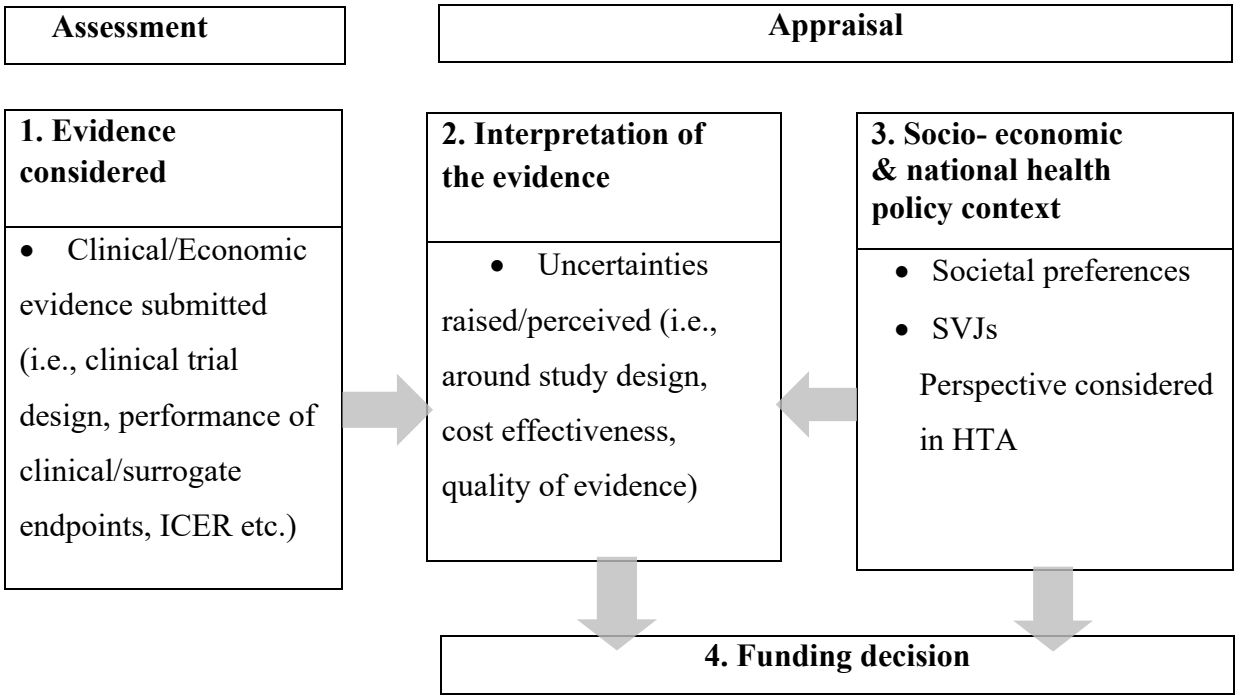
(TGA) in Australia between 1st January 2009 and 15th June 2018 (at the drug-indication pair level) in Australia (AUS), England (ENG), Scotland (SCOT) and Sweden (SE). Oncology was selected as our study therapeutic class because it has been documented to be the therapeutic class with the largest proportion (38%) of implemented MEAs; it is also the therapeutic class where MEAs continue to be increasingly implemented (Ferrario & Kanavos, 2013). Study countries were selected because they all implement MEAs, they all have long-established HTA policies and processes to guide their coverage decisions, they have both a publicly available list of MEAs and publicly available HTA reports which provide a sufficient level of information for the purposes of this analysis and they use similar criteria in their decision-making process (i.e., clinical and/or cost-effectiveness), allowing for comparability across agencies Nicod & Kanavos, 2016).

The sample used for this analysis comprises a small part of a larger sample of drugs studied for a different, broader project on HTA. Nevertheless, the aim/ scope of that project is not related to that of our study, and neither is the methodology we used for data analysis and management. The only common aspects between the two studies relate to the overarching framework used for data collection, as well as the classification and validation of dimensions studied, as described below.

4.2.4 Methodological framework for data collection

The methodology underpinning the data collection process was based on the literature (Nicod & Kanavos, 2016; Cerri et al., 2014) where it is suggested that the final outcome of an HTA appraisal is driven by (a) the clinical and cost-effectiveness evidence submitted (i.e. clinical trial design and endpoints, safety, economic models, and comparators and (b) the interpretation of this evidence, influenced by perception of uncertainty around this evidence, by setting specific preferences on risk and other, social value considerations and by the socio-economic and political context in which HTA decision-making operates. For the purposes of this analysis, a simplified methodological framework was adopted based on the assumption that the impact of the clinical and economic evidence submitted (Stage 1) on the final decision outcome (Stage 4) is captured through the respective uncertainties that this evidence has raised or not (Stage 2). Therefore, the final HTA outcome (Stage 4) is a function of the uncertainties raised (Stage 2) and other, social value and system specific considerations (Stage 3) (Figure 6).

Figure 6. Methodological framework for the analysis of the HTA decision-making process and variables included therein.



Source: The author based on the literature (Nicod & Kanavos, 2016; Cerri et al., 2014)

The HTA process was divided in four different stages corresponding to: ***(1) the evidence submitted and appraised*** (e.g. trial type, clinically meaningful endpoints; response rate/disease progression/safety endpoints, comparators, Incremental Cost Effectiveness Ratio (ICER) range and economic model used), ***(2) the interpretation of this evidence/ uncertainties raised*** (i.e. clinical and economic evidence related uncertainties around clinical benefit, study/research design and those around economic modelling and cost effectiveness respectively), ***(3) Social Value Judgements (SVJs) and HTA system-specific considerations*** (i.e. additional dimensions of societal value that a new technology adds, beyond its clinical evidence/benefit and cost-effectiveness such as the innovation and administration advantage it offers, value dimensions specific to the disease area the technology addresses such as its severity, rarity, unmet need and whether it is a condition towards the end of life, where the benefit of a treatment is valued more highly, and/or system specific considerations such as the use of a single or multiple technology appraisal (MTA) in England that shape decision-making processes for each study country, and ***(4) the final decision outcome,*** classified as; i) L= List (i.e. positive HTA recommendation), ii) LWC= List with conditions, where the technology has been accepted with restrictions but which are not classified as MEAs (e.g. product should be

used in a sub-population of its licensed indication, and/or it should be used in a second line or higher line of therapy, and/or it should be used in a specific dose only, and/or it requires monitoring, and/or it requires prescription by a specialist), iii) LWCMEA= Listed with conditions/restrictions including, among others (if any), at least one classified as MEA (e.g. simple discount, free stock, rebate, patient access scheme, commercial access agreement coverage with evidence development and/or additional data collection) and iv) DNL=Do not list (i.e. negative HTA recommendation). We preferred a four-category outcome variable over the three-outcome variable traditionally used in the HTA literature (i.e., listed, listed with conditions, rejected) as it better reflects the multiple coverage options available when studying conditional/restricted HTA decisions. Since L and DNL decisions would by definition not lead to some kind of a condition/restriction, for the purposes of this analysis we only studied drug-indication pairs with a conditional/restricted recommendation decision (i.e. LWC or LWCMEA).

4.2.5 Data collection

SVJs and uncertainties were classified and defined based on the literature (Table 4) (Angelis & Kanavos, 2017; Nicod & Kanavos, 2016b; Ferrario & Kanavos, 2015) and the classification was also discussed and validated between the authors and external referees. Data on the above stages per drug-indication pair in all study countries were extracted only from the official, publicly available HTA appraisals, which were published in the websites of the respective HTA bodies (i.e., PBAC (AUS), NICE (ENG), SMC (SCOT)), TLV (SE)) (Table 1); other relevant sources of data, such as the county councils' group on new drug therapies (NLT) in Sweden were not searched. Where needed, searches were conducted in local languages (English and Swedish) to increase accuracy and comprehensiveness of the extraction. Data extracted was put in a database stratified by HTA agency to describe and classify MEAs across the respective HTA bodies and ultimately, facilitate data analyses. Data collection was undertaken between June and November 2018 and only the final HTA recommendation reports available for the drug-indication pairs studied were used for data collection.

4.2.6 Data analysis

For the first part of our hypothesis (i.e., determining whether the uptake of MEAs differs between countries) Pearson's chi squared (χ^2) test of independence was used to test for differences in the restricted outcome (LWC or LWCMEA) between agencies. Cohen's kappa

scores (κ) of cross-country agreement levels were also measured as an additional robustness check. Agreement between agencies was measured based on whether conditional/restricted HTA outcomes across agencies included a form of MEA as a condition (or not); this allowed comparison of observed inter-rater agreement with agreement expected by chance, ranging from poor (κ = 0) to perfect (κ = 1), with negative values of κ corresponding to cases where inter-rater agreement was even less than that expected by chance (Nicod, 2017).

Finally, for the second part of our research question (i.e., understand whether specific HTA decision-making uncertainties and considerations play some role in driving divergent LWCMEA decisions between countries), variables under the HTA appraisal (Figure 1) were initially analysed by means of descriptive statistics, including percentages and crosstabulations (Excel® 2013). Assuming that all categories of uncertainties and SVJs were applicable to all drug-indication pairs studied, these were treated and coded as binary variables based on whether they have been raised and considered (or not) respectively in the HTA report for each drug- indication pair. As such, bivariate analyses were also performed, using Pearson's chi squared (χ^2) test of independence to identify which of these variables drive differences between the LWC and LWCMEA sample overall, and across agencies. For the former comparison, where uncertainty and SVJ dimensions had small sample sizes (i.e., 5 or less observations), the Fisher's exact test was also performed as a robustness check.

The SPSS® (v.24.0) was used to perform statistical tests and measure inter-rater agreement.

4.3 Results

4.3.1 Sample characteristics

74 molecules were studied across the four countries, corresponding to a total sample of n= 296 drug indication pairs. Of these,7% (n=21) were Listed, 9.5% (n=28) were Not Listed and 63% (n=186) were restricted (LWC or LWCMEA). Other outcomes included drug-indication pairs that were "Not Assessed" (10%, n=29), "Not submitted" (4%, n=12), or formed only an "Advice or Health Economic Report" (6.5%, n=20) (Table 6). A detailed description of the overall study sample characteristics including number of assessments per country, number of favourable (with or without MEA) and non-favourable funding recommendation decisions per study country, types of MEA implemented (where applicable) and their number of applied

indications across the study countries is presented in chapter 3, section 3.6 – Study sample characteristics.

Table 6. HTA variables studied and comparative descriptive statistics between restricted decisions with vs. without MEA.

All drug indication pairs studied (n=296)				
List (L)		21 (7%)		
List with restrictions	LWC	23 (8%)		
	LWCMEA	163(55%)		
Do not List (DNL)		28 (9.5%)		
Not assessed		29(10%)		
Not submitted		12 (4%)		
Economic report		20 (6.5%)		
Restricted recommendation decisions (n=186)				
Number of assessments per country				
		LWC	**LWCMEA**	
England (NICE)		1(4%)	58 (36%)	***p<0.05**
Australia (PBAC)		12 (52%)	38 (23%)	
Scotland (SMC)		3 (13%)	51 (31%)	
Sweden (TLV)		7 (31%)	15 (10%)	
Social Value Judgements				
		LWC	**LWCMEA**	
Rarity				
Considered		7(30%)	25(15%)	
Not considered		16 (70%)	138 (85%)	*p=0.07*
Disease severity				
Considered		7(30%)	67 (42%)	*p=0.33*
Not considered		16 (70%)	96 (59%)	
Unmet need				
Considered		13(56.5%)	109(67%)	*p=0.33*
Not considered		10 (43.5%)	54(%33)	
Administration advantage				
Considered		2(9%)	54(33%)	***p<0.01**
Not considered		21(91%)	109(67%)	
Innovation				
Considered		2(9%)	86(53%)	***p<0.001**
Not considered		21(91%)	77(47%)	
Special Considerations (i.e. end-of-life criteria)				
Considered		7 (30%)	92 (56%)	***p<0.05**
Not considered		16 (70%)	71(43%)	

Clinical uncertainties			
	LWC	**LWCMEA**	
Clinical benefit			
Raised	15 (65%)	118 (72%)	*p=0.47*
Not raised	8 (35%)	45 (28%)	
Study design			
Raised	8 (35%)	83 (51%)	*p=0.14*
Not raised	15 (65%)	80 (49%)	
Relevance to clinical practice			
Raised	5 (22%)	61 (37%)	*p=0.14*
Not raised	18 (78%)	102 (63%)	
Population generalizability			
Raised	3 (13%)	50 (31%)	*p=0.08*
Not raised	20 (87%)	113 (69%)	
Clinical comparator			
Raised	8 (35%)	48 (29%)	*p=0.60*
Not raised	15 (65%)	115 (71%)	
Clinical evidence			
Raised	11(48%)	77 (47%)	*p=0.95*
Not raised	12 (52%)	86 (53%)	
Economic uncertainties			
	LWC	**LWCMEA**	
Cost effectiveness			
Raised	9 (39%)	117 (72%)	***p<0.01**
Not raised	14 (61%)	46 (28%)	
Utilities			
Raised	1 (4%)	68 (42%)	***p<0.01**
Not raised	22 (96%)	95 (58%)	
Costs			
Raised	8 (35%)	75 (46%)	*p=0.31*
Not raised	15 (65%)	88 (54%)	
Modelling			
Raised	13 (57%)	118 (72%)	*p=0.95*
Not raised	10 (43%)	45 (28%)	
Model type			
Raised	1 (4%)	8 (5%)	*p=0.90*
Not raised	22 (96%)	155 (95%)	
Economic comparator			
Raised	0 (0%)	35 (22%)	***p<0.05**
Not raised	23 (100%)	128 (78%)	

Of the conditional/restricted HTA outcomes (n=186), 88% (n=163) were LWCMEA overall but only 17% (n=32) were LWCMEA across all countries for the same molecules. This was further emphasized by the Cohen's kappa scores measuring the level of inter-rater agreement between agencies across their LWCMEA outcomes. The scores ranged from -0.29 to 0.33

(Table 2), demonstrating a poor to moderate agreement. More precisely, it was shown that only SCOT and SE had a moderate agreement, whereas the rest of countries had a poor or even negative agreement between them. Cross-country differences in MEAs utilisation were further strengthened by results of the χ^2 test, which showed statistically significant differences between the study countries in terms of their LWCMEA recommendation decisions ($p<0.05$).

Table 7. K scores (κ, [95% CI]) of inter-rater agreement in the commonly assessed and restricted (LWC/LWCMEA) decisions across countries.

	England (NICE)	**Scotland** (SMC)	**Australia** (PBAC)	**Sweden*** (TLV)
England (NICE)	-	-0.03 [-0.07;0.01]	-0.05 [-0.14;0.04]	-0.12 [-0.32;0.08]
Scotland (SMC)		-	-0.05 [-0.14;0.04]	0.33 [-0.17;0.83]
Australia (PBAC)			-	-0.29 [-0.51; -0.07]
Sweden (TLV)				-

Key: Scores were generated with only the mutual drug-indication pairs that were both commonly assessed and restricted (LWC or LWCMEA) among all study countries (i.e., 15 molecules commonly assessed between England, Scotland, Australia and Sweden and 34 molecules commonly assessed and restricted between England, Scotland and Australia.

Note: *κ:* Cohen's kappa score*, CI: Confidence Interval*

4.3.2 Clinical and Economic uncertainties

Among all clinical uncertainties raised those that seemed to differ distinctly in proportion between LWC and LWCMEA were population generalisability (13% vs. 31% respectively), followed by relevance to clinical practice (22% vs. 37%) and study design (35% vs. 51%) (Table 6). Uncertainties around all other clinical evidence aspects were raised at a nearly equal proportion between the LWC and LWCMEA sample. For example, clinical evidence submitted (48% vs. 47% respectively), clinical benefit (65% vs. 72%) and clinical comparator (35% vs. 29%). Overall, it was shown by χ2 tests, and where applicable, by the Fisher's exact test, that there were no statistically significant differences between LWC and LWCMEA groups in terms of clinical uncertainties (Table 6).

Clinical uncertainties did not drive any statistically significant differences between countries within the LWC sample either. Nevertheless, looking specifically at the clinical uncertainties raised by each HTA agency when listing a drug with a MEA (i.e., LWCMEA sample) it was found that agencies differed significantly in raising uncertainties around ***Study design*** (χ^2=8.7, p<0.05), ***Clinical comparator*** (x=10.4, p<0.05), ***Population generalisability*** (χ^2=21.26, p<0.001) and ***Relevance to clinical practice*** (χ^2=13.6, p<0.0001) (Figure 7). Differences between LWC and LWCMEA groups were more prominent when studying economic uncertainties. Those that underpinned significant differences included ***utilities*** (4% vs. 42%, p<0.0001; Fisher's exact significance), followed by ***economic comparator*** (0% vs. 22%, and p<0.01; Fisher's exact significance) and ***cost-effectiveness*** (39% vs. 72%, p<0.01) (Table 6). Furthermore, uncertainties around ***utilities*** (p<0.0001), ***economic comparator*** (p<0.01), ***cost-effectiveness*** (p<0.01), ***modelling*** (p<0.0001), ***model type*** (p<0.05) and ***costs included*** (p<0.0001) also drove differences between agencies within the LWCMEA group (*Figure 7*). Finally, only ***cost-effectiveness*** (p<0.05) also generated statistically significant differences among the agencies within the LWC sample

4.3.3 Social Value Judgements

There was no statistical difference in the likelihood that most categories of social value judgements were considered for drugs that were listed on the basis of LWC vs LWCMEA. Exceptions to this were ***innovation*** (9% vs. 53%, p<0.0001; Fisher's exact significance) ***administration advantage*** (9% vs 33%, p<0.05; Fisher's exact significance) and ***special considerations*** (30% vs. 56%, p<0.05) (Table 6). In contrast, within the LWCMEA sample statistically significant differences were observed across countries in the likelihood of considering most SVJs, including ***unmet need*** (p<0.0001), ***special considerations*** (p<0.0001), ***impact on society*** (p<0.01), ***impact on Quality of Life (QoL)*** (p<0.0001), ***impact on emotional and functional burden*** (p<0.0001 respectively), ***severity of disease*** (p<0.0001), ***innovation*** (p<0.0001), and ***administration advantage*** (p<0.0001) (Figure 8). Finally, only the last three SVJs also seemed to drive statistically significant (p<0.05) cross-country differences in the LWC sample too.

Figure 7. Cross-country variation in clinical and economic uncertainties raised by HTA agencies for drug indication pairs approved with MEA.

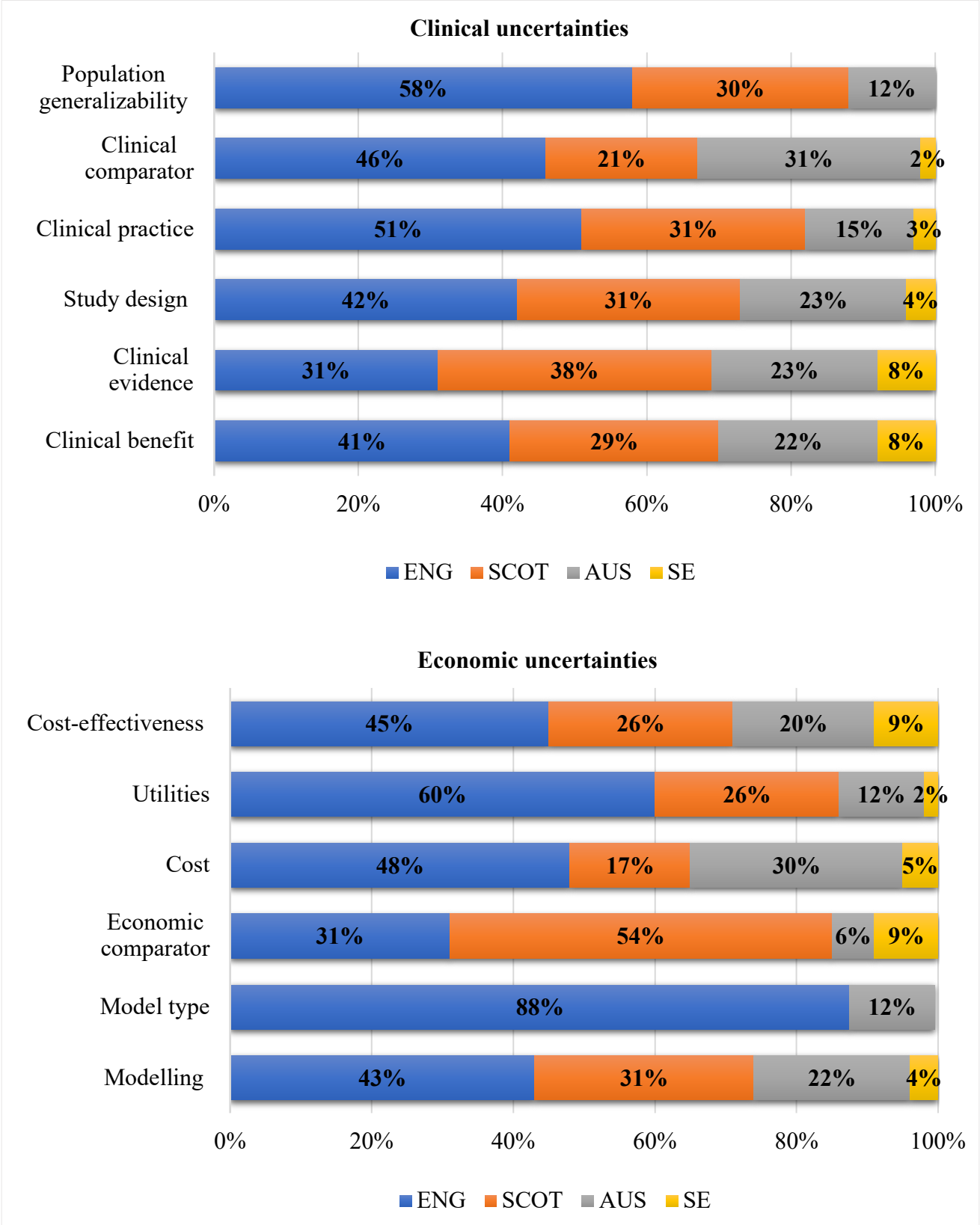
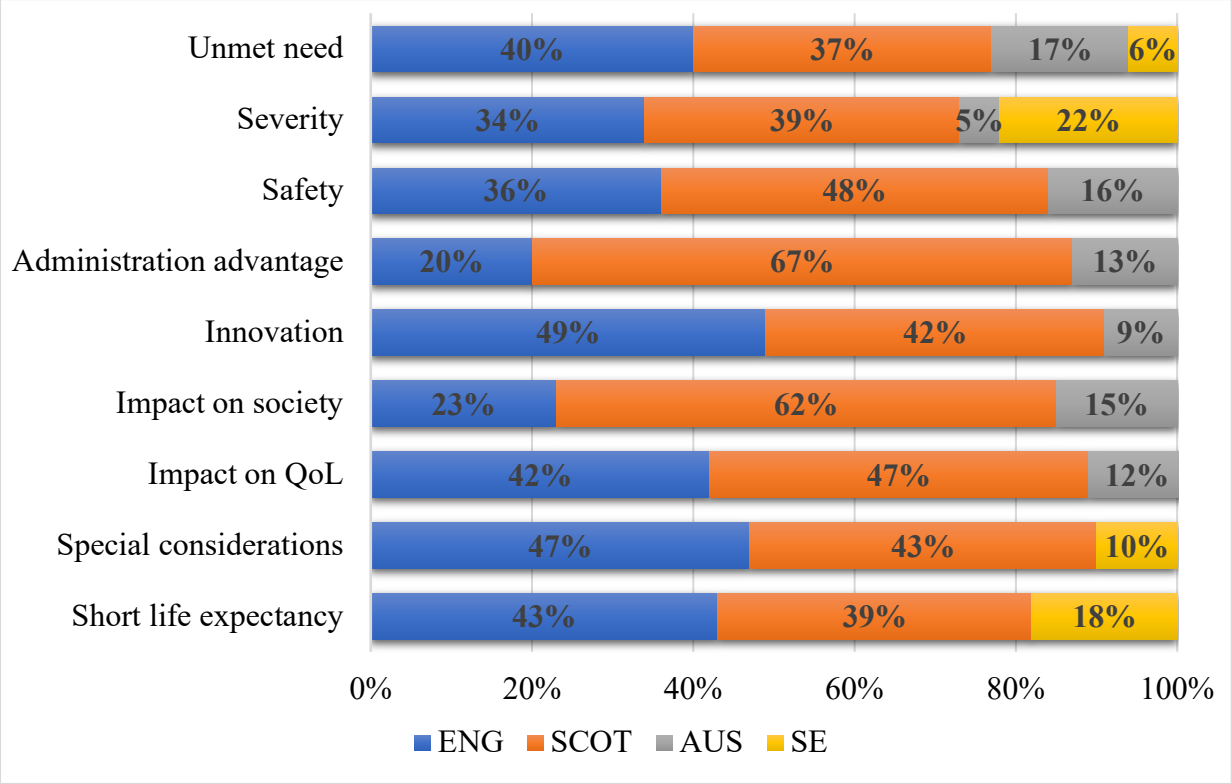


Figure 8. Cross-country variation in the SVJs considered by HTA agencies for drug indication pairs approved with a MEA.



4.4 Discussion and policy implications

We demonstrated significant disparities in the conditional/restricted recommendations across all cancer drugs appraised by four HTA agencies between 2009 and 2018. More precisely, we demonstrated a poor level of agreement in MEAs implementation across countries as indicated by the kappa scores. Our results suggest that the countries followed different strategies in dealing with the risk/uncertainty arising from the respective evidence submitted by manufacturers on new oncology therapies.

Diverging MEA outcomes between countries were influenced heavily by economic evidence uncertainties including those around cost-effectiveness, utilities and costs included in the economic model, highlighting agency-specific preferences on cost-effectiveness thresholds and evidentiary requirements for economic modelling. Similar findings around the importance of economic considerations and notably the criterion of cost-effectiveness in determining the final HTA recommendation have been described elsewhere (Maynou-Pujolras & Cairns, 2019; Nicod, 2017; Maynou-Pujolras & Cairns, 2015).

Clinical evidence uncertainties were less influential than economic towards listing a drug with a MEA; this was not surprising since in many cases it has been demonstrated that uncertainties around the strength of clinical evidence and benefit often lead to rejections commonly across agencies, without allowing any flexibility for conditions or funding negotiations (Nicod, 2017; Nicod & Kanavos, 2016). However, clinical uncertainties related to setting-specific characteristics (i.e., relevance of the technology in question and of the clinical comparator to the country/region-specific clinical practice, and/or the generalisability of trial population to the setting-specific population) were found to play a role in cross-country variation within the LWCMEA sample. This finding confirms that some agencies might place a greater emphasis on evidence related to clinical practice and trial population compared to other agencies (Nicod & Kanavos, 2016). It follows that uncertainties around these factors may also play a role in the uptake of risk-sharing negotiations across specific countries.

In terms of SVJs, our findings suggest that most social value considerations determined cross-country differences within the LWCMEA group only, except for innovation, administration advantage and severity of disease, which underpinned variation within the LWC group too. This observation highlights that considerations around Innovation and burden of disease might be crucial in allowing greater flexibility towards funding with conditions/restrictions in general, whereas considerations around impact on QoL, societal impact, emotional/functional burden, as well as other, special considerations (i.e. end of life criteria) could be influential specifically towards funding with a MEA as a restriction.

Indeed, HTA literature has recognised that factors such as the burden of disease the treatment addresses, aspects of the treatment's innovation level, but also the wider socioeconomic implications of the treatment largely affect the perceived value of new medical technologies (Kanavos & Angelis, 2013). Similarly, a number of setting-specific decision modulators (e.g., the SMC modifiers, NICE's end-of-life criteria and the human dignity principle for TLV) can contribute to a greater flexibility towards acceptance of uncertainty or higher and uncertain ICERs (Nicod & Kanavos, 2016b). Nevertheless, as shown in Figure 8, the extent to which the above factors are considered across countries in their LWCMEA recommendation decisions can fluctuate significantly, whereas even in countries where these factors are taken into account, they are not necessarily reported in their assessment process.

Ultimately, this links to discussions about the role of MEAs in the implementation of Value Based Pricing (VBP) policies, through negotiations that enable weight-adjustment of cost-effectiveness thresholds for new medicines which tackle diseases with a higher burden, demonstrate greater therapeutic innovation, and/or have wider societal benefits, such that they reflect any of these additional elements. For example, experience from TLV has shown that in Sweden risk-sharing agreements indeed complement the VBP system for out-patient drugs and enables stakeholders to mitigate different types of uncertainty (Andersson et al., 2020). Of course, greater clarity on the long-term outcomes of MEAs is also key to understand the feasibility of MEA negotiations as tool for the efficient enactment of VBP policies.

To the best of our knowledge this is the first systematic analysis that confirms cross-country differences in the uptake of MEAs and provides an understanding of the HTA decision-making variables that might influence such differences. Similar, largely descriptive studies have also identified differences in the design and implementation of MEAs across countries but still lack an in-depth analysis and transparency around the HTA determinants of MEAs (Goncalves et al., 2018, Piatkiewicz et al., 2017; Morel et al., 2013 Ferrario & Kanavos 2013; Carlson et al., 2010). To date there have been no best practice guidelines in MEAs implementation and only a few scientific papers suggest some related principles, such as the proposal by KCE in Belgium for good practice in (performance-based) MEAs (Vogler et al., 2018). As such, results from this analysis contribute to shedding light on the rationale/ strategies behind the implementation of MEAs across countries and therefore facilitate policy relevant research on the creation of implementation guidelines and/or regulations on "risk-sharing" policies. Finally, providing a transparent, evidence based description of the HTA decision-making variables that can typically influence an approval with MEA could be applied in practice by policy-makers to facilitate/accelerate HTA decision-making and therefore, allow for more timely reimbursement decisions and consequently more timely access to new, high cost medicines.

4.5 Limitations

This research contributes an improved understanding of the potential factors that drive conditional/restricted HTA recommendations with vs. without a MEA and why these two outcomes might differ significantly between countries for the same drug, presenting with similar clinical evidence across countries. Nevertheless, our findings should be interpreted with

caution since there are certain limitations in our analysis, which have hindered the accuracy and robustness of our results.

Firstly, variables under Stage 1 of the HTA process (Figure 6), such as the type of clinical evidence submitted or ICER submitted, have not been included in this analysis based on the assumption that their influence on determining an LWC or LWCMEA outcome will be captured through their respective uncertainties and whether these were raised or not in the decision-making process. Since variables under both stages have been found to have an impact on the final HTA recommendation (Nicod & Kanavos 2016; Andersson et al., 2020) future analyses could include these variables as a robustness check.

Additionally, since budget impact is only taken into account by PBAC, a budget impact specific uncertainty was not considered due to lack of comparability across countries. Nevertheless, any budget impact related concerns raised by PBAC would have already been reflected in the "cost" and "modelling" related uncertainties.
Furthermore, as the calculation of the κ scores required the assumption of paired observations to be met, we performed the calculation only on the drug-indication pairs that were assessed by all four agencies, reducing the available sample size significantly. As these analyses could have been more robust if the sample size was increased, it is suggested that a future replication of this study augments the sample size through inclusion of molecules from additional therapeutic areas. Similarly, since our analysis covered only medicines reimbursed at the national level, future analyses could also account for technologies negotiated at the hospital level.

Finally, advanced statistical modelling was not used at this stage, as our aim was to understand which of the variables play at least some role in driving key differences in the conditional/restricted HTA recommendation decisions between countries. However, in subsequent analyses the key variables identified herein can be included in a multinomial logistic regression model to also understand their level of impact on divergencies between the conditional/restricted HTA recommendation decisions and the type of MEA in place across countries.

Overall, it is important that the findings reported here are interpreted with caution given that the data collected and analysed was sourced from publicly accessible reports which may, in

some instances, represent amended versions of the assessment process to preserve manufacturers commercial sensitivities and as such, may not represent an absolute reflection of the committee's considerations.

4.6 Conclusions and way forward

MEAs are implemented globally and particularly in oncology, to address uncertainties arising from the high cost and simultaneous immature clinical evidence of new, innovative pharmaceuticals. We showed that MEAs' uptake across countries for the same drugs might differ substantially, and it is subject to setting-specific evidentiary requirements on economic modelling, the comparators, costs and utilities included therein but primarily also subject to preferences on social value considerations, such as the socioeconomic and QoL impact of the treatment appraised, as well as setting specific burden of disease. A better understanding of the criteria that determine MEAs' utilisation across countries is fundamental for future research aimed at informing country-specific, "best-practice" guidelines for successful MEA negotiations.

5. Research article II. Health technology assessment criteria as drivers of coverage with managed entry agreements: a case study of cancer medicines in four countries

"Medicine is a science of uncertainty and an art of probability"

- William Osler

Box 6. Research article II - Highlights

- MEAs' uptake was influenced by uncertainties around cost-effectiveness, uncertainties around the utilities included in the economic model and the SVJ of innovation.

- OBAs were influenced by clinical evidence uncertainties, rarity and severity of the condition and FBAs by the SVJs of innovation and societal impact of the technology in question.

- The requirement for a MEA and the type of MEA payers are looking for, varies according to the disease area and other value considerations specific to the particular medicine in question.

ABSTRACT

Background: Managed entry agreements (MEAs) continue to emerge in health technology assessment (HTA)-based decision- making, to address evidentiary uncertainties arising therein. Evidence on the HTA criteria that influence MEAs' uptake remains scarce. This study explores the HTA criteria that determine (i) if an HTA funding decision will be listed with conditions (LWC) other than a MEA, or with a MEA as a condition (LWCMEA), and ii) the MEA type implemented (i.e., financial, outcomes based, or combination). **Methods:** HTA reports of all oncology medicines approved since 2009 in Australia, England, Scotland, and Sweden were searched to capture the clinical/economic evidence uncertainties raised in the decision-making process, the Social Value Judgements (SVJs) considered therein and the final coverage decision. Binary and multinomial logit models captured the probability (odds ratio (OR)) of a coverage decision being LWCMEA vs. LWC, and of the MEA being financial, outcomes based, or combination, based on the HTA criteria studied. **Results:** 23 (12%) LWC and 163 (88%) LWCMEA decisions were identified; 136 (83.4%) comprised financial, 10 (6.2%) outcomes based and 17 (10.4%) combination MEAs. LWCMEA decisions were driven by economic model utilities' uncertain- ties ($7.16 < OR < 26.7$, $p < .05$), and the innovation ($8.5 < OR < 11.7$, $p < .05$) SVJ. Outcomes based contracts were influenced by clinical evidence ($OR = 69.2$, $p < .05$) and relevance to clinical practice ($OR = 26.4$, $p < .05$) uncertainties, and rarity ($OR = 46.2$, $p < .05$) and severity ($OR = 23.3$, $p < .05$) SVJs. Financial MEAs were influenced by innovation ($8.9 < OR < 9.3$, $p < .05$) and societal impact ($OR = 17.7$, $p < .0001$) SVJs. **Conclusions:** This study provides an empirical framework on the HTA criteria that shape payers' preferences in funding with MEAs, when faced with uncertainty.

Keywords: Managed Entry Agreements; HTA decision-making; Conditional reimbursement; Risk-sharing; Discounts

5.1 Background and study objectives

The rapid progress of therapeutic innovation and the respective introduction of new, high-cost, therapies might be favourable from the patient's perspective, but from the payer's perspective, it poses challenges in managing the market entry and long-term affordability of these therapies (EC, 2018).[5] To mitigate these pressures countries are developing policies to facilitate decision-making about the reimbursement of novel, high- cost pharmaceuticals, such as the cost-effectiveness appraisal of these technologies. In many countries worldwide, these evaluations take the form of health technology assessment (HTA), a process where the clinical and cost-effectiveness of these products is assessed by national competent authorities, to understand if these products demonstrate the "value-for- money" profile required by different healthcare systems to enable coverage (Ferrario & Kanavos, 2013; Husereau & Cameron, 2011). In the HTA process, challenges may arise due to evidentiary uncertainties generated by the immature or early phase evidence submitted by manufactures for appraisal. The uncertainties facing decision-makers have been classified into three broader categories including (i) clinical (e.g., the applicability of study endpoints and treatment population to the actual clinical practice in the country of interest), (ii) financial (e.g., the actual number of doses and treatment duration required in real-world practice and the respective aggregate budget impact) and (iii) utilisation uncertainties (e.g., the appropriate prescribing of the product for the patient population in which it is deemed to be cost-effective) (WHO, 2015; Ferrario & Kanavos, 2013). To address uncertainties arising in the HTA-based decision- making, managed entry agreements (MEAs) between payers and manufacturers are increasingly being employed in many countries as part of the process. Depending on the type of uncertainty to be addressed, literature has classified MEAs in two broader categories, namely outcome- and financial- based agreements depending on whether they aim to mitigate uncertainties related to drug performance or not respectively, while combination agreements with financial and outcome- based aspects have also been observed (KCE 2017; Ferrario & Kanavos, 2013; Garrison et al., 2013). Literature has shown that even in cases where countries implemented a MEA for the same medicine-indication pair, often presenting with similar uncertainties, there was still variation in the types of agreements implemented and the respective objective targeted by these agreements (Pauwels et al., 2017; Ferrario & Kanavos, 2015, Carlson et al., 2010). Descriptive studies have suggested that health

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system-specific considerations and perceptions of "risk" across settings might play a role in explaining such differences (Ferrario & Kanavos, 2015; WHO, 2015; Morel et al., 2013). Furthermore, a descriptive, comparative analysis of MEAs for cancer medicines in different settings, found that cross-country differences may arise chiefly due to payers' preferences on social value considerations, such as the socioeconomic and Quality of Life (QoL) impact of the treatment appraised, followed by setting-specific requirements on the economic model, and the comparators, costs, and utilities included in the model (Efthymiadou & Kanavos, 2021).

Despite the growing utilisation of MEAs, quantitative, empirical research on the HTA factors that have an impact on the uptake of MEAs across settings remains scarce (Antonanzas et al., 2019; Akehurst et al., 2016). This has significant implications for the transparency of "best-practice" guidelines on MEA negotiation and implementation processes across and within countries (Antonanzas et al., 2019; Garrison et al., 2013).

5.2 Methods

5.2.1 Sample selection

All oncology medicines which obtained regulatory approval by the European Medicines Agency (EMA) in Europe and by the Therapeutic Goods Administration (TGA) in Australia between 1st January 2009 and 15th June 2018 (at the medicine-indication pair level) were studied in Australia (AUS), England (ENG), Scotland (SCOT) and Sweden (SE). Oncology was selected as the study therapeutic class because it has been documented to be the therapeutic class with the largest proportion of implemented MEAs and the therapeutic class where MEAs continue to be increasingly implemented (Ferrario & Kanavos, 2013).

5.2.2 Data collection

The conceptual framework underpinning data collection operates under the overarching hypothesis that HTA cover- age decisions (whether positive, negative or restricted) are primarily shaped by the HTA process itself, including the evidence appraised therein (whether clinical, economic or otherwise), the way this evidence is interpreted/assessed by the decision-makers, and the broader socioeconomic and political context in which the decision-making takes place (Efthymiadou & Kanavos, 2021; Nicod & Kanavos, 2016; Maynou-Pujolras & Cairns, 2015).

Essentially, this framework divides the HTA process and relevant variables of interest in four "buckets" where it is hypothesised that a combination of variables within "buck- ets" (A), (B) and (C), determine the observed outcome in "bucket" (D) as follows: (A) clinical and economic evidence appraised (e.g., trial characteristics, comparators, Incremental Cost Effectiveness Ratio (ICER) and economic model specifications), (B) interpretation/assessment of this evidence (i.e., clinical and economic evidence related uncertainties raised), (C) societal and system-specific context in which HTA-based decision-making operates (i.e., dimensions of value that a technology adds in the society/setting of interest, such as the unmet need it targets in terms of therapeutic treatment availability, the societal benefit it offers in terms of improved patient QoL, functional ability outcomes, all referred to as Social Value Judgements (SVJs)) and system-specific processes for decision-making (e.g., the use of a single or multiple technology appraisal in England), and (D) coverage decision outcome categorised as: (i) L = List (i.e., positive coverage decision), (ii) LWC = List with one or more conditions which are not classified as MEAs (e.g., dosing restrictions, clinical restrictions relating to treatment eligible sub-population, etc.), (iii) LWCMEA = List with one or more conditions including at least one restriction classified as MEA and iv) DNL = Do not list (i.e., negative coverage decision).

Data on the above "buckets", per medicine-indication pair in all study countries were extracted from publicly available HTA appraisals published in the respective HTA bodies' websites, namely PBAC (AUS), NICE (ENG), TLV (SE) and SMC (SCOT). A database stratified by HTA agency was built to describe and classify MEAs across the respective HTA bodies and facilitate data analysis.

5.2.3 Data analysis

Restricted HTA outcomes were coded as a binary variable (i.e., LWC vs. LWCMEA), while the type of MEA was coded as a multinomial variable (i.e., financial ("F"), out- comes ("O") based or combination ("C")), based on taxonomies that have been described in the literature (Ferrario & Kanavos, 2013; Garrison et al., 2013; Carlson et al., 2010).

Finally, assuming that all categories of uncertain- ties and SVJs were applicable to all drug-indication pairs studied, these were treated and coded as binary variables based on whether they have been raised and considered (or not), respectively, in the HTA-based decision-making process (Efthymiadou & Kanavos, 2021). More specifically, the mention/raise of an

uncertainty or SVJ—regardless of its weight/impact on the decision-making process—has been classified as "raised" or "considered", while in cases where there is no mention of a specific uncertainty or SVJ this was classified as "not raised" or "not considered", respectively, for each drug-indication pair.

For the purposes of this analysis, a panel data design was not feasible as the study sample comprised one decision per medicine-indication pair per country in a particular year as opposed to annual decisions; similarly, since the response variables are categorical, they could not be modelled as a linear combination of explanatory variables either (Maynou-Pujolras & Cairns, 2015). Consequently, the relationships that this research article explored were described as probabilities and as such, a statistical model was designed to estimate the probability of a scheme being concluded and subsequently its type, based on the identified HTA variables of significance. Therefore, the associations studied were described as prob- abilities, estimated by means of a binary and a multinomial logit model. For the first part of the analysis, binary logistic regression was used to estimate the probability of a technology receiving restricted coverage with at least one restriction in the form of a MEA (as opposed to one or more restrictions without a MEA) based on a set of HTA explanatory variables, hypothesised to influence HTA-based decision-making (Nicod & Kanavos, 2016; Maynou-Pujolras & Cairns, 2015). Additionally, as a robustness check, Pearson's Chi- squared tests were performed to identify which HTA criteria determine statistically significant differences between LWC and LWCMEA coverage decisions for each study country. Finally, for the second part of the analysis, multinomial logistic regression was used to model the probability of an implemented MEA taking one of the three outcomes "F", "O" or "C" given a set of HTA criteria/ explanatory variables associated with the medicine-indication pair in question.

5.3 Results

5.3.1 LWC vs. LWCMEA coverage decision

Of the restricted coverage decisions studied (n = 186), 88% (n = 163) were LWCMEA and 12% (n = 23) were LWC. A number of binary logit models were performed to ascertain the effects of different HTA criteria on the likelihood of receiving a LWCMEA as opposed to a LWC coverage decision. The statistically significant models with the best predictability rate are presented below (Table 8). Values highlighted in bold correspond to the effect size/

likelihood (i.e., OR) and the respective p-value of the HTA criteria that were found to be of statistical significance within the different models.

The first model (χ^2 = 47.7, p < 0.0001) explained 43% (Nagelkerke R^2) of the variance in restricted coverage decisions and correctly classified 92% of cases. Medicine-indication pairs with utility and cost-effectiveness related uncertainties were approximately 27 (OR=26.731, p<0.05) and 4 (OR=3.926, p<0.05) times, respectively, more likely to receive a LWCMEA instead of a LWC coverage decision. The SVJs of innovation and rarity were associated with an increased (OR=8.504, p<0.05) and decreased (OR=.147, p<0.05) likelihood of a LWCMEA (as opposed to LWC) coverage decision, respectively.

The second model (χ^2 = 51.3, p < 0.0001) explained 46% (Nagelkerke R^2) of the variance in restricted outcomes and correctly classified 91% of cases. Medicine-indication pairs with utility and cost-effectiveness related uncertain- ties were approximately 21 (OR=20.97, p<0.05) and 4.5 (OR=4.361, p< 0.05) times respectively, more likely to receive a LWCMEA instead of a LWC coverage decision. The SVJs of innovation and rarity were associated with an increased (OR=10.632, p<0.05) and decreased (OR=.165, p<0.05) likelihood of a LWCMEA (as opposed to LWC) coverage decision, respectively.

The third model (χ^2 = 18.25, p < 0.0001) explained 30% (Nagelkerke R^2) of the variance in restricted coverage decisions and correctly classified 88% of cases. Medicine-indication pairs with utility and economic comparator related uncertainties were approximately 7 (OR=7.169, p<0.01) and 4 (OR=4.147, p<0.05) times, respectively, more likely to receive a LWCMEA instead of a LWC coverage decision. The SVJ of innovation was associated with an increased (OR=11.727, p<0.01) likelihood of a LWCMEA (as opposed to LWC) coverage decision.

Finally, the fourth model (χ^2 = 19.45, p < 0.001) explained 19% (Nagelkerke R^2) of the variance in restricted outcomes and correctly classified 87% of cases. Medicine-indication pairs with cost-effectiveness related uncertainties were approximately 3 (OR=3.24, p<0.05) times more likely to be classified as LWCMEA instead of LWC. The SVJs of special considerations and rarity were associated with an increased (OR=3.014, p<0.05) and decreased (OR=.254, p<0.05) likelihood of a LWCMEA (as opposed to LWC) coverage decision, respectively.

5.3.2 Country-specific outcomes

Pearson's chi-squared tests were also performed to identify any HTA criteria that determine statistically significant differences between LWC and LWCMEA coverage decisions for each study country. Cost-effectiveness uncertainties determined statistically significant differences between the LWC and LWCMEA groups for England (χ^2 = 8.98, p = 0.003), Scotland (χ^2 = 3.97, p = 0.046) and Australia (χ^2 = 5.02, p = 0.025). Additionally, uncertainties around the economic model used and the utilities included in the model highlighted statistically significant differences between LWC and LWCMEA coverage outcomes in England (χ^2 = 5.65, p = 0.017) and Australia (χ^2 = 3.10, p = 0.028), respectively. Finally, uncertainties around clinical evidence and clinical benefit, and the SVJ of innovation, underscored statistically significant differences between LWC and LWC- MEA groups for Scotland (χ^2= 3.68, p = 0.04), England (χ^2 = 4.98, p = 0.026) and Australia (χ^2 = 3.10, p = 0.028), respectively (see Appendix 3).

Table 8. Binary logit models, predicting the likelihood (Odds Ratio (OR)) of a funding decision being restricted with vs. without MEA, based on the set of HTA predictors studied.

	Model 1		**Model 2**		**Model 3**		**Model 4**	
HTA Predictor	*OR*	*p*	*OR*	*p*	*OR*	*p*	*OR*	*p*
Clinical uncertainties								
Population generalisability	1.859	.506	2.112	.430	.444	.505	2.352	.219
Study design	1.861	.359	1.977	.319	.535	.464		
Clinical comparator	.585	.459	.594	.477	.835	.361		
Relevance to clinical practice	.415	.241	.493	.349				
Clinical evidence					.292	.589		
Clinical benefit							.791	.688
Economic uncertainties								
Economic modelling	.695	.612	.579	.463	.386	.535	1.264	.672
Cost effectiveness	**3.926**	**.034**	**4.361**	**.029**	**6.700**	**.010**	**3.240**	**.022**
Utilities	**26.731**	**.018**	**20.970**	**.028**	**7.169**	**.007**		
Model type	1.198	.898	1.954	.653				
Costs	.906	.878	.846	.796				
Economic comparator			13.204	.997	**4.147**	**.042**		
Social Value Judgements								
Rarity	**.147**	**.024**	**.165**	**.040**	3.443	.064	**.254**	**.017**
Special considerations	.553	.452	.478	.359	.361	.548	**3.014**	**.040**
Severity	2.683	.148	2.326	.208	.160	.689		
Unmet need	.905	.880	.834	.789	.003	.956		
Innovation	**8.504**	**.029**	**10.632**	**.026**	**11.727**	**.001**		
Administration advantage	4.721	.160	4.709	.184	2.506	.113		
Impact on society	.292	.356	.259	.316	.035	.852		
Impact on QoL	1.038	.962	.993	.993	.084	.772		
Impact on emotional burden	19.047	.998	16.154	.998				
Impact on functional burden	1.245	.893	.392	.612				
Constant	1.819	.291	1.898	.259	3.667	.000	2.686	.033
Model statistics	x^2	*p*	x^2	*p*	x^2	*p*	x^2	*p*
Likelihood ratio test	47.659	.000	51.297		18.25	.000	19.45	.003
Hosmer & Lemeshow test	12.348	.136	7.289	.506	.279	.870	5.97	.543
Predictability (%)	92%		91%		87%		87%	

5.3.3 Type of MEA

163 MEAs were identified, of which 83.4% (*n* = 136) were "F", 6.2% (n = 10) were "O" and 10.4% (*n* = 17) were "C". A number of multinomial logit models were performed to identify the sets of HTA criteria, including clinical/eco- nomic uncertainties and SVJs, that best predicted the likelihood of a MEA in place for the study medicine-indication pairs being "F", "O" or "C" (Table 9; Figure 9). Values highlighted in bold correspond to the effect size/likelihood (i.e., OR) and the respective p-value of the HTA criteria that were found to be of statistical significance within the different models.

The first model (χ^2 =38.61, p<0.0001) explained 42% (Nagelkerke R^2) of the variance in MEA types. Medicine-indication pairs with uncertainties raised around relevance to clinical practice (OR=.072, p< 0.05 and OR=.056, p<0.05) and social value considerations around rarity (OR=.073, p<0.05 and OR=.04, p<0.05) were more likely to be funded with an "O", as opposed to a "F" and a "C" agreement respectively. On the contrary, the social value consideration of innovation was as associated with an approximately 9.5 (OR=9.346, p<0.05) times higher likelihood of a "F" as opposed to an "O" agreement.

The second model (χ^2 = 41.79, p < 0.0001) explained 45% (Nagelkerke R^2) of the variance in MEA types. Medicine-indication pairs with uncertainties raised around clinical evidence (OR=.066, p<0.05) and relevance to clinical practice (OR=.084, p<0.05), and social value considerations around rarity (OR=.061, p<.05) were more likely to be funded under an "O" as opposed to a "F" agreement. Similarly, medicine-indication pairs with social value considerations around rarity were more likely (OR=.034, p<0.05) to lead to an "O" as opposed to a "C" agreement. On the contrary, medicine-indication pairs with social value considerations around innovation and impact on society were associated with an approximately 9 (OR=8.999, p<0.05) and 18 (OR=17.732, p<0.0001) times higher likelihood of coverage with a "F" as opposed to an "O" agreement.

The third model (χ^2 = 47.94, p < 0.0001) explained 50% (Nagelkerke R^2) of the variance in MEA types. Medicine-indication pairs with uncertainties raised around clinical evidence (OR=69.221, p<0.05) and relevance to clinical practice (OR=26.4, p< 0.05), and social value considerations around rarity (OR=46.207, p<0.05) and severity (OR=23.349, p<0.05), had a higher likelihood of coverage with an "O" instead of a "F" agreement. Additionally, medicine-

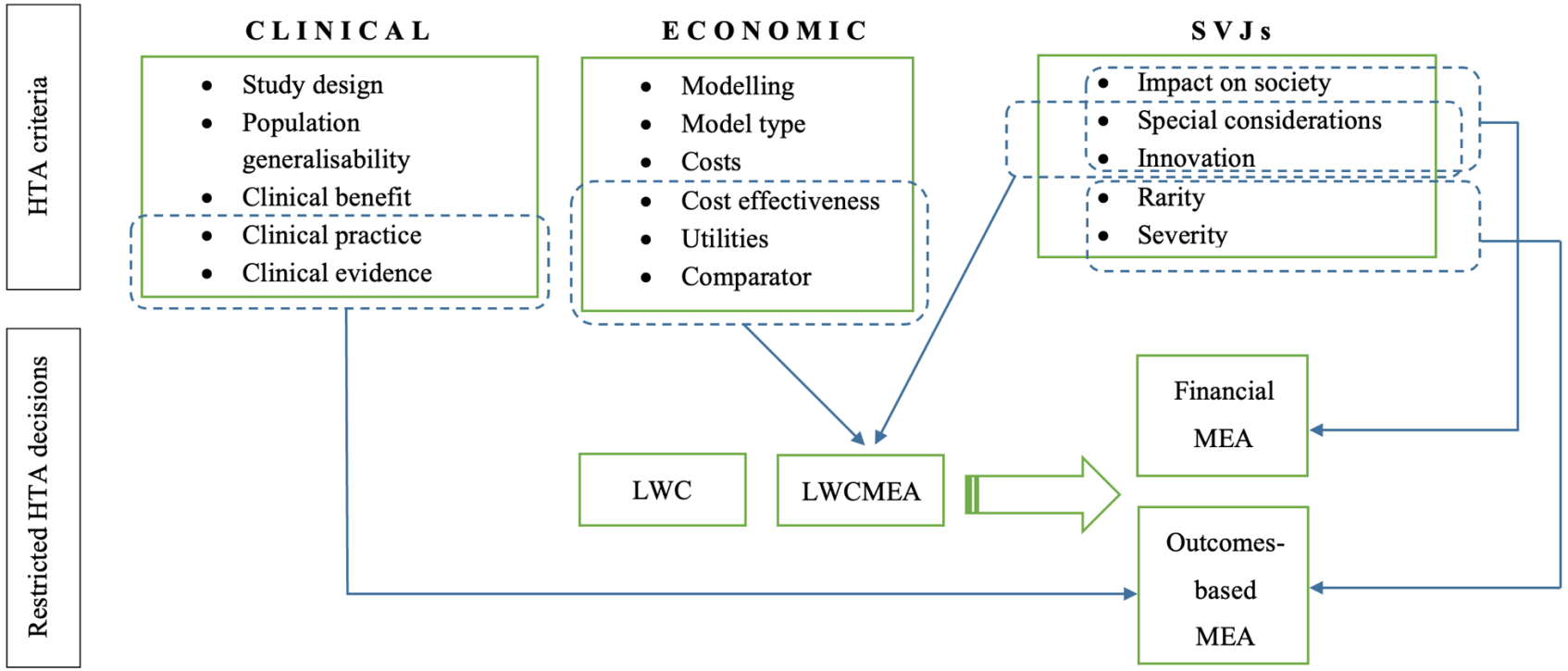
indication pairs with social value considerations around innovation (OR=.038, $p<0.05$) and special considerations (OR=.148, $p<0.05$) were associated with a higher likelihood of coverage with a “F” instead of a “C” agreement.

Table 9. Multinomial logit models, predicting the likelihood (Odds Ratio (OR)) and respective statistical significance (*p*) of a MEA being financial or outcomes based or a combination of both, based on the different sets of HTA criteria studied

	Model 1				**Model 2**				**Model 3**			
	Financial vs. outcomes[a]		*Combination vs. outcomes*[a]		*Financial vs. outcomes*[a]		*Combination vs. outcomes*[a]		*Combination vs. financial*[a]		*Outcomes vs. financial*[a]	
HTA predictor	*OR*	*p*	*OR*	*p*	*OR*	*p*	*OR*	*p*	*OR*	*p*	*OR*	*p*
Clinical evidence	.097	.080	.233	.332	**.066**	**.045**	.153	.234	5.262	.078	**69.221**	**.023**
Cost effectiveness	3.033	.437	.663	.800	3.793	.379	.691	.828	.327	.207	.310	.460
Innovation	**9.346**	**.042**	.276	.412	**8.999**	**.047**	.188	.331	**.038**	**.013**	.072	.085
Rarity	**.073**	**.032**	**.040**	**.048**	**.061**	**.029**	**.034**	**.046**	.977	.986	**46.207**	**.041**
Clinical practice	**.072**	**.043**	**.056**	**.044**	**.084**	**.047**	.065	.070	.786	.779	**26.400**	**.046**
Clinical benefit	4.830	.177	16.491	.059	1.000	.264	1.000	.110				
Clinical comparator	.726	.776	.627	.736								
Impact on society					**17.732**	**.000**	18.416	[b]				
Modelling									.662	.641	.685	.768
Special considerations									**.148**	**.047**	.139	.212
Utilities									1.719	.575	.257	.365
Severity									3.490	.278	**23.349**	**.049**
Intercept		.011		.124		.006		.056		.426		.012

OR odds ratio, *p p* value
[a]Reference category of the multinomial model, [b]No statistics are computed because variable is a constant

Figure 9. Analytical framework on the HTA criteria driving restricted coverage decisions with a MEA (LWCMEA) and the respective type of MEA



HTA: Health Technology Assessment, LWC: List with conditions, LWCMEA: List with conditions, including a MEA, MEA: Managed Entry Agreement, SVJs: Social Value Judgements. The categories of the HTA criteria included in this analysis and subsequently used in the above framework are based on previously published relevant research and all respective definitions are described in detail therein (Efthymiadou & Kanavos, 2021).

Source: The author; the framework is fully conceptualised by the author, based on background from relevant literature (Efthymiadou & Kanavos, 2021; Nicod & Kanavos, 2016; Ferrario & Kanavos, 2013)

5.4 Discussion and policy implications

This paper explored the sets of HTA criteria, including clinical/economic uncertainties and SVJs, that might contribute to a higher likelihood of restricted HTA recommendations including a MEA as part of the restriction or not, and subsequently identified the HTA-relevant criteria that determine the respective type of a MEA in place (Figure 9). This is the first study to date to model the HTA criteria that determine both the utilisation and the typology of MEAs in oncology therapies across countries.

Coverage with a MEA was predominantly driven by uncertainties around the utilities of the economic model, and the SVJ of innovation. Outcome-based contracts were primarily influenced by uncertainties on the clinical evidence and relevance to clinical practice, followed by the rarity and severity of the condition. Financial MEAs were influenced by the SVJs of innovation and societal impact of the technology in question. Similar findings arise from the limited and largely descriptive evidence available in the relevant literature. A recent review of outcome-based MEAs in the OECD countries concluded that these may indeed be more common for products with orphan indications, while a case study presented therein concluded that outcome-based schemes in England mostly tried to address uncertainty around the magnitude of long-term clinical benefit, and concerns around the duration of therapy in routine clinical practice (Wenzl & Chapman, 2019). It has also been suggested that outcome-based contracts typically aim to address uncertainties around efficacy or effectiveness in the general population, long-term clinical evidence on clinically significant endpoints (i.e., clinical rather than surrogate markers), as well as safety, and numbers likely to be treated in real-world practice (Garrison et al., 2013). Finally, using a theoretical model, Antonanzas et al. (2011) analysed situations in which payers will prefer a MEA over non-MEA and concluded that payers' decisions will depend on monitoring costs, marginal production costs, and the utility patients will derive from treatment.

Beyond its empirical study design, another strength of this analysis is the holistic approach considered in the HTA criteria driving MEAs, accounting for the interconnected impact of both uncertainties and SVJs on the final HTA/MEA outcomes, as opposed to the existing literature that has primarily studied the impact of uncertainties. This is important because the emphasis placed on HTA criteria differs between HTA stakeholders across or even within countries; some countries focus on disease severity and drug efficacy, others concentrate on cost-

effectiveness, whereas in some countries, payers and HTA stakeholder experts have different preferences on the HTA process and hence, divergent views on which criteria are the most significant within their systems (Akehurst et al., 2017). Specifically, for MEAs, it arises that the requirement for an agreement and the type of agreement preferred by payers, is subject to the disease area and other setting and medicine specific, value considerations (Dunlop et al., 2018).

Furthermore, despite significant efforts to create good practice guidelines on design, the implementation, and evaluation of MEAs (WHO, 2018; NICE, 2018; SMC, 2019; PBS, 2017; DoH; Garrison et al., 2013), there are still gaps in understanding the conditions that lead to acceptance of proposed MEAs from the payers' perspective. For example, in England, rejections of manufacturer proposed agreements (i.e., Patient Access Schemes (PAS)) are still observed, highlighting that despite existing guidelines on the submission of PAS, we still lack an understanding of the considerations that render a MEA successful from the point that a company submits a PAS proposal and until this is accepted by NICE (Pharmaforum 2015; DoH). On that front, the findings presented here can enhance transparency in existing guidelines by promoting a shared understanding on the aspects that determine value in MEA negotiations from the payer's' perspective. This can guide both manufacturers—to tailor agreement proposals such that they align with the value perceptions of different payers, and payers—to establish more streamlined processes in decision-making under uncertainty.

5.5 Limitations

Despite the empirical contribution of this study in the field of MEA research, the results presented herein should be interpreted with caution due to certain methodological discrepancies that possibly undermine the robustness of the study.

First, country-specific policies, purchasing framework and context in which pricing and reimbursement decision-making operates have not been incorporated in the analysis per se. It is believed that their potential confounding effect has been captured through criteria around HTA system-specific considerations such as SVJs. Of course, even though the SVJ classification used in this analysis is largely applicable to all important SVJs considered across countries (Efthymiadou & Kanavos, 2021; Nicod & Kanavos, 2016), SVJs still remain highly subjective and dependent on the setting-specific context in which they are considered.

Therefore, the SVJ variables included in this analysis might not be entirely representative of all the system-specific considerations that are of "weight" in HTA-based decision-making across the study countries. In addition, reference in the literature has been made on the impact of the overall country-specific healthcare and welfare characteristics on HTA-based decision-making, such as healthcare spending per capita, societal willingness-to-pay and the structure of the healthcare system (Cerri et al., 2014). As such, to enhance accuracy of the results, these factors should be explicitly included in future studies modelling the uptake of MEAs.

Second, based on the methodology followed in this analysis, whether an uncertainty has been resolved or not reflects the impact of the implemented MEA, while the mention/raise of an uncertainty during the appraisal (whether resolved or not following the proposed MEA) reflects a potential determinant/reason behind the implementation of a MEA as a funding modality. On that front, this specific analysis does not differentiate between resolved/unresolved uncertainties; it aims to capture all the uncertainties raised (as per the HTA reports/public summary documents) to understand which of these had a greater impact in determining LWCMEA coverage decisions. However, it is of critical importance to conduct further analyses to capture the uncertainties that remain following the proposed MEA, as an evaluation of its impact.

Finally, the limited sample size studied hinders the overall power, sensitivity and specificity of the models. Future replication of these models would benefit from a larger study sample, possibly by including coverage decisions of medicines in other therapeutic areas too, although caution should be exercised to account for potential comparability issues arising from differences in the value that different SVJs reflect for payers in different disease areas. Overall, due to setting-specific nuances in HTA-based and reimbursement decision-making, the criteria and their relative weight in the decision-making process, as identified in this analysis, are not necessarily generalisable across settings and should be interpreted on an individual basis and adapted to the respective setting-specific context in question.

5.6 Conclusions & way forward

The growing interest in MEAs and their increased implementation across countries globally, necessitates an enhanced transparency on the aspects that determine value in MEA negotiations. On that front, the findings of this study provide a better understanding on the

decision-making criteria that shape payers' preferences in coverage with a MEA or not. Empirical research on the HTA criteria driving MEAs is key to encourage a transparent, cross-country learning on how MEAs can be tailored to align with payers' perceptions on "value" and ultimately, promote more efficient MEA negotiations and increased opportunities for coverage through MEAs. There are still barriers to overcome for MEAs to be implemented more widely and efficiently, such as their increased administrative burden, the absence of standardised processes to evaluate their outcomes and the confidentiality around the final prices and discounts negotiated under these agreements.

6. Research article III. Impact of Managed Entry Agreements on availability of and timely access to medicines: an ex-post evaluation of agreements implemented for oncology therapies in four countries.

"*In medicine, there is always a balance between risk and benefit*"

- Mark Walport

Box 7. Research article III – Highlights

- This is the first study to date to conduct a post-implementation evaluation of MEAs across countries, to quantify their impact on availability of and timely access to medicines.

- Evidence resubmission with a MEA, increased the likelihood of a positive reimbursement following previous coverage rejection, although absence of clinical benefit uncertainties and the use of a clinically relevant endpoint in the resubmitted evidence were equally important.

- Presence specifically of an OBA can delay reimbursement decision-making, although regardless of their type, MEAs can only improve time to decision-making if they have a clear rationale and truly address the uncertainties raised by the technology in question.

ABSTRACT

Background: Despite the increased utilisation of Managed Entry Agreements (MEAs), empirical studies assessing their impact on achieving better access to medicines remains scarce. In this study we evaluated the role of MEAs on enhancing availability of and timely access to a sample of oncology medicines that had received at least one prior rejection from reimbursement. **Methods:** Funding decisions and their respective timelines for all oncology medicines approved between 2009 and 2018 in Australia, England, Scotland and Sweden were studied. A number of binary logit models captured the probability (Odds ratio (OR)) of a previous coverage rejection being reversed to positive after resubmission with vs. without a MEA. Gamma generalised linear models were used to understand if there is any association between time to final funding decision and the presence of MEA, among other decision-making variables, and if so, the strength and direction of this association (Beta coefficient (B)). **Results:** Of the 59 previously rejected medicine-indication pairs studied, 88.2% ($n = 45$) received a favourable decision after resubmission with MEA vs. 11.8% ($n = 6$) without. Average time from original submission to final funding decision was 404 ($\pm$ 254) and 452 ($\pm$ 364) days for submissions without vs. with MEA respectively. Resubmissions with a MEA had a higher likelihood of receiving a favourable funding decision compared to those without MEA ($43.36 < OR < 202$, $p < 0.05$), although approval specifically with an outcomes-based agreement was associated with an increase in the time to final funding decision ($B = 0.89$, $p < 0.01$). A statistically significant decrease in time to final funding decision was observed for resubmissions in Australia and Scotland compared to England and Sweden, and for resubmissions with a clinically relevant instead of a surrogate endpoint. **Conclusions:** MEAs can improve availability of medicines by increasing the likelihood of reimbursement for medicines that would have otherwise remained rejected from reimbursement due to their evidentiary uncertainties. Nevertheless, approval with a MEA can increase the time to final funding decision, while the true, added value for patients and healthcare systems of the interventions approved with MEAs in comparison to other available interventions remains unknown.

Keywords: Risk sharing agreements, Managed entry agreements, Reimbursement, Access delays, Impact assessment

6.1 Background and study objectives

The restricting cost containment environment in which healthcare systems are required to operate, introduces challenges on policy decisions about the coverage of highly priced pharmaceuticals.[6] These challenges often arise as the evidence presented by manufacturers is not always sufficient to estimate the real-life budget impact, clinical and cost-effectiveness of these high-cost pharmaceuticals. More importantly, the uncertainties posed by the immature evidence submitted by manufacturers may prevent or delay healthcare payers from reaching conclusions on coverage decisions, thus affecting patient access (Vogler et al., 2018).

Against this background, there is an interest from healthcare payers and manufacturers to collaboratively manage the entry of new pharmaceuticals in the market by linking price and reimbursement levels to real-world performance or utilization of medical products with the aim of sharing the risk surrounding the introduction of new technologies with uncertain evidence on their clinical and/or cost-effectiveness profiles. Prices can be linked to future outcomes and/or volumes and the specific conditions of the negotiations are drawn up into product listing agreements usually summarised as "RSAs", "MEAs" or "PAS" (Garrison et al., 2015; Ferrario & Kanavos, 2013; Klemp et al., 2011). The main types of these agreements are financial-based and health outcomes-based agreements, or occasionally combination of both types. The former includes agreements at the population level (e.g., simple discounts or price-volume agreements) or at the patient level (e.g., utilisation, time, or cost capping schemes), while the latter includes performance-linked schemes (e.g., conditional treatment continuation, outcome guarantee and coverage with evidence development) (Neyt et al., 2020).

It has been suggested that MEAs can improve access to innovative medicines by addressing decision-making related uncertainties and hence, preventing rejection from reimbursement due to uncertain clinical and cost-effectiveness evidence (Thanimalai et al., 2021; Wenzl & Chapman, 2019; Ferrario & Kanavos 2015). Nevertheless, these agreements have not yet gained widespread acceptance and literature has also identified some notable barriers to their implementation, primarily because their sustainability is unclear and their effectiveness in

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meeting their objectives has yet to be evaluated (Antonanzas et al., 2019). Key issues around the efficiency of MEAs relate to the often lengthy or stalled MEA negotiations causing access delays, and the risk for a product reimbursed with a MEA being delisted following expiry of the agreement thus, impeding patient access (Neyt et al., 2020). Another area of concern around the implementation of MEAs arises due to the administrative burden they are often associated with (Wenzl & Chapman, 2019), especially for agreements that require advanced infrastructure systems to support new data generation (Kanavos & Mills, 2015).

Despite the significant attention placed on the implementation of MEAs, the body of evidence on the performance of MEAs to date is weak, as there is still little information on their real-life impact on patients and healthcare systems (Gamba et al., 2020; Gonçalves et al., 2018). The main body of literature attempting to evaluate MEAs is based on theoretical models that assess the economic impact of MEAs (Zaric et al., 2021, Barros, 2011, Gandjour, 2008, Zaric and O'Brien, 2005; Zaric and Xie, 2009; Fagnani et al., 2016). Additionally, the role of MEAs in achieving a meaningful impact on key policy objectives such as cost containment, improved access and reward of innovation, has been discussed in the literature chiefly in the context of describing their "strengths and weaknesses" (Wenzl & Chapman, 2019; Kanavos et al., 2017, Ferrario & Kanavos, 2013).

The key challenge in conducting empirical impact assessments for MEAs arises due to the confidentiality and limited information available on the specific negotiating terms and operational details of these agreements (i.e., timeframe, patient eligibility, indicators used to monitor outcomes etc.) (Gamba et al.,2020; Ferrario & Kanavos 2013). Only a few empirical studies exist on the real-life impact of implemented MEAs on pharmaceutical expenditure (Van de Vooren et al., 2015; Navarria et al., 2015), list prices (Gamba et al., 2020), faster access to cancer medicines (Russo et al., 2010) and on the ability of performance-based schemes to collect meaningful, long-term outcomes data for patients (Boggild et al., 2009; Pickin et al., 2009). Additionally, existing empirical literature primarily reflects case studies within one specific setting/country and hence, comprehensive evidence about the broader effectiveness of MEAs in meeting their anticipated objectives remains scarce (Antonanzas et al., 2019; Garattini & Curto, 2016; Hollis 2016). For example, Russo et al., (2010) assessed the impact of MEAs on access delays only from the Italian healthcare system perspective and concluded that the impact of MEAs remains equivocal due to diverse health system priorities, different assessment criteria, different market access/purchasing strategies and market sizes across

different countries. Other studies concluded that despite MEAs' potential to improve access, there is no consensus on which MEA types and implementation strategies are the most effective in optimising reimbursement decision-making (Zaric et al., 2021).

Drawing more robust conclusions about the pragmatic impact of MEAs is paramount to understand if these agreements represent a sustainable policy tool for improved coverage across countries. This could also help purchasers to identify the most efficient MEA negotiation practices by understanding which situations call for the use of one type of MEA instead of another, and what trade-offs are involved in choosing different contracts (Zaric et al., 2021). To that end, structured ex-post evaluations of MEAs are essential to assess the impact of existing schemes on a number of key policy goals such as access to medicines, budget control and encouragement of innovation (Ferrario & Kanavos 2015; Garrison et al., 2013; Kemp et al., 2011). In practice, these evaluations can take the form of quantitative models that enable the outcomes of these agreements to be compared with those in situations without them (Antonanzas et al., 2019; Gamba et al.,2020).

We are not aware of any other empirical studies that involve direct comparisons of MEAs to understand how these agreements influence the level of and/or speed of access to medicines across countries. Therefore, the objective of this study was to contribute evidence around the impact that completed agreements or resubmissions with an agreement have had on a) the levels of access (i.e., resulting in more "listing" recommendations) and b) the time taken to the final decision outcome. These objectives were selected for impact assessment because first, they reflect a key policy goal targeted by health systems across borders (EC, 2008) and second, because of relevant data availability that ensures feasibility of the required data analysis.

6.2 Methods

6.2.1 Sample selection

This study is based on a retrospective analysis of HTA appraisals for all oncology (ATC-L01/L02) medicines which obtained regulatory approval in Europe by the EMA and by the TGA in Australia between 1st January 2009 and 15th June 2018 (at the medicine-indication pair level) in Australia, England, Scotland and Sweden.

Oncology was the therapeutic area of choice because it has been documented to be the therapeutic class with the largest proportion of implemented MEAs, while also being the therapeutic class where MEAs continue to be increasingly implemented (Ferrario & Kanavos, 2013). Study countries were selected because they all implement MEAs, they all have long-established HTA policies and processes to guide their coverage decisions/ recommendations, they have both a publicly available list of MEAs and publicly available HTA reports which provide sufficient information for the purposes of this analysis (Nicod & Kanavos, 2016). Additionally, these countries were selected because, apart from the cost-effectiveness perspective, they also use other, different principles to shape their decision-making around pricing and reimbursement of medicines (e.g., England also considers the national health and personal social services perspective, and Sweden also takes into account the human value and solidarity principle. Therefore, countries were selected such that they would allow for comparability across agencies, while reflecting the diversity in HTA coverage decisions/recommendations and the respective HTA determinants of access across settings (Nicod & Kanavos, 2016).

6.2.2 Variables of interest

From the sample described above, all medicine-indication pairs with a resubmission following an HTA rejection and all medicine-indication pairs with a resubmission following completion/expiry of a previously agreed MEA identified and isolated separately for analysis; none of the respective MEAs were implemented across multiple indications of a specific molecule and/or were part of a Multi-Year Multi-Indication (MYMI) agreement. Further information about the medicine-indication pairs studied is provided in supplementary material (see Appendix 4). Among these medicine-indication pairs, three main categories of variables were collected and studied for the purposes of this study. These included:

(1) ***Previous and final decision outcome*** (i.e., prior to and following a resubmission with and without a MEA) classified as (i) favourable recommendation/ decision, including "List" (L) without restrictions/criteria, "List with criteria" (LWC) and "LWC with MEA as part of the listing criteria" (LWCMEA), and (ii) non-favourable or "do not list" (DNL) HTA funding recommendation/decision.

(2) ***HTA decision-making determinants,*** based on a conceptual framework described elsewhere (Efthymiadou & Kanavos, 2021; Nicod & Kanavos, 2016) dividing the HTA

appraisal and assessment processes in three main stages and respective variables therein, corresponding to (i) the evidence submitted (e.g., trial characteristics and endpoints used, size of clinical benefit and existence or not of a MEA), (ii) the interpretation of this evidence (i.e., clinical and economic evidence related uncertainties raised), and (iii) Social SVJs and system-specific considerations (i.e., dimensions of value that a technology adds, beyond its clinical evidence/benefit and cost-effectiveness such as innovation, the severity, rarity and unmet need of the targeted disease or process specific characteristics, as well as type of HTA system.

(3) **Time** from previous submission to resubmission with vs. without MEA and to final decision outcome.

Data on the above variables per medicine-indication pair in all study countries were extracted only from the official, publicly available HTA appraisals, which were published in the websites of the respective HTA bodies, namely the PBAC in Australia, the NICE in England, the SMC in Scotland and the TLV in Sweden; other relevant sources of data, such as the county councils' group on new drug therapies in Sweden were not searched. Data collection was undertaken between June and December 2018 and data extracted was put in a database stratified by HTA agency.

6.2.3 Data analysis

Funding decision outcome was coded as a binary variable (e.g., positive and negative reimbursement decision), uncertainties and SVJs were coded as binary variables based on whether they have been raised and considered (or not) respectively in the decision-making process, and variables around the evidence submitted were treated as binary (i.e., existence of MEA or not), continuous (i.e., time to final funding decision) or categorical (i.e., type of MEA, type of endpoint etc.) depending on their specification.

For the first part of the analysis Pearson's chi-squared and where applicable, *t*-tests were performed for all HTA decision-making determinants, and the variables driving significant differences between positive and negative recommendation outcomes, were selected for further analysis. Subsequently, we examined the probability of a previously negative funding decision being reversed to positive following a resubmission, based on the key HTA variables of

significance identified, including existence/non-existence of MEA (as a proxy for the impact of MEAs on enhancing availability of medicines)[7].

As the dependent variable for the first part of the analysis is categorical, a non-linear, cumulative logit model was chosen, namely a binary logit model, to model the probability (P) of a previously rejected technology receiving a favourable funding decision after resubmission ($y_i = 1$) (as opposed to remaining rejected), based on a set of explanatory variables (x_i), under the following equation (4):

$$P(y_i = 1 \mid x_i) = \frac{exp(x_i\beta)}{1+exp(x_i\beta)} \quad \textbf{(4)}$$

Where:

- y is a binary response variable with:
  - $y_i = 1$ if the resubmission resulted in a positive recommendation decision
  - $y_i = 0$ if the resubmission resulted in a negative recommendation decision

- $x = (x_1, x_2, ..., x_k)$ is a set of HTA explanatory variables hypothesised to influence HTA decision-making (based on the conceptual framework described in section 3.3), and a distinct explanatory variable on presence of a MEA (or not) as part of the resubmission whereby:

  • x_i is the observed value/outcome of the respective explanatory variables tested and

- β is a vector of parameters to be estimated and presented as odds ratios (e.g., a one-unit change in the jth variable, x_j, is associated with the odds ratio, $exp(\beta_j)$ (Dakin et al., 2015).

[7] Accounting for the reversibility of negative to positive funding decisions as a proxy to availability of medicines is an assumption made for the purposes of simplicity in running the binary logit model. This assumption has been recognised by the author as a limitation of this analysis, based on the fact that inclusion in the positive reimbursement list does not always translate in equal availability of medicines; beyond a favourable funding decision several other, macro-economic, country specific and healthcare system specific factors determine the actual availability of and patient access to medicines. More details on how the results of this model should be interpreted to account for the above limitation are given in chapter 7, section 7.2 (3) - Policy implications and 7.4- Limitations from the conduct of this research.

For the second part of the analysis we captured the relationship between the time to final funding decision and existence of a MEA (including both resubmissions with MEA following a previously negative funding decision and resubmissions following expiry of a MEA), as a proxy for the impact of MEAs on market access delays[8]. First, Mann–Whitney U and Kruskal–Wallis (where applicable) tests were performed to assess if there is a statistically significant association between any of the HTA predictors (including presence of a MEA or not) and the average time to final funding decision. Subsequently, given the non-normally distributed, exponential (i.e., *gamma*) distribution of the average time to final funding decision, a gamma generalised linear model with log link function was performed to identify the strength and direction of the above association. This model was employed as the best fit of a regression model for a non-Gaussian distribution, and is described by the following equation (5):

$$g(\mu_i) = \boldsymbol{X}_i^{\mathbf{T}}\boldsymbol{\beta} = \beta_0 + \sum_{j=1}^{P} x_{ij}\beta_j \qquad (\mathbf{5})$$

Where:

- $\mu_i = \mathbb{E}(Y_i)$ is the expected value of the response Y_i given the predictors
- $g(\cdot)$ is a smooth and monotonic link function that connects μ_i to the predictors
- $\mathbf{X}_i^T = (x_{i0}, x_{i1}, \ldots, x_{ip})$ is the i-th observation's known predictor vector with $X_{i0} = 1$ and
- $\boldsymbol{\beta}=(\beta_0,\beta_1,\ldots,\beta p)^{\mathrm{T}}$ is the unknown vector of regression coefficients.

A log-link function was applied in the above to exponentiate the linear predictors as follows:

$$ln(\mu) = \beta_0 + \beta_1 X \Rightarrow \mu = \exp(\beta_0 + \beta_1 X)$$

where μ is the predicted value of Y given X, $\exp(\beta_0)$ is the effect on the mean of μ when X=0 and $\exp(\beta_1)$ is the multiplicative effect on the mean of Y for a one-unit increase in X.

The SPSS® (v.24.0) was used to perform the econometric models and statistical tests, and Excel® 2013 to generate descriptive statistics, where relevant.

[8] Accounting for the time to final funding decision as a proxy to timely access to medicines is an assumption made for the purposes of simplicity in running the generalised linear model. As with the binary logit model, this assumption has also been recognised by the author as a limitation of this analysis, given that a positive reimbursement decision does not always reflect access to medicines, regardless of how promptly the funding decisions might have been reached. More details on how the results of this model should be interpreted to account for the above limitation are given in chapter 7, sections 7.2 (3) - Policy implications and 7.4 – Limitations from the conduct of this research.

6.3 Results

6.3.1 Impact of MEAs on reimbursement decisions

Descriptive statistics

Of the 59 resubmissions studied, 1.7% (n = 1) were reversed to L, 8.5% (n = 5) were reversed to LWC, 76.3% (n = 45) reversed to LWCMEA, and 13.5% (n = 8) remained rejected. Overall, of the 59 previously rejected medicine-indication pairs 86.5% (n = 51) received a positive reimbursement decision after resubmission and of these, 88.2% (n = 45) achieved so with a MEA vs. 11.8% (n = 6) without (Table 10). Furthermore, χ^2 tests were also performed to assess if there is any statistically significant association between any of the HTA predictors and/or molecule specific characteristics and the final recommendation decision following a resubmission. It was demonstrated that a statistically significant difference between positive and negative decisions following resubmission is underscored by the existence or not of a MEA (p< .000) and existence or not of cost effectiveness uncertainties (p<0.05) (Table 10).

Table 10. Descriptive statistics on the final recommendation decision outcomes after resubmission and statistical significance (p) of their HTA determinants across all sample.

Funding decision outcome after resubmission, across all sample (n=59)					
List (L)		1 (1.7%)			
List with restrictions	LWC	5 (8.5%)			
	LWCMEA	45 (76.3%)			
Do not List (DNL)		8 (13.5%)			
Funding decisions following resubmissions per country					
	Remained non-favourable (DNL)	**Reversed to favourable (L/LWC/LWCMEA)**			***p*-value**
		L	**LWC**	**LWCMEA**	
England (NICE) (n=6)	0%	0%	1 (16.7%)	5 (83.3%)	*.163*
Australia (PBAC) (n=33)	7 (21%)	0%	4 (12%)	22 (67%)	
Scotland (SMC) (n=15)	0%	1 (6.7%)	0%	14 (93.3%)	
Sweden (TLV) (n=5)	1 (20%)	0%	0%	4 (80%)	
HTA determinants of funding decision following resubmission					

	Non- favourable (DNL) (n=8)	Favourable (L/LWC/LWCMEA) (n=51)	*p*-value
Molecule specific characteristics			
MEA in place			
Yes	2 (25%)	45 (88%)	***<.000***
No	6 (75%)	6 (12%)	
Endpoint			
Surrogate	5 (62.5%)	27 (53%)	.342
Clinical	1(12.5%)	18 (35%)	
Combination	2 (25%)	5 (10%)	
n/a*	0%	1 (2%)	
Rarity			
Orphan	1 (12.5%)	15 (29.4%)	.317
Non orphan	7 (87.5%)	36 (70.6%)	
Type of MA			
Standard	6 (25%)	37 (72.5%)	.885
Non-standard	2 (75%)	14 (27.5%)	
Study type			
RCT	7 (87.5%)	48 (94%)	.489
Non-RCT /Observational	1 (12.5%)	3 (6%)	
Social value judgments			
Disease severity			
Considered	2 (25%)	15 (29.4%)	*.798*
Not considered	6 (75%)	36 (70.6%)	
Unmet need			
Considered	4 (50%)	31(60.8%)	*.564*
Not considered	4 (50%)	20 (39.2%)	
Administration advantage			
Considered	0%	16 (31.4%)	*.063*
Not considered	8 (100%)	35 (68.6%)	
Innovation			
Considered	1 (12.5%)	18 (35.3%)	*.20*
Not considered	7 (87.5%)	33 (64.7%)	
Short life expectancy			
Considered	0%	8 (15.7%)	*.228*
Not considered	8 (100%)	43 (84.3%)	
Societal impact			
Considered	0%	7 (13.7%)	.264
Not considered	8 (100%)	44 (86.3%)	
Special Considerations (i.e., end-of-life criteria)			
Considered	2 (25%)	17 (33.3%)	.639
Not considered	6 (75%)	34 (66.6%)	
Clinical uncertainties			
Clinical benefit			

Raised	7 (87.5%)	32 (62.7%)	*.169*
Not raised	1 (12.5%)	19 (37.3%)	
Study design			
Raised	2 (25%)	18 (35.3%)	*.567*
Not raised	6 (75%)	33 (64.7%)	
Relevance to clinical practice			
Raised	1(12.5%)	12 (32.5%)	*.484*
Not raised	7(87.5%)	39 (76.5%)	
Population generalizability			
Raised	1(12.5%)	8 (15.7%)	*.816*
Not raised	7(87.5%)	43 (84.3%)	
Clinical comparator			
Raised	2 (25%)	17 (33.3%)	*.639*
Not raised	6 (75%)	34 (66.6%)	
Clinical evidence			
Raised	4 (50%)	22 (%)	*.716*
Not raised	4 (50%)	29 (%)	
Economic uncertainties			
Cost effectiveness			
Raised	6 (75%)	27 (52.3%)	***.027***
Not raised	2 (25%)	24 (47%)	
Utilities			
Raised	3 (37.5%)	10 (19.6%)	*.256*
Not raised	5 (62.5%)	41 (80.4%)	
Costs			
Raised	6 (75%)	24 (47%)	*.142*
Not raised	2 (25%)	27 (53%)	
Modelling			
Raised	6 (75%)	30 (58.8%)	*.383*
Not raised	2 (25%)	21 (41.2%)	
Model type			
Raised	0%)	1 (2%)	*.690*
Not raised	8 (100%)	50 (98%)	
Economic comparator			
Raised	0%)	5 (10%)	*.355*
Not raised	8 (100%)	46 (90%)	

Key: *n/a: endpoint not applicable for the type of study used in the evidence submitted (i.e., indirect comparison**,** health economic report).

Note:

- L: List, LWC: List with criteria; LWCMEA: List with criteria which include a MEA; DNL: Do not list.
- HTA: Heath Technology Assessment, MA: Marketing authorization; MEA: Managed Entry Agreement, RCT: Randomized Controlled Trial.
- PBAC: Pharmaceutical Benefits Advisory Committee, NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Consortium, TLV: Dental and Pharmaceutical Benefits Board.

Binary logit model

According to the χ^2 tests presented above only the existence or not of a MEA ($p < 0.001$) and existence or not of cost effectiveness uncertainties ($p< 0.05$), were shown to play a role in determining the funding decision outcome following resubmission of evidence for a previously rejected medicine-indication pair. A number of binary logit models were performed to ascertain the effects of the above variables, in consideration with a combination of other HTA predictors, on determining the likelihood of a previously non-favourable coverage decision being reversed to favourable. [9,10] The models with the best predictability rate are presented below (Table 11).

The first model was statistically significant ($\chi^2 = 30.84$, $p = 0.002$), it explained 75.3% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified 94.8% of cases. In this model, a resubmission with a MEA was the only positive predictor of receiving a favourable funding decision instead of non-favourable (OR = 43.36, $p = 0.017$). Other HTA parameters included in the model did not have a statistically significant effect in the overall model.

The second model was statistically significant ($\chi^2 = 30.84$, $p = 0.001$), it explained 74.8% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified 94.8% of cases. Resubmission with a MEA was the only positive predictor of a previously negative coverage decision being reversed to positive, although the positive effect was stronger (OR = 63.35, $p = 0.012$) compared to the previous model. Additionally, resubmission with a surrogate endpoint was a negative predictor (OR = 0.017, $p = 0.03$) of a previous rejection being reversed to a favourable funding decision.

The third model was statistically significant ($\chi^2 = 25.7$, $p = 0.004$), it explained 69.5% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified

[9] The HTA predictors included in the models are based on results from research article I and comprise variables that were shown to play at least some role in shaping the outcomes of decision-making under uncertainty.

[10] The effects of the two variables found by the χ^2 tests to be statistically significant in determining the funding decision outcome following resubmission of evidence for a previously rejected medicine-indication pair (i.e., resubmission with vs. with MEA and resubmission with vs. without cost effectiveness uncertainties) could not be studied together in the same model due to violation in the assumption of multicollinearity Therefore, their relevant effects were studied by including only one of the two variables in different models and subsequently, comparing their contribution and significance between the respective models.

94.6% of cases. Resubmission with a MEA was the only positive predictor of a previously negative coverage decision being reversed to positive, and the positive effect was the strongest (OR = 202, $p = 0.007$) compared to the previous models. Additionally, in this model there were two negative predictors in achieving a positive reimbursement decision, namely the use of a surrogate instead of clinical outcome and the presence of clinical benefit uncertainties in the resubmitted evidence, with the former being a slightly stronger negative predictor (OR = 0.019, $p = 0.042$) compared to the latter (OR = 0.021, $p = 0.044$).

The fourth model was statistically significant ($\chi^2 = 28.73$, $p = 0.001$), it explained 70.8% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified 94.8% of cases. In this model, a resubmission without a MEA was a negative predictor (OR = 0.005, $p = 0.004$) of a non-favourable decision being reversed to favourable. Additionally, resubmission without clinical benefit uncertainties in the evidence submitted was the strongest positive predictor (OR = 53.608, $p = 0.024$) of a previously non-favourable decision being reversed to favourable, followed by resubmission with a clinically relevant endpoint (OR = 50.965, $p = 0.037$) as opposed to a surrogate.

Finally, since the presence of cost-effectiveness uncertainties seemed to drive a statistically significant difference between a favourable and non-favourable funding decision outcome following a resubmission (Table 10), a number of models were also performed to ascertain the effect of the "cost effectiveness uncertainties" variable on reversing previously negative decisions. Only one model was found to be of statistical significance ($\chi^2 = 46.538$, $p < 0.001$) (Model 5; Table 11) but this had a relatively poor predictability and variance explanation (Nagelkerke R^2) rates (82% and 54.6% respectively), compared to the models presented above. Moreover, none of the predictors included in this model, including the "cost-effectiveness uncertainties" variable contributed a statistically significant effect in the model.

6.3.2 Impact of MEAs on time to reimbursement decisions

Descriptive statistics

Medicine-indication pairs with a resubmission following a previously negative funding decision and those with a resubmission/re-evaluation following MEA expiry were studied.

Across the 71 re-submissions and re-evaluations studied, 83% (n=59) were resubmissions following a previous rejection and 17% (n=12) were resubmissions/re-evaluations after expiry of a MEA. Average time to final recommendation decision across all sample was 525 (±386) days, and this was 452 (±364) and 404 (±254) days for medicine-indication pairs approved with vs. without a MEA respectively (Table 12, Figure 10).

The Mann-Whitney U and Kruskal-Wallis tests demonstrated that a statistically significant difference in mean time to final recommendation decision was underscored by the type of HTA agency (χ^2=23.587, p< 0.001) and MEA type (χ^2=14.634, p=0.002) and the SVJs of disease severity (U= 342.5, p=0.013) and societal impact (U=159.5, p=0.044). Among the above predictors, the greatest differences in average time to final recommendation decision were demonstrated between the different types of MEAs and different HTA agencies (Table 12). More precisely, in terms of differences underpinned by the different MEA types, it was shown that shortest mean time to final funding decision was 422 (±231) days for medicine-indication pairs with a combination of a financial and outcomes-based schemes, followed by 476 (±407) days for medicine-indication pairs with a financial agreement and amounting up to 957 (±231) days for medicine-indication pairs approved with an outcomes-based agreement (Figure 10). Finally, in terms of time differences between HTA agencies, the shortest mean time to final funding decision was 342 (±249) days for the Scottish HTA agency, followed by 378 (±242) days for the Australian agency, 837 (±302) days for the Swedish agency and reaching an average of 938 (±559) days for the English agency (Table 12, Figure 11).

Table 11. Binary logit models, predicting the likelihood/ odds ratio (OR) of a previously negative coverage decision being reversed to a favourable funding decision, based on the set of HTA predictors studied in the model.

	Model 1		**Model 2**		**Model 3**		**Model 4***		**Model 5**	
HTA Predictor	*OR*	*p*	*OR*	*p*	*OR*	*p*	*OR*	*p*	*OR*	*p*
HTA agency		.916		1.0						.180
MEA in place	**43.367**	**.017**	**63.353**	**.012**	**202**	**.008**	**.005**	**.004**		
Orphan	62.563	.091	91.296	.108	108.5	.178	.004	.065		
Year MA					1.659	.337				
Endpoint										
Surrogate	.024	.063	**.017**	**.030**	**.019**	**.042**	.113	.289	.000	.997
Clinical	.001	.124	.007	.066	.005	.054	**50.965**	**.037**	.000	.997
Study type					2.089	.798	.490	.800		
Uncertainties										
Clinical evidence			2.734	.505	5.673	.367	.403	.567	3.04	385
Clinical benefit	.094	.206	.065	.132	**.021**	**.044**	**53.608**	**.024**	.000	.997
Utilities	.022	.251								
Cost effectiveness									.000	1.0
Social Value Judgements										
Special considerations			.000	.999						
Severity	.731	.905							.477	.705
Unmet need					2.582	.563	.658	.774	.341	.388
Administration advantage	16.392	.998								
Constant	.000	.998	.195	.713	.000	.335	.632	.772	61.4	.999
Model statistics	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*
Likelihood ratio test	31.159	.002	30.846	.001	25.673	.004	28.733	.001	46.53	.000
Hosmer & Lemeshow test†	1.761	.972	1.769	.971	5.111	.646	5.763	.568	5.104	.647
Predictability (%)	94.8%		94.6%		94.8%				94.6%	
Nagelkerke R^2	75.3%		69.5%		74.8%				69.5%	

Key: * The first outcome of each HTA predictor was used as a reference category for the fourth model.

†The Hosmer-Lemeshow test has been used here as is a goodness of fit test to indicate how well the data fits each of the models that were ran. Specifically, this test calculates if the observed event rates match the expected event rates in population subgroups (Glen, 2016). Therefore, It is not provided here as a comparison or grading metric between the different competing models, neither it has been used for selecting the best model (Fagerland & Hosmer, 2012).

Note: HTA: Heath Technology Assessment, MA: Marketing authorization; MEA: Managed Entry Agreement, OR: Odds Ratio, *p*: *p*-value.

Table 12. Time (days) from initial to final funding decision after resubmission, and statistical significance (*p*) of their HTA determinants across all sample.

Time from previous submission to final funding decision		
	n (%)	**Days, mean (SD)**
Resubmission with MEA	47 (66%)	452 (±364)
Resubmission without MEA	12 (17%)	404 (±254)
Resubmission after MEA expiry	12 (17%)	935 (±330)
Time determinants		
	Days, mean (SD)	***p*- value**
HTA agency		
England (NICE)	938 (±559)	***.000***
Australia (PBAC)	378 (±242)	
Scotland (SMC)	342 (±249)	
Sweden (TLV)	837 (±302)	
Molecule specific characteristics		
MEA in place		
Yes	550 (±404)	*.394*
No	404 (±254)	
MEA Type		
Financial	476 (±407)	***.002***
Outcomes based	957 (±231)	
Combination	422 (±231)	
Endpoint		
Surrogate	514 (±324)	*.659*
Clinical	494 (±514)	
Surrogate & Clinical	570 (±351)	
n/a*	380 (±0)	
Rarity		
Orphan	554 (±372)	*.559*
Non orphan	512 (±396)	
Type of MA		
Standard	491 (±397)	*.182*
Non-standard	597 (±359)	
Social value judgments		
Disease severity		
Considered	687 (±432)	***.013***
Not considered	437 (±335)	
Unmet need		
Considered	504 (±414)	*.465*
Not considered	539 (±349)	
Administration advantage		
Considered	487 (±472)	*.370*
Not considered	529 (±357)	

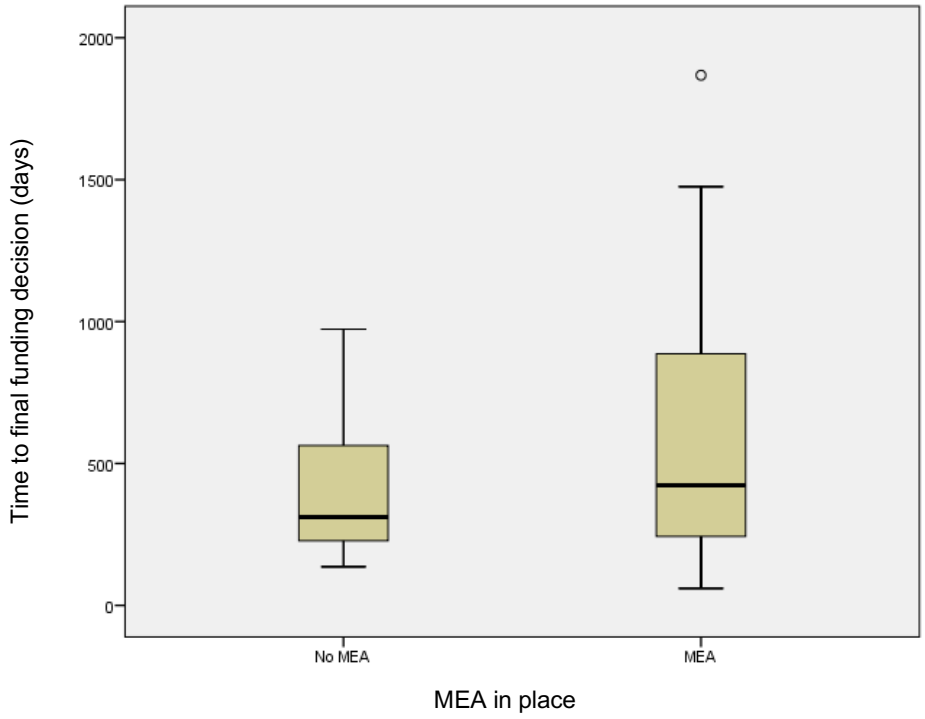
Innovation		
Considered	492 (±454)	*.397*
Not considered	530 (±356)	
Short life expectancy		
Considered	719 (±598)	*.290*
Not considered	486 (±333)	
Societal impact		
Considered	282 (±182)	***.044***
Not considered	554 (±395)	
Special Considerations (i.e., end-of-life criteria)		
Considered	618 (±462)	.179
Not considered	467 (±332)	
Clinical uncertainties		
Clinical benefit		
Raised	528 (±385)	*.718*
Not raised	500 (±394)	
Study design		
Raised	574 (±472)	.726
Not raised	492 (±337)	
Relevance to clinical practice		
Raised	624 (±379)	.150
Not raised	480 (±384)	
Population generalizability		
Raised	545 (±596)	*.233*
Not raised	514 (±332)	
Clinical comparator		
Raised	563 (±471)	.918
Not raised	500 (±345)	
Clinical evidence		
Raised	471 (±353)	*.284*
Not raised	561 (±411)	
Economic uncertainties		
Cost effectiveness		
Raised	583 (±433)	*.304*
Not raised	429 (±283)	
Utilities		
Raised	572 (±529)	*.889*
Not raised	503 (±336)	
Costs		
Raised	497 (±405)	.458
Not raised	539 (±370)	
Modelling		
Raised	491 (±389)	*.311*
Not raised	563 (±381)	
Model type		
Raised	365 (±0)	.785
Not raised	521 (±387)	

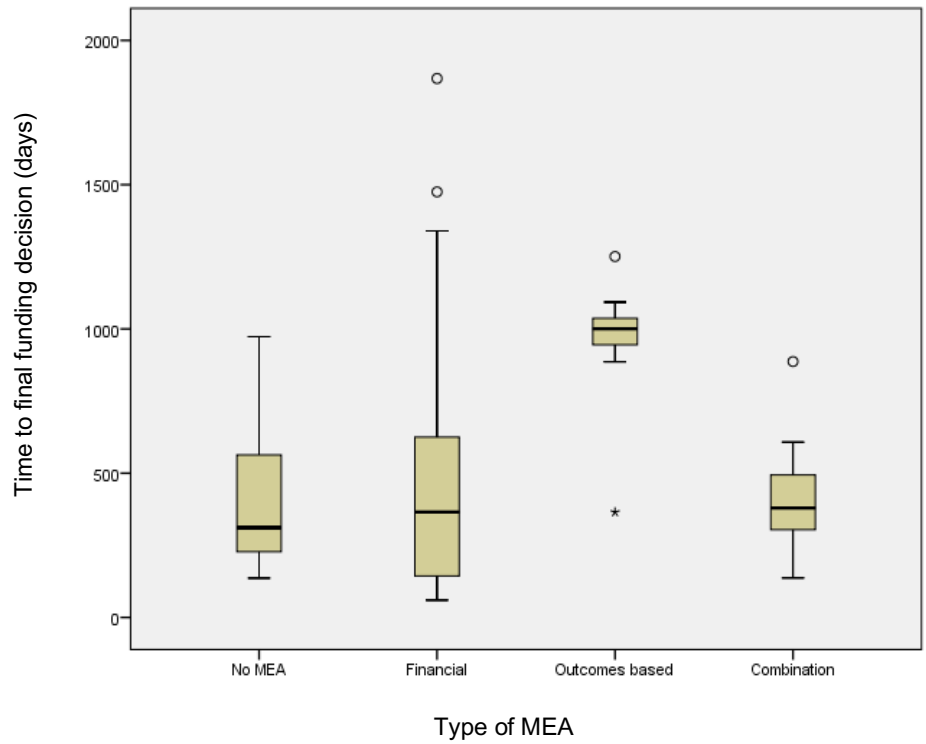
Economic comparator		
Raised	727 (±420)	*.099*
Not raised	499 (±379)	

Key: *n/a: endpoint not applicable for the type of study used in the evidence submitted (i.e., indirect comparison).

Note: HTA: Heath Technology Assessment, MA: Marketing authorization; MEA: Managed Entry Agreement, SD: Standard deviation. PBAC: Pharmaceutical Benefits Advisory Committee, NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Consortium, TLV: Dental and Pharmaceutical Benefits Board.

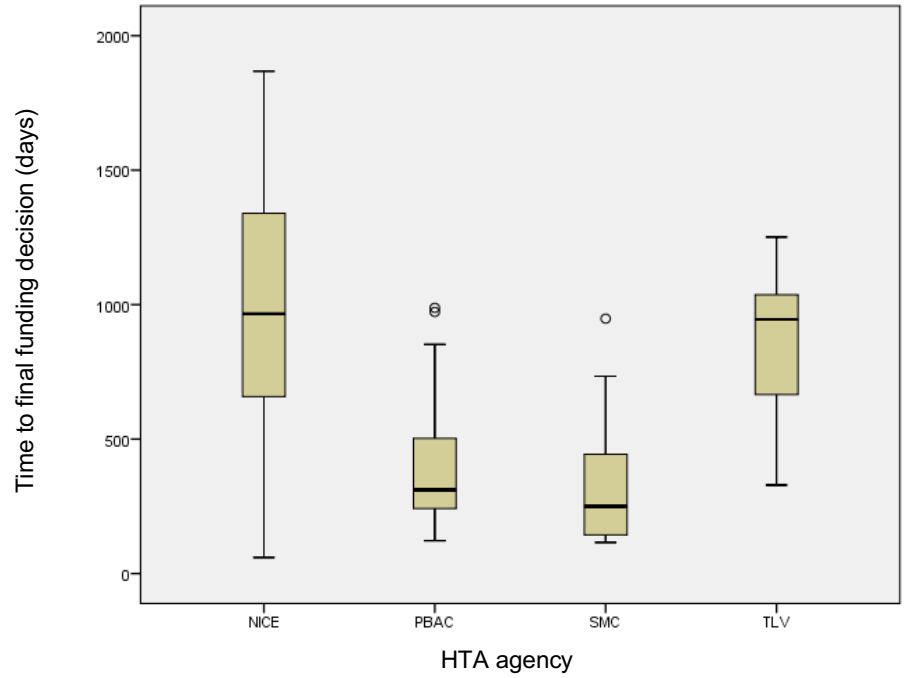
Figure 10. Average time from initial to final funding decision following resubmission without vs. with MEA, and the respective time exhibited by resubmissions with different MEA types.

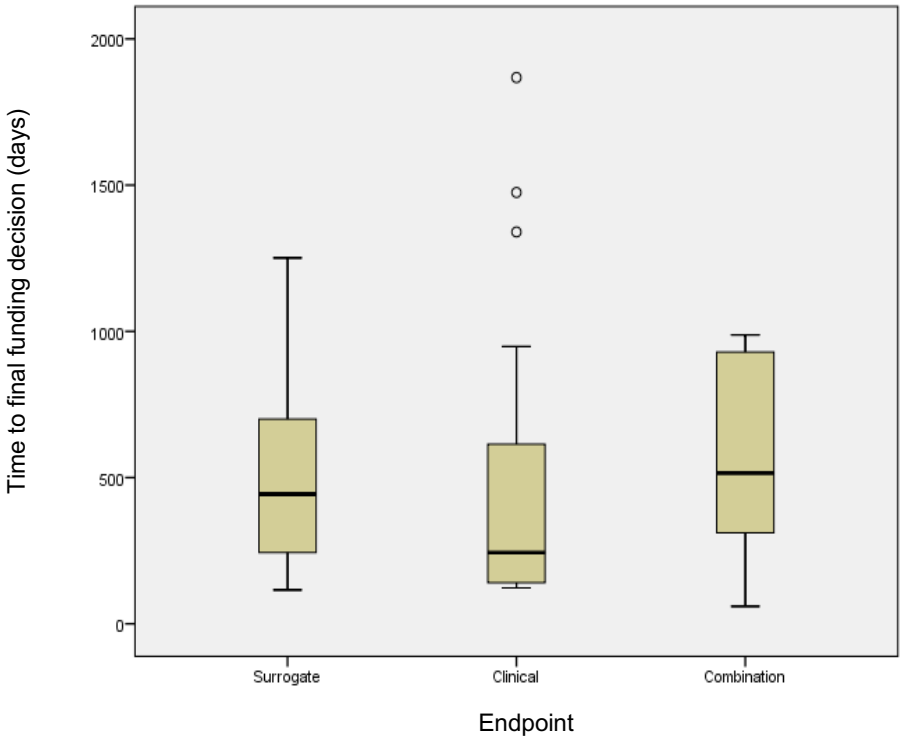




Key: Time represents average days from first submission to final funding decision after a resubmission; Horizontal lines indicate medians; Boxes indicate the interquartile range; Single points indicate outliers.

Figure 11. Average time from initial to final funding decision after a resubmission, between the different HTA agencies and types of endpoints.





Key: Time represents average days from first submission to final funding decision after a resubmission; Horizontal lines indicate the medians; Boxes indicate the interquartile range; Single points indicate outliers.

Note: PBAC: Pharmaceutical Benefits Advisory Committee (Australia), NICE: National Institute for Health and Care Excellence (England), SMC: Scottish Medicines Consortium (Scotland), TLV: Dental and Pharmaceutical Benefits Board (Sweden).

Generalised linear model

Gamma generalised linear models were performed to ascertain the effects of several HTA predictors on the average time taken to reach a final recommendation decision (Table 13).

Table 13. Generalised linear models, predicting the association between a set of HTA predictors and time to final reimbursement decision.

	Model 1		**Model 2**		**Model 3**		**Model 4**	
HTA Predictor	B	*p*	B	*p*	B	*p*	B	*P*
HTA agency		***.000***		***.007***				***.000***
NICE	-.030	*.926*	.245	*.528*			-.018	*.955*
PBAC	**-1.019**	***.001***	-.709	*.053*			**-.986**	***.001***
SMC	**-.815**	***.003***	-.453	*.226*			**-.790**	***.004***
MEA in place	-.179	*.416*						
Type of MEA				*.453*		***.000***		
Financial			-.100	*.706*	-.145	*.569*		
Outcomes based			.379	*.299*	**.897**	***.008***		
Orphan	.088	*.618*			.287	*.132*		
Endpoint		*.054*		*.146*		*.756*		*.085*
Surrogate	-.301	*.205*	-.340	*.132*	-.057	*.815*	-.324	*.143*
Clinical	**-.612**	***.022***	**-.562**	***.034***	-.098	*.690*	**-.559**	***.033***
Surrogate & Clinical	-1.037	*.089*	-.834	*.197*	-.716	*.284*	-1.039	*.091*
Uncertainties								
Study design	-.262	*.118*	-.285	*.089*	**-.361**	***.019***	**-.329**	***.043***
Clinical evidence	.247	*.114*	**.336**	***.038***	**.482**	***.002***	.221	*.150*
Clinical benefit	-.212	*.238*	-.189	*.288*				
Cost effectiveness	.050	*.934*	.052	*.929*			.041	*.943*
Social Value Judgements								
Severity	.176	*.378*	.136	*.502*	-.221	*.173*	.136	*.490*
Societal impact	**.623**	***.005***	**.690**	***.002***	**.628**	***.007***	**.603**	***.004***
Constant	17.133	*.841*	-28.672	*.735*	5.620	*.000*	3.545	*.965*
Model statistics	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*
Likelihood ratio test	45.30	*.000*	47.011	*.000*	34.702	*.000*	43.436	.000
Deviance (Value/df)	.407		.406		.430		.395	

Note: B: Regression coefficient, df: Degrees of freedom, HTA: Heath Technology Assessment, MEA: Managed Entry Agreement, *p*: *p*-value, PBAC: Pharmaceutical Benefits Advisory Committee, NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Consortium, TLV: Dental and Pharmaceutical Benefits Board.

In the first model, variables with a statistically significant impact on time to final funding decision were HTA agency ($p < 0.001$), the use of clinical endpoint in the evidence submitted ($p = 0.022$) and the SVJ of societal impact ($p = 0.005$). The Australian and Scottish agencies were associated with a reduction in time to final funding decision, as was the use of a clinically relevant endpoint in the evidence submitted. Absence of considerations around the societal impact of the technology in question increased the time to final funding decision, whereas the presence of a MEA did not have a statistically significant contribution in the overall model.

The second model examined the impact of HTA agency and the type of MEA on the average time to final funding decision. Variables with a statistically significant contribution in the model were HTA agency ($p = 0.007$), the type of endpoint used in the clinical evidence submitted ($p = 0.034$), clinical evidence uncertainties ($p = 0.038$) and the SVJ of societal impact of the technology in question ($p = 0.002$). Submissions with a clinically relevant endpoint were associated with a reduction in time to decision-making. Raising considerations around the societal impact of the technology in question and raising uncertainties around the clinical evidence submitted had a positive impact (i.e., increase) on time to final funding decision. Finally, the type of MEA did not have a statistically significant contribution in the overall model.

Controlling for HTA agency, the third model examined the role of the type of MEA on time to final decision. Variables with a statistically significant contribution in the model were the type of MEA ($p < 0.001$), the HTA agency ($p = 0.007$), uncertainties around the study design ($p = 0.019$) and the clinical evidence submitted ($p = 0.038$), and the SVJ of the societal impact of the technology ($p = 0.002$). Submissions with an outcomes-based agreement increased the time to decision-making. Raising considerations around the societal impact of the technology and raising uncertainties around the clinical evidence submitted increased the time to final funding decision, whereas presence of study design uncertainties had a negative impact (i.e., decrease) on time to final funding decision.

6.4 Discussion and policy implications

We conducted an analysis of oncology medicines previously rejected from reimbursement, to understand if any MEAs implemented upon evidence resubmission of the above medicines had an impact on enhancing the availability of and timely access to these medicines. Our results suggest that presence of MEAs has the potential to improve the availability of new oncology

therapies, by increasing their likelihood for reimbursement if they have previously been rejected. However, presence specifically of outcomes-based agreements can cause significant time delays in reimbursement decision-making and hence, time to access.

Only a few studies have provided a quantitative evaluation of the impact of MEAs on access to medicines (Gonçalves et al., 2018; Choi et al., 2018, Medaffcon, 2018; Urbinati et al., 2017; Russo et al., 2010). In Italy, it was shown that the introduction of MEAs contributed substantially to an improvement in patients' access to cancer medicines (Gonçalves et al., 2018; Urbinati et al., 2017), whereas in Finland and South Korea it was estimated that about 20% and 60% of patented medicines respectively were granted reimbursement due to the presence of a MEA, and of the 60% reimbursed in the later, 23% were previously rejected (Medaffcon, 2018; Choi et al., 2018). Similarly, in Australia, MEAs have been implemented as part of the government's plan to enhance access to medicines, estimating that MEA implementation can help achieve coverage for about one-third of new medicine-indication pairs (Robinson et al., 2017).

It has also been suggested that reimbursement with a MEA, regardless of its type, can improve time to patient access (Russo et al. 2010; Cook et al., 2008). We found that, medicine-indication pairs approved with a MEA exhibited longer average time to final reimbursement decision, although only the presence of an outcomes-based agreement specifically (as opposed to presence of a MEA in general) was associated with a statistically significant increase of about 480 days to final funding decision. Comparable findings have been reported by a study of oncology medicines in the Italian setting, which showed an increase in the national time to market of about 150 days for medicines approved with an outcomes-based agreement compared to those approved with a financial scheme (Urbinati et al., 2017).

This finding is not surprising; the complexity of outcomes-based contracts in comparison to more simple financial schemes, their negotiation process can often be burdensome and time consuming for manufacturers and payers. Additionally, the collection of additional evidence and if required, the future monitoring and re-assessment of the product, as well as the need to align interpretations of the collected and required data between the different stakeholders involved in reimbursement decision-making may introduce further delays (Bentata et al., 2020; Wilsdon & Barron, 2016; Kanavos & Mills, 2015).

Discrepancies in the conclusions of existing literature around the impact of MEAs on time to access may be explained on the grounds that regardless of their type, MEAs can only improve time to market access if negotiation processes are well structured and based on sufficient preparation ahead of time such that the proposed schemes have a clear rationale and truly address the uncertainties raised by the competent authorities assessing the technology in question (Lucas, 2016). Growing concerns have been expressed in the literature that MEAs are increasingly used as "an operational tool" to agree on commercial price negotiations and confidential discounts rather than as a tool for managing the actual risk arising from immature data (Wilsdon et al., 2014). Therefore, even simple financial schemes need to be implemented such that they meaningfully address the uncertainties that a new therapy presents with, rather than implemented simply as a tool to achieve lower prices. More importantly, when financial schemes are used solely as a cost containment process on top of other cost containment policies, they can add little benefit in terms of outcomes for patients and increase delays in the long term (Haninger, 2016); for example, they might grant access to interventions which might prove cost-ineffective in the long-run with the consequence that these technologies will be delisted after expiry of the agreement and eventually harm patient access, if there is no comprehensive risk management plan in place, in case of delisting (Vitry et al., 2015).

The findings arising from this study suggest that presence of a MEA per se may not always guarantee a favourable funding decision and/or faster access to oncology medicines. There are additional HTA decision-making variables which determine the final reimbursement decision and the time taken to final decision. More precisely, this study highlights that successful and timely access to oncology therapies is also subject to submission of clinical evidence which presents with minimal uncertainties and is primarily based on clinically relevant instead of surrogate endpoints. Literature has also underscored the importance that HTA decision-makers place on submitting evidence with clinically meaningful outcomes relating to mortality, morbidity, and quality of life (Angelis et al., 2020). Even though the use of surrogate measures in cancer medicines' trials is not associated with an HTA decision to reject a medicine (Pinto et al., 2020), a gap between the surrogate endpoint and the final clinical endpoint creates additional uncertainty for decision-makers. Consequently, in this case, decision-makers often need to engage in additional validation processes to extrapolate findings beyond the submitted evidence to estimate the expected true benefits to patients and health systems, and this translates in further delays on the time required to reach a final reimbursement decision (Satherley et al., 2017; Ciani et al., 2016).

Additionally, it was demonstrated that uncertainties around the study design had a statistically significant contribution in the model explaining time to final reimbursement decision. This was not surprising given that the trial design is often taken into consideration by some HTA agencies, such as SMC where for example, an active-controlled trial is preferred over a placebo one (Charokopou et al., 2015). In the generalised linear model, the "study design uncertainties" variable was negatively associated with time, potentially demonstrating that this specific type of clinical uncertainty might lead to a confident, outright rejection and thus, shorten time to decision-making. This is in alignment with the results presented elsewhere (Efthymiadou & Kanavos, 2021) demonstrating that the presence of clinically relevant uncertainties is not typically associated with the flexibility to enter into negotiations for restricted reimbursement.

Finally, it was demonstrated that time to final funding decision can also be influenced by the HTA agency involved in the decision-making process. In our study, the Australian and Scottish HTA agencies exhibited significantly shorter timelines to final funding decision compared to the Swedish and English agencies. Comparable findings have been reported elsewhere. For example, a study assessing the delays introduced by HTA processes across countries in their coverage decisions for oncology medicines, showed that in England median time from EMA regulatory approval date to NICE decision was 783 days, as opposed to an average of 231 days required for SMC decisions (Wilsdon & Serota, 2011). Similarly, more recent figures estimated the mean length of time from EMA authorization to HTA funding decision for oncology and all products at 436 and 335 days respectively for NICE, compared to for example 389 and 262 days respectively for TLV (Akehurst et al., 2017). Overall, it has been reported that NICE exhibits relatively higher timelines to final funding decision compared to other European HTA agencies (Akehurst et al., 2017). On the contrary, as demonstrated in this study, Australia has been reported to have the fastest median timelines from TGA approval to HTA recommendation at national level (127 days) compared to other jurisdictions, including England (386 days), Scotland (293 days) and Sweden (217 days) (Cai et al., 2018).

Relevant literature suggests that these differences in time to decision-making are shaped by agency specific characteristics and procedures. Specifically for oncology medicines, evidence demonstrates that divergent HTA methodologies across countries underline differences in the time required for new products to enter the market when considering the average time between date of regulatory approval and date of funding decision (Bergmann et al. 2014). For example, since 2011, the TGA/PBAC parallel process has been introduced in Australia and this played

an important role in streamlining the regulatory and reimbursement processes, leading to a significantly shortened time gap between marketing authorisation and first funding decision (Cai et al., 2018; Vitry et al., 2016). On the contrary, in England, delays may often occur due to NICE specific modalities such as switching to the Cancer Drugs Fund during the review process (Ambrose et al., 2018). Additionally, in England, time delays due to NICE procedures related specifically to MEA implementation processes have been reported. For example, the PASLU process may delay submissions to NICE, whereby specifically for Single Technology Appraisals the existence of a PAS can result in an average time delay of up to four months compared to Multiple Technology Appraisals with a PAS (Ambrose et al., 2018; O'Neill et al., 2012). In other markets, there is greater flexibly in the negotiation of these agreements with the result that this can eventually accelerate the decision-making process (EFPIA, 2020), such as in Italy where presence of an agreement typically leads to shorter time to patient access (Gonçalves et al., 2018; Russo et al., 2010). The above further highlights that time delays associated with the presence of MEAs, as observed in this research article, can also be attributed to agency specific procedures for the implementation and negotiation of MEAs (Pauwels et al., 2017).

This is the first study to date to conduct a post-implementation evaluation of MEAs across countries, to quantify their impact on two key healthcare system policy goals, namely availability of and timely access to medicines. Since the on-going literature debate on the weaknesses of MEAs is primarily generated by the poor and inconclusive evidence as to whether these agreements have managed to meet their objectives, this study addresses important literature gaps on structured, impact assessment studies of MEAs. More importantly, the conclusions arising from this study can facilitate future policy relevant research around the sustainability of MEAs as an effective funding modality that can be applied for greater and faster access to medicines. Another strength of this study is the holistic approach taken in studying the HTA factors that determine coverage decision outcomes and timelines, whereby we accounted for the role of MEAs as well as the interconnected impact of both uncertainties, SVJs and clinical evidence characteristics, as opposed to existing literature that studies the impact of evidentiary uncertainties or MEAs individually.

Our study is not without limitations. First, accuracy of the models performed would have benefited from a larger sample size; although this study provides a good basis for future analyses, it is recommended that replication of similar analyses in the future could increase the sample size, possibly by including assessments of medicines for other therapeutic areas.

Second, we recognize that the cost-effectiveness and "added value" profile of the studied medicine-indication pairs is not equivalent within and across countries and hence, the need to apply a MEA would not always be equally applicable for all medicine-indication pairs studied. To address the limitation of having an unbalanced panel as our study sample, the impact of MEAs on promoting availability was studied only on medicine-indication pairs that were previously rejected, such that a common selection criterion (i.e., previously cost-ineffective profile) would be established for all medicine-indication pairs in the analysis.

Third, accounting for the reversibility of negative to positive funding decisions as a proxy to availability of medicines is an assumption made for the purposes of simplicity in running the binary logit model. This assumption is a potential limitation of the analysis, since a positive reimbursement decision does not always translate in equal availability of the respective medicine; beyond a favourable funding decision other, macro-economic, country specific and healthcare system specific factors determine the actual availability of and patient access to medicines (Kamphuis et al., 2021). Similarly, accounting for the time to final funding decision as a proxy to timely access to medicines was an assumption made for simplicity in running the generalised linear model. This is also a potential limitation of our study, given that (as described above) a positive reimbursement decision does not always reflect ready access to the respective medicine, regardless of how promptly the funding decisions might have been reached. Finally, in the above context, it is also important to recognise that binding HTA outcomes (e.g., Sweden) typically correspond to funding decisions, whereas non-binding HTA outcomes (e.g., England, Scotland, Australia) correspond to recommendations, which are not always translated into funding decisions. However, given that the (non-binding) HTA recommendations in England, Scotland and Australia have been found to largely shape the final funding decisions in these countries (Fontrier et al., 2021), we treated the HTA outcomes across all study countries as "funding decisions"; based on that, the terms "recommendation", "decision" and "decision outcome" all refer to "funding decisions" and have been used interchangeably throughout the text.

Finally, none of the MEAs included in this analysis were implemented across multiple indications of a specific molecule and/or were part of a MYMI agreement. As such, we acknowledge that in our impact assessment study we do not account for and/or explicitly discuss the potential benefits in patient access arising from the novel approach of applying MEAs across multiple indications and years. This approach arises as an increasingly promising strategy to achieve faster and broader patient access by reducing the administrative burden associated with conducting the same upfront evaluation process for each indication of the same product, while aligning price to the value that the product offers for each indication without the need for indication-based pricing (Lawlor et al., 2021). Nevertheless, the introduction of MYMI agreements is also subject to country specific legal arrangements which can contribute to unnecessary delays in the negotiation process. Therefore, understanding the extent to which MYMI agreements can enhance the positive impact of traditional MEA mechanisms on greater and more timely access to medicines, especially in oncology, arises as a priority topic for future impact assessment studies on MEAs.

6.5 Conclusions and way forward

Despite the application of MEAs being heterogenous across countries and often associated with high administrative burden and potential time delays, MEAs can still contribute to enhanced accessibility at the level of individual countries by allowing patient access to medicines that would not be reimbursed otherwise. However, presence of a MEA itself does not necessarily grant a timely and favourable funding decision as other factors such as the quality of clinical evidence submitted, and the type of endpoint used therein are also paramount in shaping the final funding decision and the respective timelines to decision-making. Of course, even though MEAs offer a higher likelihood for positive reimbursement, the question remains on whether the technologies approved with a MEA add true value in outcomes for patients and healthcare systems, whether they truly address the decision-making uncertainties characterising a technology and whether outcomes-based schemes measure meaningful clinical markers from the payers' and patients' perspective. Overall, it arises that only if applied strategically, MEAs can become a mainstay in the future of medicine availability, in reducing the financial burden for healthcare systems and in allowing faster access to new, innovative medicines.

7. Conclusions, policy implications and limitations

7.1 Conclusions

The ever greater proportion of HTA submissions for promising, high cost technologies that have an immature evidence base highlights a paradigm shift in reimbursement policies whereby coverage decisions are not solely focused on clinical efficacy and safety outcomes but they also seek to resolve and mitigate the impact of uncertainty related to insufficient evidence from controlled clinical studies around the real world cost- effectiveness and utilization of these new technologies (Carlson et al., 2010). In the above context of uncertainty, a number of principal healthcare policy goals are commonly targeted by countries worldwide, such as cost containment, greater access to medicines and industry innovation (EC, 2008). MEAs have been increasingly used in many settings as a pharmaceutical reimbursement "tool" to address these objectives (Ferrario & Kanavos, 2015) and manage the entry of such products. However, despite the recognised potential of MEAs to address decision-making uncertainties from the payer, industry and patient perspective, the confidential environment in which they operate and the scarcity of empirical evidence about their true impact on achieving their goals leaves important gaps for the sustainable implementation of MEAs in the future (Garrison et al., 2015).

To address the above gaps, this thesis had three broader objectives, namely, to understand the extent to which the uptake of MEAs for cancer medicines differs across countries, to map the HTA variables that drive the uptake and different types of MEAs implemented across settings, and third, to evaluate the impact of implemented MEAs on improved availability of and timely access to cancer medicines. Three distinct but intricately linked research articles addressed the above objectives of this thesis.

First, research article I demonstrated that there is a poor level of agreement between countries on whether new oncology therapies with evidentiary uncertainties will be funded with a MEA or not, to mitigate these uncertainties, and these diverging MEA outcomes were influenced primarily by agency-specific preferences on cost-effectiveness thresholds and evidentiary requirements for economic modelling. Second, research article II demonstrated that the specific HTA decision-making variables that determine the uptake of MEAs across countries relate to: (i) uncertainties around cost-effectiveness, (ii) uncertainties around the utilities included in the economic model and (iii) the SVJ of innovation; OBAs were specifically driven by uncertainties around generalisability to clinical practice, and clinical benefit/ evidence, while FBAs by the SVJs of innovation and societal impact of the technology under assessment.

Third, the final research article demonstrated that previously rejected medicines were significantly more likely to receive a favourable funding decision following a resubmission with a MEA, although successful and timely access to oncology therapies was also subject to submission of clinical evidence which presents with minimal uncertainties and is primarily based on clinically relevant instead of surrogate endpoints; therefore, presence of a MEA per se may not always guarantee a favourable funding decision and/or faster access to oncology therapies. Finally, in terms of impact on timelines, it was shown that approval with an outcomes-based MEA significantly increased the timing to final funding decision, although regardless of the MEA type, MEAs can only improve time to market access if the negotiation processes are well structured and based on sufficient preparation ahead of time.

Overall, it arises that if implemented appropriately, MEAs can play a predominant role in increased and faster access to new medicines, although further research is needed to understand the true, added value for patients and healthcare systems of the interventions approved with MEAs compared to other available interventions. Additionally, as the requirement for an agreement and the type of agreement payers are looking for, seem to vary according to the disease area and other social value considerations specific to the particular medicine in question, MEAs could potentially be used as complementary to VBP, through negotiations that enable weight adjustment of cost-effectiveness thresholds based on the therapeutic innovation, and/or wider societal benefits a new technology can offer. With the growing implementation of MEAs across countries worldwide, the above findings and policy implications arising from this thesis are of critical importance in adjudging the true impact and sustainability of these agreements.

7.2 Contribution to the literature

The overarching objective of this thesis was to contribute to the literature, first, by understanding the mechanisms of the MEA implementation practices across countries and second, by assessing the impact of implemented agreements on achieving greater and more timely market access for oncology therapies. This is the first empirical study, to date, that explored by means of econometric modelling, both the role of HTA decision-making variables in shaping the utilisation trends and types of MEAs across countries, as well as the role/weight of MEAs in relation to HTA decision-making factors in driving favourable (or non-favourable) funding recommendation decisions across settings and their respective timelines/ time delays.

Essentially, this thesis covers at least some of the gap in empirical contributions currently needed in the literature in order to enhance the transparency in MEA implementation mechanisms and ultimately, enable cross country learning and sharing of experiences around the utilisation of these agreements as an efficient mechanism to introduce new, high-cost medicines.

The focus on the therapeutic area of oncology was a distinct feature of this thesis. This is a significant contribution in the context of access to medicines research because cancer medicines present with unique challenges for reimbursement and subsequent access to patients. First, the cancer as a diagnosis poses challenges for healthcare payers to resist calls for reimbursement of exceptionally costly medicines with marginal clinical benefit (Van de Vooren et al., 2015). Additionally, despite the uncertain evidence on benefit for many new oncology therapies, their respective prices have grown dramatically across the globe, over the past decade; prices are projected to escalate further based on an increased demand generated by the growing number of cancer patients that need to be treated globally. Given that affordability is such a major issue when it comes to financing highly priced cancer medicines, HTA approaches on their own are increasingly proving to be insufficient in addressing the problem of patient access to cancer medicines. In response to this, it is expected that MEAs will continue to be primarily employed in the therapeutic area of oncology, aiming to facilitate reimbursement of cancer medicines. On that front, specifically research article III represents a unique empirical contribution to the literature, essential to understand if current schemes in oncology have worked in terms of better and more timely access to cancer medicines, and if not, how they can be applied more efficiently in the future.

Of course, the high prices of cancer medicines is a global, multi-faceted problem which requires global, multi-stakeholder, co-ordinated efforts to be addressed, beyond the implementation of efficient managed access mechanisms. This is a universal problem that calls for greater transparency of pharmaceutical price-setting mechanisms from the manufacturers' perspective, a greater engagement in VBP approaches from the payers' perspective, and greater awareness/communication of pricing issues from other stakeholders' perspective including the media and consumer and health professional organisations (Vitry et al., 2016). Multi-stakeholder action from payers, social entities, clinicians, patient & caregiver engagement, and industry, is paramount in achieving fair pricing and affordability of cancer medicines, while ensuring meaningful improvement in clinical and quality of life outcomes for patients (see also chapter 8- Areas for further research).

7.3 *Policy implications*

The findings of this thesis highlight a number of key policy implications in relation to reimbursement decision-making under uncertainty and provide a foundation for addressing the respective policy relevant challenges that exist. Specifically, the results and conclusions arising from this thesis can be used in practice by policy- makers to:

1. Facilitate policy relevant research around the development of transparent, "best-practice" guidelines for implementing MEAs, through a shared understanding of the determinants/ decision-making factors that explain the implementation of a MEA as part of coverage decisions across countries. In practice, this can help to facilitate/accelerate the implementation processes and more importantly to address the yet unresolved issues with the confidentiality of MEA negotiations.
2. Identify the aspects that shape the concept of "value" in decision-making under uncertainty and therefore, explain the rationale behind payers' flexibility to provide coverage with a MEA or not. Essentially, this can contribute to better tailoring of proposed schemes such that they align with the value perceptions of different payers and hence, leading to more successful MEA negotiations and subsequent increased opportunities for funding through MEA schemes.
3. Identify the extent to which MEAs can, and have changed or improved access across settings, as well as the specific conditions or features of MEAs that matter in achieving improved access. This is critical in optimising funding mechanisms under uncertainty through an improved understanding of the extent to which MEAs can achieve their targeted objectives, and crucially, on how they can be applied so they deliver the impact they aimed to have.
4. Understand the Restructure and re-design HTA "best-practices" and processes such that they enable more streamlined and timely MEA proposal submissions and negotiations.

More importantly, addressing the above points is collectively of vital importance from a policy-making perspective, to understand if the concept of "risk-sharing" represents a sustainable solution to introduce new, high-cost medicines in the future. Therefore, the empirical findings of this thesis can provide valuable conclusions about the long-term viability of managed entry approaches, by shedding a light on the broader implications that arise in relation to the policy relevant areas listed above and described in more detail as follows:

1. *Facilitating policy relevant research around the development of transparent, "best-practice" guidelines for implementing MEAs, which can be used in practice to facilitate/accelerate their negotiation processes and enhance transparency therein.*

As the importance and utilisation of managed access mechanisms in pharmaceuticals is expected to grow across countries, a greater level of granularity in the guidelines for conducting managed access negotiations and implementing MEAs, arises as a high-priority research area in the context of HTA decision-making under uncertainty. Towards that goal, research articles I and II provide an empirical evidence base that serves as a valuable foundation for enhanced transparency in the existing guidelines by promoting a shared understanding on the aspects that drive value in MEA negotiations from the payers' perspective.

Establishing transparent and universal "best-practice" frameworks for MEA negotiations is of uttermost importance especially when considering that pricing and reimbursement mechanisms differ significantly across countries based on how the respective healthcare systems operate and therefore, payers are required to tailor their decisions according to what reflects good value for money within their systems. Furthermore, even though some HTA bodies have issued guidance on their specific approaches and expectations for MEAs, their implementation often remains based on informal and implicit methods and judgments, and there is a case for operationalising them in a more explicit and transparent manner (Coyle et al., 2020). Additionally, despite the availability of frameworks for MEA negotiation and implementation, not all healthcare systems have the capacity to operationalise these frameworks successfully (Thanimalai et al., 2021). Therefore, understanding the common grounds that determine successful MEA implementation between countries can help establish universally applicable frameworks and best practices for decision-making under uncertainty that help to automate and accelerate MEA negotiations and hence, reimbursement decisions. Finally, given the multitude of different MEA schemes and the way they can be implemented in different settings, research efforts comparable to research articles I and II of this thesis, which explore how and which MEAs have been applied in different healthcare systems are important for: i) bridging the gap between the wealth of descriptive literature and the dearth of empirical research in the field and ii) subsequently also contribute in the development of national standardised templates for MEA implementation which would allow manufacturers and payers to readily design and/or negotiate an agreement that would benefit the healthcare system in question (Williamson et al., 2010). The latter is especially critical when considering that according to stakeholders,

establishing effective guiding frameworks and governance procedures for the implementation of MEAs based on standardised decision-making criteria is paramount in reducing lengthy negotiations and overall, in launching and operating MEAs successfully (Thanimalai et al., 2021; Michelsen et al., 2020).

Currently there is an absence of established and/or explicit multi-dimensional value frameworks for the purposes of HTA decision-making, and value assessment approaches in the context of HTA primarily operate under the principles of comparative clinical and cost-effectiveness. As a result, the definition of what constitutes "overall value" of a treatment in the context of HTA decision-making remains inconclusive given that beyond clinical and cost-effectiveness, other value considerations, often setting-specific, may be of importance in shaping such decisions.

The results arising from research articles I and II, addressed specifically the above gap, by providing a clearer picture on the criteria that shape the concept of "value" in reimbursement decision-making under uncertainty across and within countries. For example, research article I demonstrated that diverging MEA outcomes between countries were influenced heavily by economic evidence uncertainties including those around cost-effectiveness, utilities and costs included in the economic model. It was shown that the value/weight placed on cost-effectiveness thresholds and evidentiary requirements for economic modelling was greater for NICE in England compared to the other study countries.

Additionally, clinical uncertainties related to setting-specific characteristics (e.g., relevance of the technology in question and of the clinical comparator to the country/region-specific clinical practice, and/or the generalisability of trial population to the setting-specific population) were found to be more extensively considered by NICE and TLV (as opposed to the other HTA agencies studied) when dealing with uncertainty in HTA decision-making. Similarly, a number of setting-specific dimensions of value beyond those of clinical and cost effectiveness such as the SMC modifiers, NICE's end-of-life criteria and the human dignity principle for TLV are decision-making modulators that may explain decision-makers' greater flexibility on accepting uncertainty or higher and uncertain ICERs. It follows, that these are dimensions of "value" that may play a role in explaining the uptake of MEAs within specific countries.

In addition, research article II demonstrated that there are also value dimensions that can be equally important in determining the uptake of MEAs across countries. For example, when controlling for HTA agency, it was shown that MEAs uptake was heavily influenced by uncertainties around the utilities included and the SVJ of innovation.

Merging practical learnings about the implementation of MEAs (such as the examples described above arising from research articles I and II) together with the extensive literature available on the opportunities and weaknesses of MEAs can help to understand to what extent certain MEAs are more or less feasible in higher and lower-income settings respectively, and how barriers for their implementation could be overcome (Vreman et al., 2020). In the same context, it can contribute towards the development of a comprehensive value framework to guide the implementation of MEAs across countries. This framework could be used by individual settings, or across settings, when, collaborative approaches are required at the supra-national (e.g., pan European) level. Shared understanding on the practices followed and common pitfalls experienced across countries with MEA negotiations can foster discussions and support collaboration to determine common, decision-relevant endpoints/ uncertainties when considering funding with a MEA and therefore, standardise MEA negotiation processes within and across countries (Facey et al., 2021). Ultimately, this approach could also help to reduce duplication of effort in the MEA negotiation process both for payers and manufacturers across countries and contribute to improved timelines and reduced administrative burden associated with the implementation of MEAs.

Of course, providing greater transparency around the rationale and evidence base that support reimbursement decisions with MEAs is fundamental in resolving the historically debated issues with the confidentiality of MEA negotiations across settings. However, even when transparent guidelines and procedures are followed, transparency on the rationale behind the high prices requested by pharmaceutical companies would still be required for public information purposes, while better involvement of patients in decision-making processes is also critical in strengthening the legitimacy and public acceptability of funding decisions (Vitry et al., 2016).

2. *Identifying the aspects that shape the concept of "value" in decision-making under uncertainty and therefore, unravelling the rationale behind payers' flexibility to provide funding with a MEA or not.*

Research article II provided an overview of the payers' decision-making preferences that determine whether a restricted funding decision will comprise a MEA as part of the restriction or not, and if so, the variables that can also explain what type of MEA will be more suitable as part of this restriction. Strengthening our understanding on the above is particularly important, given that MEAs can optimally achieve their goals only when they are tailored to the specific circumstances in which they operate and to the preferences of the decision-maker in question (Vreman et al., 2020). Results from this research article, coupled with findings from the literature demonstrate that payers' preferences for providing coverage with a MEA, as well as they type of MEA preferred, are primarily shaped by value considerations specific to the particular medicine in question, such as the burden of the specific disease it targets and the therapeutic advancement it offers within this disease are (Dunlop et al., 2018). Therefore, it arises that for a successful MEA negotiation, both from the manufacturer's and payer's perspective, MEAs should be tailored such that they include a careful consideration of the characteristics of the therapy to be reimbursed, the characteristics of the healthcare payment system, the possibilities for different payment structures with the respective healthcare system, and preferences of the decision-maker regarding financial vs. outcomes-based agreements, individual or population based agreements, and the combination of multiple mechanisms (Vreman et al., 2020).

Essentially, this study showcases that beyond resolving clinical and economic uncertainties, successful managed access strategies also depend on whether additional, broader elements of value are being addressed by the new therapy in question. Shedding a light on these additional aspects of value is important as often these are only implicitly considered by decision-makers as part of their decision-making process. Making these aspects explicit would provide greater transparency and consistency in the appraisal and price determination process, especially when a diverse range of stakeholders are involved in decision-making. Additionally, enhancing transparency around these broader value elements that are deemed important by decision-makers and by society can help experts to make more informed choices when it comes to decision-making under uncertainty (Coyle et al., 2020).

More specifically, results arising from research article II show that the additional dimensions of societal impact of the technology in question, innovation, disease severity and rarity are fundamental in determining whether payers will offer funding with a MEA for a new technology, and if so, the respective type of MEA that will be implemented. Literature has also demonstrated that other elements of value beyond the societal benefit and severity of disease may often be considered significant in decision-making, such as the value of having a treatment choice among alternative therapies with different administration and safety profile and the value of scientific spill-over[11] for future drug development purposes (Coyle et al., 2020; Angelis & Kanavos, 2017).

A value-based approach in technology assessment has been typically followed by the Swedish HTA agency, whereby decision-making takes a broader societal perspective that places a great emphasis on the societal costs and gains a new treatment offers. However, even for HTA agencies that have traditionally based their assessments on pure cost-effectiveness principles, additional aspects of value are increasingly being considered in the decision-making process. For example, NICE in England, which has historically applied the cost-effectiveness and cost per QALY approach in its decision-making, has published a guidance since 2013 to define a revised role of NICE in assessing the value of new medicines in the context of VBP. According to this new approach towards value-based technology assessments and decision-making, three additional elements of societal value are considered more explicitly and systematically by NICE in its assessments. Namely, these three attributes include the 'burden of illness' (i.e., the impairment in quality and length of life generated by living with a disease or condition, compared to the QoL that people would be expected to have without the condition), the 'wider societal benefits' that would be gained by treating a specific disease or condition and the 'therapeutic improvement and innovation' that a new treatment has to offer. Specifically, the former two elements are used by NICE as decision 'modifiers', to decide if a technology with

[11] Scientific "spill-over" effect (or dynamic efficiency) refers to any case where a new technology can have R&D implications for the development of subsequent technologies, primarily including implications around the diffusion of scientific and/or technical knowledge for the purposes of long- term product innovation at future market conditions; innovation "spill-over effects" have been defined in the literature as "the R&D favourable externalities that can contribute to the development of future innovation(s)" (Angelis & Kanavos, 2017).

an ICER surpassing the £20,000 per QALY threshold would still be eligible for funding (NICE, 2014).

In response to the increasingly "value focused" approach taken by HTA agencies in their assessments, several value frameworks have been described in the literature and established by relevant professional societies. Specifically for cancer, many groups have developed frameworks to evaluate the value of oncology therapies for patients and the society, such as the ESMO MCBS which grades value based on the magnitude of the broader benefit that the treatment offers for patients (including QoL considerations), the ASCO Value Framework, which explicitly takes into account patient benefit and QoL in the context cost, and a Canadian drug assessment framework, developed to promote transparency and consistency in oncology medicines' reimbursement decisions, which includes valuation of unmet need, equity, and disease severity as part of structured decision-making (Leighl et al., 2021). Similar efforts have also been made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force on Value Assessment Frameworks to support the incorporation of additional value elements into the broader HTA valuation frameworks (Garrison et al., 2018).

In light of the above, a key policy implication underscored by the findings of this research relates to the feasibility of applying MEAs as part of value-based approaches in technology assessment and reimbursement. As described above, research articles I and II demonstrated that successful MEA uptake is highly dependent on additional dimensions of value beyond clinical and financial uncertainties. Therefore, as VBP includes a consideration of all aspects of value deemed relevant, it can be concluded that MEAs have the potential to complement and enhance VBP policies. For example, literature has shown that the VBP system in Sweden, aims to accelerate patient access by conducting ex-ante VBP assessments[12] as a form of risk sharing to speed up reimbursement and uptake of promising new technologies despite their uncertainties; essentially, this system is employed as a risk sharing approach to avoid delays and/or complete exclusion from reimbursement until the requested satisfactory evidence is provided by the manufacturer (Persson et al., 2010). With many healthcare systems particularly

[12] TLV implements both ex-ante and ex-post assessments. The former applies to new products where evaluation occurs prior to market launch, with decisions being made within three to four months. The latter refers to evaluations of products that are already on the market prior to the introduction of new pricing arrangements in 2002.

in Europe being directed towards value-based reimbursement approached, further research to understand and draw more robust conclusions on the interconnected role between MEAs and VBP policies mechanisms is essential (see chapter 8- Areas for further research).

3. *Optimising funding mechanisms under uncertainty through an improved understanding of the extent to which MEAs can achieve their targeted objectives, and crucially, on how they can be applied so they deliver the impact they aimed to have.*

As described in detail in the literature review (see chapter 2, section 2.3) there is a growing, on-going literature debate on the weaknesses of MEAs and this is primarily generated due to the poor and inconclusive evidence as to whether managed access/entry agreements have succeeded in meeting their objectives. The results arising from research article III, addressed specifically this gap, by providing a clearer picture on the extent to which MEAs can and have changed or improved access across settings, as well as on the specific conditions or features of MEAs that matter in achieving improved access to medicines outcomes. The findings arising from research article III provide a much-needed post-implementation evaluation of MEAs that fills important literature gaps in structured, empirical, impact assessments of MEAs. More importantly, systematic evaluations of established MEAs, such as the case study presented in research article III, are crucial for the development of more successful schemes in the future. Given that there is a growing interest in MEA implementation across countries and that future managed entry negotiations and mechanisms are highly likely to suffer similar caveats as previously implemented schemes, to counter this potential risk, enhanced knowledge regarding the conditions under which MEAs can effectively achieve their proposed goals is necessary to avoid experiencing common pitfalls when setting up new agreements (Makady et al., 2019).

In research article III, an impact assessment study was conducted to understand if a number of MEAs implemented for a set of oncology medicines have had an impact on enhancing the availability of and timely access to these medicines. Findings of this research showed that indeed, when manufacturers propose the listing of a new technology with a MEA, this is significantly more likely to be granted coverage as opposed to products without a proposed MEA. Nevertheless, a notable policy implication highlighted by this impact assessment study is that presence of a MEA per se should not be regarded as a panacea or one-size fits all approach to achieve coverage for high-cost products presenting with evidentiary uncertainties. Whether these agreements can be successfully implemented and deliver a positive impact for

patient access is highly setting specific and dependent on how these contracts are negotiated, designed and managed (Van de Vooren et al., 2015). For instance, in terms of the potential impact of MEAs on timing to access, it was demonstrated that the HTA agency/ setting where these agreements are negotiated and implemented (rather than the presence/absence of a MEA per se) largely determines the respective time to final funding decision. More precisely, among the study countries/ HTA agencies it was found that the Australian and Scottish agencies were associated with a reduction in the decision-making time. As discussed in Research article III divergencies in time to reaching a final coverage decision are primarily driven by HTA agency/country specific modalities and procedures followed in the decision-making process. For example, NICE (England) exhibited the longest time (i.e., 938 (±559) days) to final funding decision compared to the other study HTA agencies. This was not surprising given the more administratively complex NICE specific processes related to MEAs implementation, such as often switching to the CDF during the review process and introducing new patient access schemes (Ambrose et al., 2018), or the PASLU process for MEA submissions (described in section 3.1.2) which has been documented to result in significant time delays (Ambrose et al., 2018; O'Neill et al., 2012). On the contrary, SMC (Scotland) exhibited the shortest time (i.e., 342 (±249) days) to final funding decision compared to the other study HTA agencies. Historically, Scotland is one of the first HTA agencies where manufacturers submit a dossier to request reimbursement for their products (Charokopou et al., 2015), which can arguably play a role in driving generally shorter timelines to final recommendation decisions regardless of the presence/absence of a MEA. However, the SMC processes specifically in relation to MEA implementation may also influence shorter timelines. Under the current SMC processes for PAS submissions, simple discount schemes (as opposed to outcomes-based/complex schemes) are typically recommended, whereby manufacturers agree one price for a medicine with the PASAG, regardless of the multiple indications the medicine might be used for, or the outcomes it delivers for patients (AbbVie, 2020) encouraging more streamlined, timely negotiations.

More specifically, the case study presented in Research Article III demonstrated that in combination with the presence of an agreement, favourable funding decisions and timely access to medicines were also subject to submissions with a clinically relevant as opposed to surrogate endpoint in the evidence submitted by manufacturers, as well as submissions with evidence which is free of clinical evidence uncertainties, especially around the study design. These findings are corroborated and complemented by the findings of research article I, as well as

findings from the literature which demonstrate that for products presenting with uncertainties around the strength or quality of their clinical evidence and clinical benefit the possibility for payers to enable restrictions or funding negotiations to mitigate these uncertainties is limited and therefore, rejections are highly likely (Nicod 2017, Nicod & Kanavos, 2016).

Similarly, evidentiary uncertainties around the design of the clinical trial tend to be an impediment to a product's introduction in the market and manufacturers should always take this into consideration when trying to meet payers' evidentiary requirements for reimbursement along with other, regulatory and marketing authorization requirements (Charokopou et al., 2015). Additionally, even though surrogate endpoints in oncology are acceptable for accelerated or conditional marketing authorization approval and are not directly associated with the final recommendation decision (Ciani et al., 2021; Pinto et al., 2020) their value for reimbursement and funding decision-making purposes is not always recognised as valid across all countries and healthcare payers (Godman et al., 2018) and ultimately this can lead to additional challenges and delays in decision-making, as it was also confirmed by the second part of the impact assessment conducted in research article III. Indeed, among healthcare stakeholders, payers tend to have the highest demands around the magnitude of clinical benefit required as proof of survival gains for oncology treatments, even when clinically relevant endpoints have been used in the trials. (Toumi et al., 2017). In the same context, calls from ASCO experts have necessitated a raise in the bar for clinical trials of cancer medicines, with overall survival included as the preferred primary outcome in such studies (Ellis et al., 2014).

Of course, uncertainties arising from equivocal clinical trial results could be mitigated by the implementation of an outcomes or performance-based contract to collect further evidence and improve their cost-effectiveness profile. However, there is a risk that outcomes-based schemes may eventually contribute little to robust, meaningful conclusions in practice, given that data collection performed under these programmes may suffer from lack of randomisation and the uncertain relationship between short-term surrogate and hard endpoints (Van de Vooren et al., 2015). Therefore, for outcomes-based schemes to achieve their targeted objectives and address uncertainties in a constructive way, it is necessary to establish a greater understanding and adoption of a consensus on surrogate endpoint validation and acceptability between manufacturers, payers and the different healthcare stakeholders involved in the negotiation and implementation of these agreements (FDA, 2021). In the same context, successful outcomes-based contracts that rely on the collection of surrogate measures, necessitate a careful

reconsideration and harmonisation of practices on the issue of surrogacy across HTA agencies globally (Ciani et al., 2021). Early dialogue and scientific advice can be a catalyst for implementing meaningful performance-based schemes in a timely manner, as they provide an opportunity for both manufacturers and payers to align on the endpoint requirements to tackle a certain decision uncertainty around clinical outcomes and agree on the appropriateness of using a surrogate measure for the decision problem.

The above is particularly relevant when considering that in the econometric model conducted under research article III, which predicted time to final recommendation decision, the presence of a MEA per se did not contribute to access delays but submissions specifically with a PBA had a statistically significant, positive contribution in the model.

The negotiation process for outcomes based agreements is well known in the literature for its challenging and time consuming nature, as is actual process of additional data collection for the purposes of PBAs, and the future monitoring and re-evaluation of the product subject to a PBA, while issues around obtaining alignment in expectations/interpretation of collected data and data coverage requirements between regulators and payers usually cause further delays (Bentata et al., 2020; Kanavos & Mills, 2015; Wilsdon & Barron, 2016). Specific concerns related to administrative burdens exist around OBAs, as they are complex, and many countries still do not have experience with this type of MEAs or lack the administrative infrastructure to facilitate their implementation (Bouvy et al., 2018). Therefore, for outcomes-based contracts to be implemented efficiently and with minimal delays in the process, existing challenges in the tracking of outcomes across diseases for which longer data collection periods are required, such as disease progression following oncology therapy, need to be addressed by including strict follow-up requirements, aligned financial terms of the contract, and sometimes automated data collection solutions (KPMG, 2020).

Based on the above, simple financial based contracts are often regarded as a more straightforward and efficient solution for healthcare payers to reduce expenditure on highly priced cancer medicines, while achieving higher levels of access for patients (Van de Vooren et al., 2015). Indeed, it arises from the impact assessment study presented in this thesis that financial based schemes offered greater and more timely opportunities for favourable funding of cancer medicines compared to outcomes-based contracts. From the manufacturers' and patients' perspective financial based schemes may represent a straightforward, expeditious approach towards launching and accessing, respectively, novel cancer therapies (Van de Vooren et al., 2015). Nevertheless, as the often overwhelmingly high prices of these therapies

are kept commercial-in-confidence, from the healthcare payers' perspective granting reimbursement under a financial based scheme bares the risk of making available to patients highly priced but modestly effective medicines. Therefore, even simple financial based schemes, still need to be applied with caution and aimed at achieving meaningful outcomes in terms of patient access to effective interventions, rather than solely being applied as a cost containment tool. This is especially important when taking into account recent findings from the literature which accentuate the inherent potential of MEA mechanisms to cause a substantial increase in list prices of pharmaceuticals (Gamba et al., 2020). Therefore, when financial MEAs are applied simply as an inadvertent response to high prices, there is a risk of spiralling a continuous growth in prices of pharmaceuticals, for as long as price negotiations continue to operate in a confidential environment. The above can primarily penalise smaller countries which lack the infrastructure on setting up procedures and the bargaining power needed to negotiate lower prices, as well as countries which rely on external reference pricing (i.e., countries whereby pharmaceuticals are priced based on referencing the respective prices observed in a basket of other countries) (Van de Vooren et al., 2015). Additionally, applying FBAs as a cost containment measure can have potentially harmful implications for the long-term financing of and access to medicines subject to these agreements, as granting access to interventions which might prove cost-ineffective in the long-run, can lead to the delisting of these technologies after expiry of the agreement, eventually causing delays to patients' treatment pathways. As such, to ensure that MEAs achieve a meaningful impact for payers, manufacturers and most importantly, for the end users of the technologies in question (i.e., patients and their caregivers), a comprehensive risk management plan may also need to be established when discontinuation of funding at the national level is an option for medicines funded under a MEA (Vitry et al., 2015). This also links to discussions about the true added value of the interventions approved with a MEA (whether financial or outcomes based), compared to their available alternatives and whether the contracts implemented resolved the uncertainties they were meant to resolve (see also section 8 – Areas for further research). Assessing the true impact of MEAs in resolving decision-making uncertainties for payers was beyond the scope of this thesis. Nevertheless, recent evidence suggests that at least some types of MEAs such as coverage with evidence generation and pay for outcome schemes have not always resulted in resolving the uncertainties they were meant to address (Vreman et al., 2020).

4. *Restructuring and re-designing HTA "best-practices" and processes such that they enable more streamlined and timely MEA proposal submissions and negotiations.*

Finally, another major policy implication underlined by the conclusions of the case study presented in research article III, is that the type of HTA agency plays a key role in defining timely access to medicines, including both the feasibility to implement MEAs and their timely negotiation. First, in the context of HTA, agency specific time delays may often be generated by the multitude of stakeholders (such as purchasers/commissioners of care, regulators, national and regional competent authorities for pricing and reimbursement, the healthcare system itself, the pharmaceutical industry, patients or patient associations and carers) and their respective perspectives/requirements intertwined in value assessment and funding negotiation procedures (Kamphuis et al., 2021). Second, HTA specific processes for MEA negotiations determine whether an additional delay will occur, as, for example, prolonged or fragmented negotiations automatically contribute to patient access delays. A notable example is the PASLU process for MEA submissions in England and the associated lengthier times to final reimbursement decision observed for NICE compared to other HTA agencies studied in this analysis. Third, contextual differences around data collection infrastructure and supply chain of specialty medicines influence the feasibility of applying different types of MEAs across countries or between regions/territories within countries (Pauwels et al., 2017). Therefore, a key lesson to be learnt across countries as "best practice" in relation to optimal implementation of MEAs within HTAs, includes the design of more streamlined processes for MEA proposal submissions and negotiations.

Overall, the conclusions and policy implications arising about the impact of MEAs and other HTA relevant variables on availability of and timely access to medicines, should be explicated within a broader concept of "access to medicines", whereby even when a pharmaceutical product has received a favourable and timely funding decision at the HTA level, accessibility in practice may still not be guaranteed as it is equally determined by further geographical, healthcare system and supply chain factors. From the "market access" perspective, purchasing arrangements and negotiations can significantly influence the extent and time in which medicines can become available in their respective markets. In addition, they can create supply discrepancies which may result in unequal access based on whether purchasing of medicines occurs at the national, regional or hospital level. Furthermore, accessibility of innovations is also subject to authorisation for these agents to be prescribed, which relies on healthcare system ability and promptness to execute administrative procedures and adopt funding decisions, and

organisational/ infrastructural capacity to inform and update clinical care guidelines to reflect newly approved technologies (Vintura, 2020b). Ultimately, from the "patients' access" perspective, access to a newly approved medicine is also highly dependent on their eligibility and affordability to reach the right healthcare professionals with the capacity to prescribe the medicine in question.

7.4 Limitations from the conduct of this research

The author recognises that a number of methodological limitations were encountered while carrying out both the overarching research/data collection required for all research articles, and the individual analyses for each article of this thesis. Overall, a common limitation across all research articles relates to the fact that the study sample was limited to oncology medicines and therefore, findings of all three research articles may not be generalizable to the entire market of pharmaceuticals subject to MEAs. Even though these products correspond to the majority of MEAs implemented to date, the author recognizes that the results presented in this thesis should be interpreted with caution as they may not be entirely generalizable and transferable to the MEA implementation practices and determinants in other therapeutic areas.

Furthermore, the author is aware that the use of GoogleTranslate® to collect and interpret additional data from Swedish HTA reports, and other national sources, such as the county councils funding decisions, that had to be searched for the purposes of all research articles introduced the risk of translation inaccuracies and false interpretation of the available evidence. However, in an effort to eliminate this risk, where possible, help with translations was sought from a native speaker.

The author also acknowledges that most of the documentation submitted to the HTA agencies by the manufacturers and generated during the evaluation process is for the most part commercial in confidence and detailed information cannot always be released publicly. This entailed the risk of unavailability of information or fragmented data, particularly around sensitive information such as prices and ICER figures. However, publicly available reports summarizing the evidence submitted and the rationale supporting the final funding decision recommendations are publicly available through the websites of all the national HTA agencies studied in this research. These publicly available reports were used for the data collection performed in the context of this thesis and to the best of the author's knowledge the information

included therein was sufficient and comprehensive enough for the purposes of the specific analyses conducted in this thesis. Of course, due to fragmented information communication in the publicly available versions of the HTA reports, the author cannot rule out possible discrepancies in the data collected, caused by misconceptions about the exact rationale of the HTA agencies decisions and potential misinterpretation of scientific data that was required to be collected.

Similarly, the specifications of MEA negotiations per se are also confidential, and relevant sensitive information such as proposed prices and details of proposed risk-sharing arrangements are often redacted from the summary HTA reports. In some cases, details on the content of the agreement were unavailable, fragmented or difficult to extract. Nevertheless, this information would be related mostly to the specific details of the agreements, price discounts and the outcomes in terms of price savings or impact on cost-effective use, which were not directly required for the purposes of data collection. Data on the existence, broader type (i.e., financial/outcomes based or combination agreement) and start/end (where applicable) dates of MEAs was required and this was readily available for collection. To the best of the author's knowledge all relevant information under the above-mentioned variables relating to the implemented MEAs within the study sample, has been collected and captured in the analyses of this thesis. However, the possibility cannot be excluded that the major database built for the purposes of this thesis may not include the entirety of MEAs implemented for the medicine-indication pairs studied in this research and that this might have resulted in an underestimation of the total number of agreements in place for the therapeutic area studied.

Additionally, given the interconnected role of the decision-making variables considered in the context of reimbursement decisions, a potentially high collinearity and simultaneous causality of the variables studied in the models (e.g., one or more independent variables jointly determined by the dependent variable on "existence or not of a MEA") cannot be excluded. Potential ways to address this endogeneity bias in future replication of this analysis would include data clustering such that data points of the same group would have higher inter-similarity/collinearity between them, and lower intra-similarity/ collinearity with data points in other clusters and using the broader cluster labels as independent variables. Overall, it is important to highlight that throughout the chapters, the findings are presented as associations between the response and explanatory variables, describing the effect size and direction of these associations. When interpreting the results, it is essential to consider that they do not

provide causal estimates and therefore, do not necessarily explain if a specific outcome is the result of the occurrence of another event – i.e., if there is a causal relationship between the response and explanatory variables found to have an association. This is a key limitation of this research and should be accounted for in any future replication of the study.

Finally, other, research article specific risks and limitations are listed as follows:

- **Research article II:** Reference in the literature has been made to the impact of the overall country specific healthcare and welfare characteristics on HTA decision-making, such as healthcare spending per capita, societal WTP, the structure of the healthcare system, as well as ethical and social considerations (Cerri et al., 2014). However, it is acknowledged that country specific policies, purchasing framework and context in which HTA reimbursement decision-making operates were not necessarily captured in the database used for this analysis. Nevertheless, in order to control for their potential confounding effect, the analysis captured other, HTA system-specific considerations such as social value judgements and other national considerations (see chapter 5, section 5.2.2- Data collection). Finally, in order to combine all relevant data in a single analysis and run the proposed model, several assumptions had to be made (described in more detail in chapter 5, section 5.2.3- Data analysis) and this is recognised as a limitation of the analysis conducted for this chapter.

- **Research article III;** Providing an evaluation of the currently implemented schemes in terms of their overall impact from a societal perspective was beyond the scope of this research. Therefore, it is acknowledged that the MEA impact assessment case studies that were presented in chapter 6, might have provided over- or under- estimated impact evaluations, given that they did not take into account the counter effects of the financial and administrative burden required to implement these schemes: neither did they capture the difficulty and delays arising from a withdrawal of reimbursement or coverage decision once an agreement expires or stops being implemented due to certain outcomes not been confirmed through additional data collection. Additionally, as described in the methodology section of the respective chapter (see chapter 6, section 6.2.3- Data analysis), the metric of reversing non-favourable to favourable funding decisions has been used as a proxy to enhanced availability of medicines, and the metric of time to final funding decision as a proxy to timely access to medicines. Therefore,

this impact assessment study has been designed based on the key assumption that positive and more timely reimbursement decisions also reflect improved and more prompt availability of medicines. The author recognises that this may have provided an overestimation about the impact of MEAs on improving availability and timely access to medicines given that even if a product achieves a positive reimbursement decision, it may not become readily available for use in the actual practice (Kamphuis et al., 2021). Factors external to HTA, relating to for example, the country or setting specific regulatory framework in which purchasing, prescribing, and supplying of medicines operates, as well as companies' different launching strategies across countries heavily determine the extent and promptness in which medicines; a) will acquire positive reimbursement status and b) become available for patients in the respective market once they acquire positive reimbursement status. Therefore, future replication of the analyses conducted for this chapter could introduce country fixed effects in the respective models to account for the different level of impact that these country-specific, external factors might have on the availability of and timely access to medicines.

Another limitation of the analysis performed for this chapter relates to the choice of model when assessing the impact of MEAs on time taken to final funding decision. Typically, survival models and particularly the Cox proportional hazards model is the model of choice when studying time-to-event data subject to right censoring (Cox, 1972), and with respect to multiple variables at once. However, survival models may also be expressed as GLMs when there is no censoring; in this case, an advantage of the GLM-based models over survival models is that they can be made flexible to address the complexity of the observed hazard function accordingly (Kerans et al., 2019). As such, since the observations are uncensored in this analysis, a GLM was chosen. Literature has recognised that it is straightforward to perform a time-to-event analysis within a GLM framework and that results are at least as good as, and often superior to, those from survival models (Columbia Public Health, 2022). Nevertheless, as GLMs have rarely been used to analyse time-to-event data, there is limited experience in their performance for such analyses, and therefore, the results presented in this chapter about the potential of MEAs to increase timely access to medicines should be interpreted with caution. A Cox regression could be employed in future replication of this analysis, as a more widely used/acceptable methodology.

8. Areas for further research

The findings of this thesis and the respective policy implications as described above underscore a number of critical areas in policy relevant research around MEAs and managed access mechanisms that need to be examined further.

First, this thesis demonstrated that MEAs offer a higher likelihood for positive reimbursement and thus we can conclude that they indeed have a positive impact in terms of improved availability/ level of access to medicines for patients. However, future impact assessment studies should also conduct a pragmatic evaluation based on primary evidence from the end users of technologies reimbursed with MEAs, including patients, their caregivers, and clinicians, to understand whether these schemes have been impactful in granting access to technologies offering a meaningful added value/benefit for these individuals compared to alternative treatment options.

Second, future research should focus on benchmarking and comparative assessments based on primary evidence from payers and clinicians, to quantify the extent to which concluded MEAs addressed the uncertainties they were aimed to resolve and specifically for performance-based schemes the extent to which they managed to reduce clinical evidence uncertainties by measuring meaningful therapeutic outcomes. Extensive and more conclusive research specifically on the impact of performance based MEAs is paramount, as more countries are experimenting with such contracts, but systematic evaluations from countries that have already implemented these contracts are either completely lacking or they are limited and the results about the outcomes of these schemes that have been reported therein are mixed and inconsistent (Vreman et al., 2020).

Third, the results of this analysis highlight the increasing role that additional dimensions of value play in shaping pricing and reimbursement decision-making, including determining whether a MEA will be implemented as part of a funding decision or not. As value-based approaches in pricing and reimbursement are gaining more prominence especially in European markets, it is essential to study more extensively the interconnected relationship between MEAs and VBP. More importantly, understanding the extent to which implementing MEAs can be used to complement value-based assessments in the context of HTA is also crucial to

draw better conclusions about the sustainability of MEAs as a reimbursement tool/policy in the future.

Fourth, findings of this research confirm that MEAs can offer a solution towards enabling access to medicines that would have otherwise been directly excluded from coverage due to their high costs coupled with their evidentiary uncertainties. Certainly, the use of MEAs represents one option to address decision uncertainty as a barrier to market access. Nevertheless, MEAs are not always suitable or feasible to implement. Alternative models of payment have been discussed in the literature as a response to the remaining and growing challenges facing the financing of new medicines at ever increasing prices, along with financing increased volumes due to the growth in the numbers of patient populations that need to be treated across countries. This has resulted in the development of novel payment models to better manage the entry of new medicines, as well as new financial models/ strategies to improve prescribing efficiency; the main financing mechanisms employed by these models have been described in more detail in chapter 1, section 1.5- Issues with MEAs, and alternative mechanisms of access. In response to the growing interest of payers and healthcare systems in these novel funding approaches, comparative assessments between MEAs and new payment models, are needed to understand the relative impact, advantages, disadvantages, and opportunities associated with each of these funding mechanisms, in terms of enhancing availability and access to more efficient technologies in a timely manner. Furthermore, in the context of providing greater evidence around these new payment models and how they compare to MEA mechanisms, it is specifically important that future efforts conducting impact assessment studies on MEAs, also account in their analyses for the role and potential benefits in patient access arising from the novel approach of applying MEAs across multiple indications and years (i.e., MYMI agreements), in cases where such agreements have been implemented. So far, experience with MYMI agreements in Belgium, Denmark and the Netherlands has demonstrated their potential to minimize significantly the time taken for reimbursement approval of medicines with multiple indications (Bentley, 2018). For example, the mean time to patient access was reduced by nearly twelve months in Belgium and by more than three months in the Netherlands (Lawlor et al., 2021). According to the literature, these agreements arise as an increasingly promising strategy to achieve faster and broader patient access by reducing the administrative burden associated with conducting the same upfront evaluation process for each indication of the same product, while aligning price to the value that the product offers for each indication without the need for indication-based pricing (Lawlor et al.,

2021). Nevertheless, the introduction of MYMI agreements is also subject to country specific legal arrangements which can contribute to unnecessary delays in the negotiation process. With discussions about the role of MYMI agreements gaining increased traction in the recent literature, understanding the extent to which MYMI agreements can enhance the positive impact of traditional MEA mechanisms on greater and more timely access to medicines, especially in oncology, arises as a priority topic in the MEA relevant research. Overall, the increasing budgetary pressures combined with the unmet need that remains despite the continuous introduction of new pharmaceuticals in the market, make an urgent call for efforts to scrutinise the effectiveness and value of newly introduced medicines in the future; especially in oncology given the ever-increasing prices of cancer therapies.

Fifth, future literature should focus on scrutinising discrepancies between affordability and value of cancer medicines and understand how these two concepts can be addressed through relevant ongoing activities employed across countries, such as establishing minimum effectiveness targets for premium pricing, re-evaluating prices following patent expiry of a cancer medicines, integrating patients' perspectives as a key component of decision-making and placing more emphasis on multicriteria decision analysis (Godman et al., 2018; Cherny et al., 2016).

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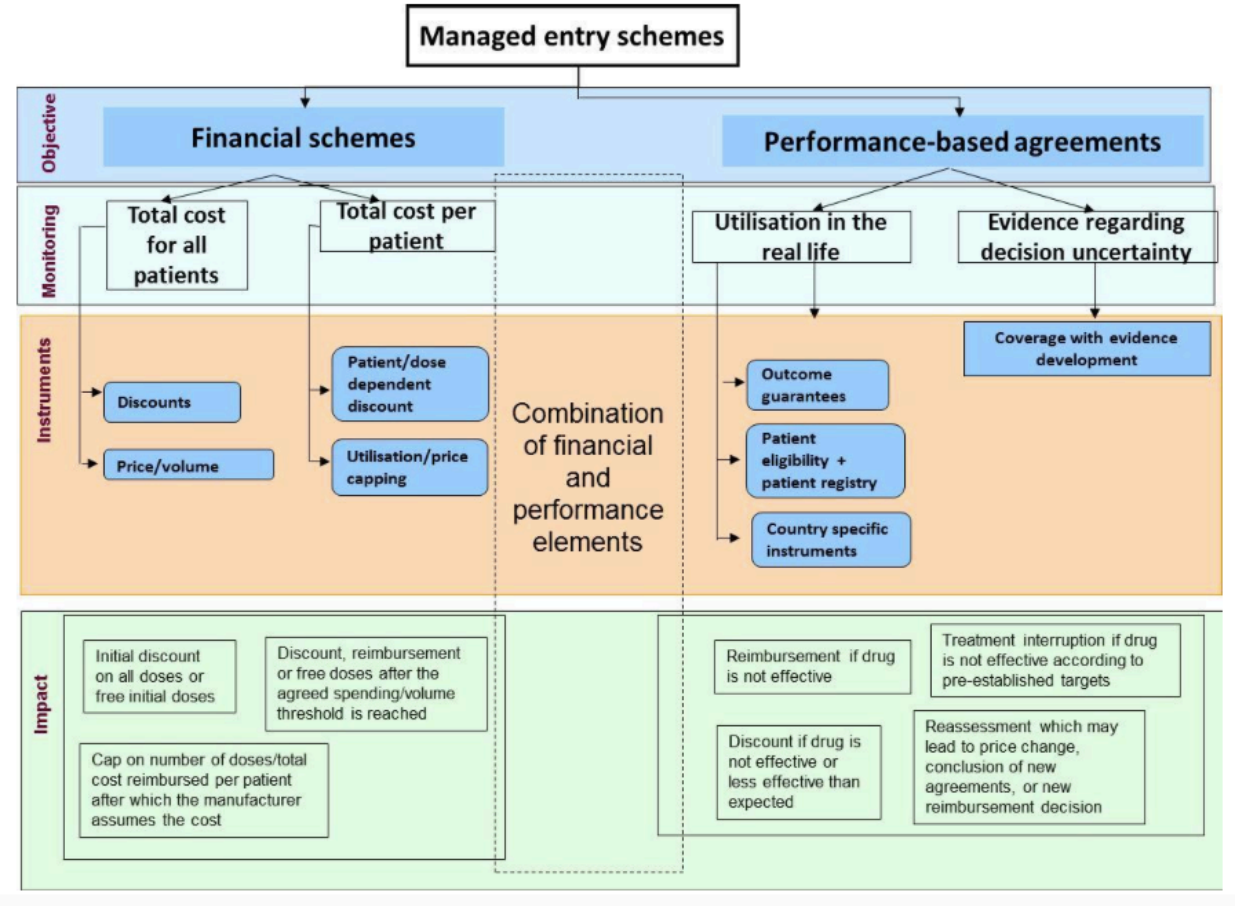
10. Appendix

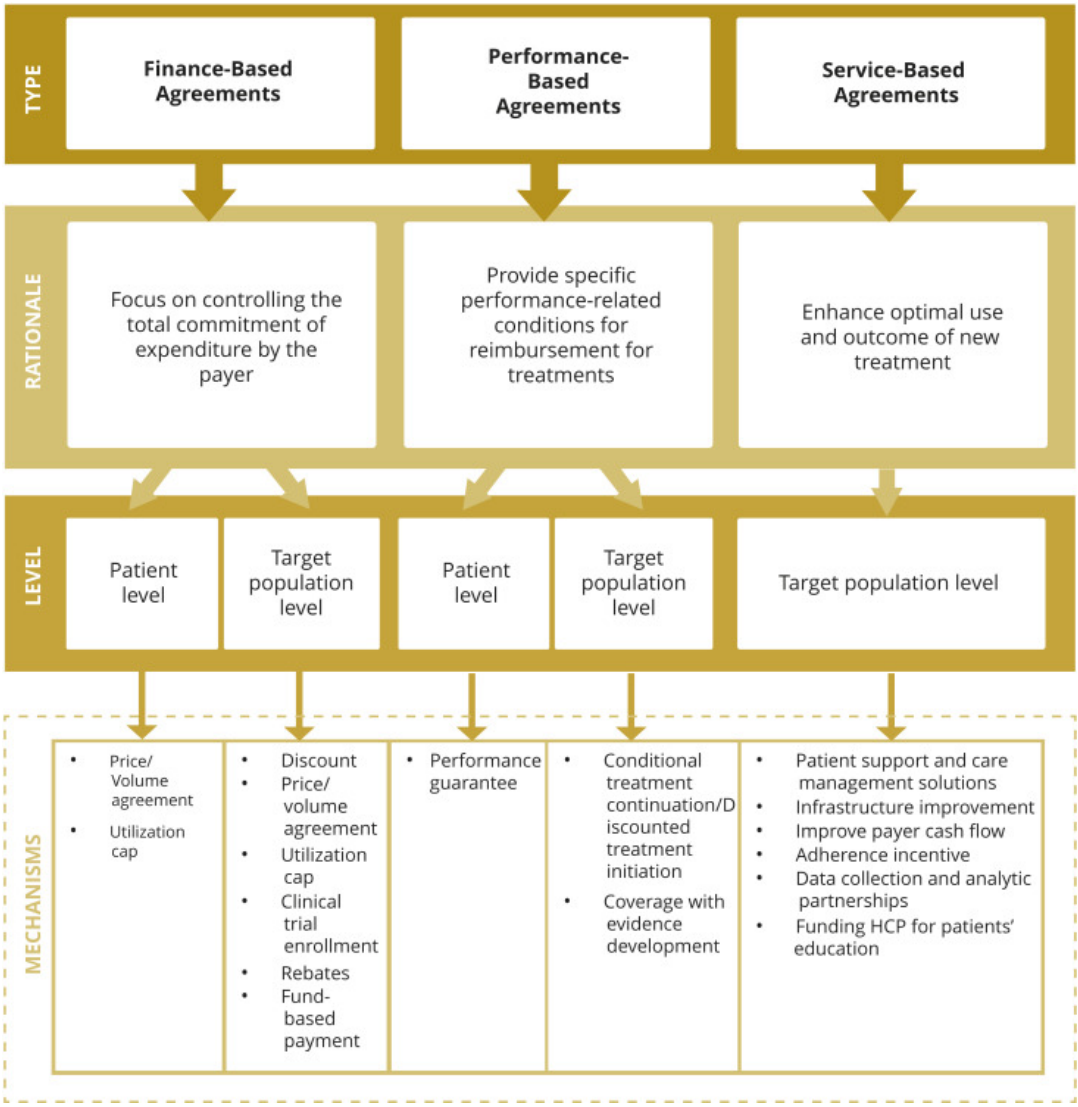
10.1 Appendix 1: MEA taxonomies

Appendix Figure 1. MEA taxonomy focusing on the impact/objectives targeted by the different MEA types.



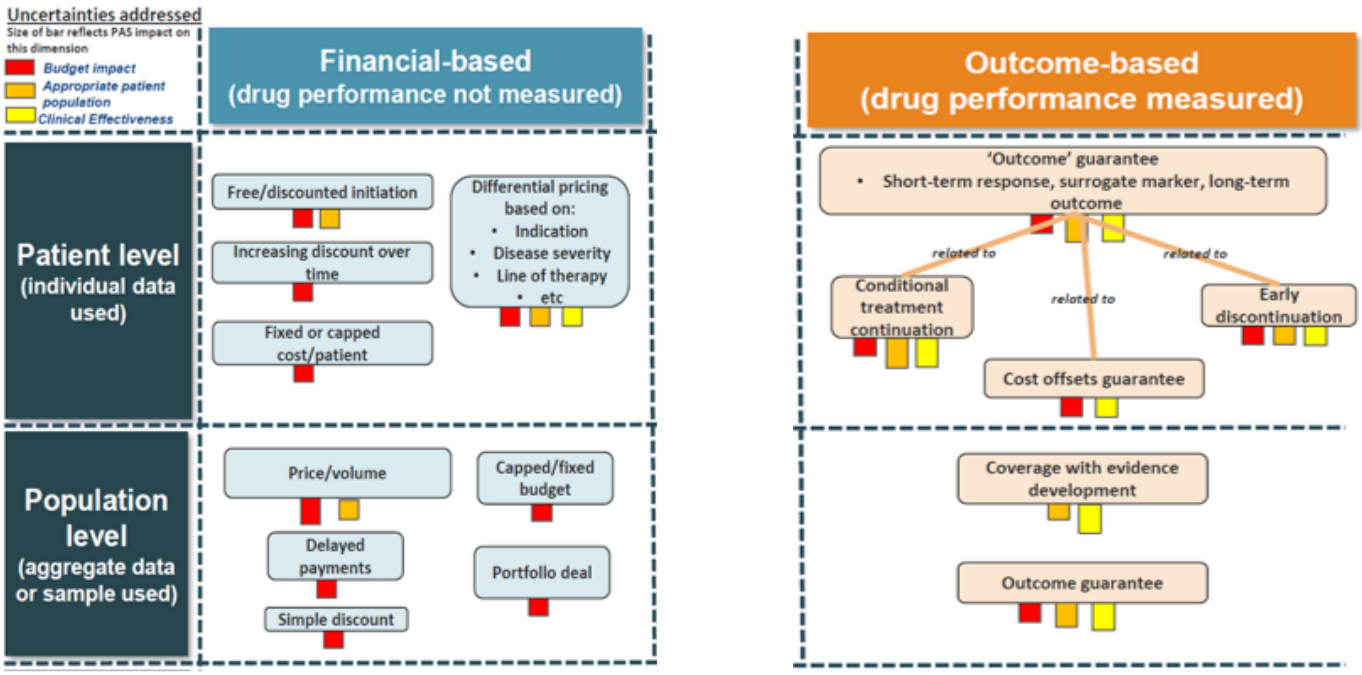
Source: Ferrario & Kanavos, 2013.

Appendix Figure 2. MEA taxonomy focusing on the level at which MEA is targeted (i.e., patient or population level) and the respective tools used to implement the different types of MEAs.



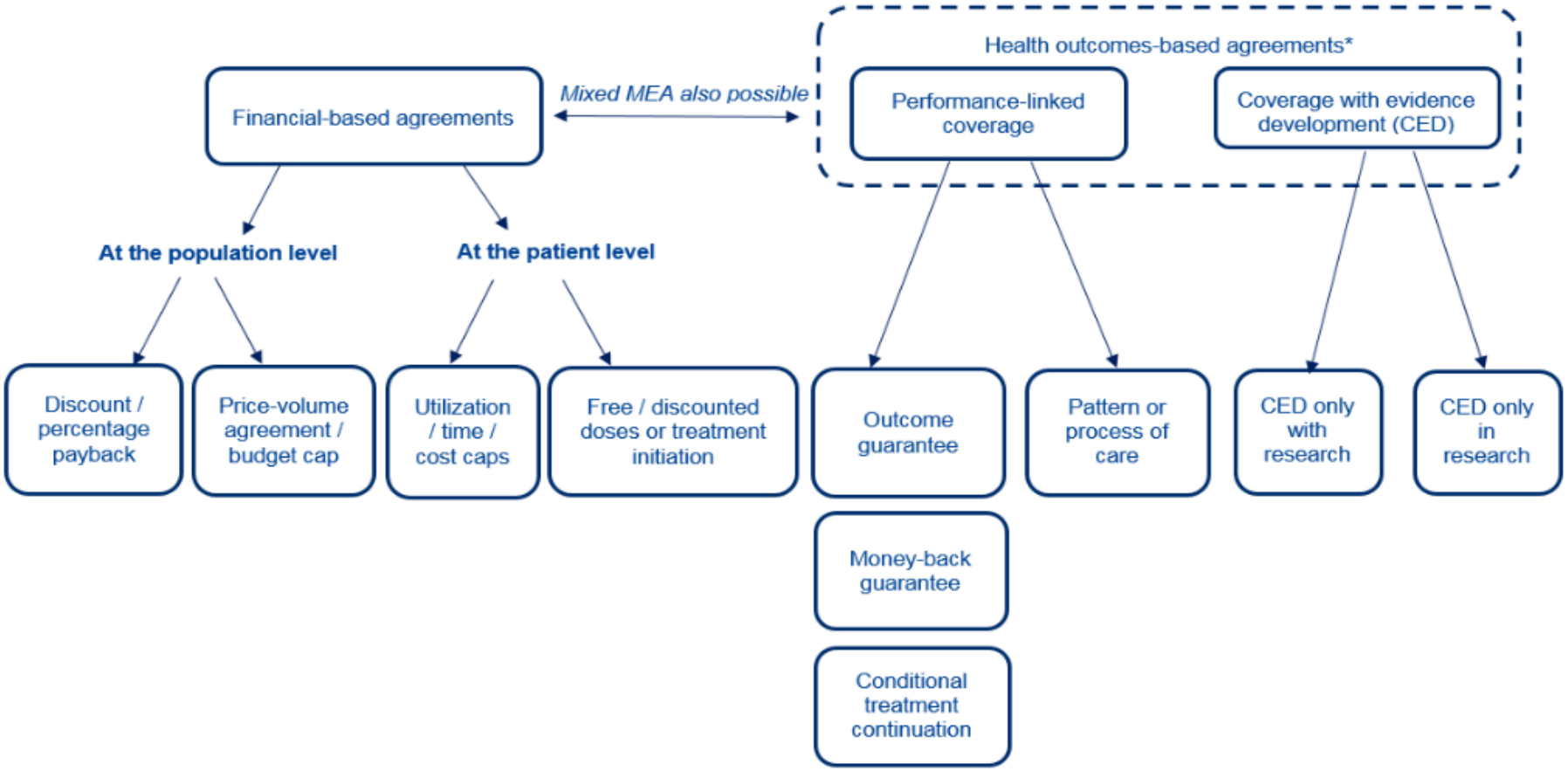
Source: Dabbous et al., 2020

Appendix Figure 3. MEA taxonomy focusing on the level at which each type of MEA targets different uncertainties.



Source: Lucas (2017)

Appendix Figure 4. MEA taxonomy focusing on the respective tools used to implement the different types of MEAs.



Source: KCE, 2017

10.2 Appendix 2: Study molecules

Molecule	Brand name	Manufacturer	ATC code	Indication (as per EMA)
Pixantrone	Pixuvri®	CTI Life Sciences Ltd	L01DB11	Monotherapy with Pixuvri is indicated in adult patients with multiple relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL). The use of pixantrone treatment has not been shown to be effective in 5-fold and multiple-line therapy in patients who were refractory to prior therapy.
Ipilimumab-2	Yervoy®	Bristol-Myers Squibb	L01XC11	previously untreated advanced (unresectable or metastatic) melanoma
Osimertinib	Tagrisso®	AstraZeneca	L01XE35	used in patients with non-small cell lung cancer whose cancer is advanced or has spread and has a particular mutation called T790M. The mutation is a change in the gene of the protein epidermal growth factor receptor, EGFR
Afatinib-1	Giotrif®	Boehringer Ingelheim	L01XE13	for treatment of locally advanced or metastatic non-small cell lung cancer with mutations of epidermal growth factor receptor (EGFR) previously untreated with other EGFR tyrosine kinase inhibitors
Cabozantinib-2	Cometriq®	Swedish Orphan	L01XE26	COMETRIQ® is indicated for the treatment of medullary thyroid carcinoma in adult patients with progressive, non-resectable, locally advanced or metastatic disease.
Olaratumab	Lartruvo®	Eli Lilly	L01XC27	Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin
Bevacizumab-1	Avastin®	Hoffmann-La Roche	L01XC07	in combination with carboplatin and paclitaxel for 'the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer
Bevacizumab-2	Avastin®	Hoffmann-La Roche	L01XC07	in combination with carboplatin and gemcitabine for 'treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents

Pembrolizumab-2	Keytruda®	Merck Sharp & Dohme	L01XC18	KEYTRUDA is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with PD-L1 expressing tumors after prior chemotherapy in adults. Patients with EGFR- or ALK-positive tumor mutations should already have received a therapy approved for these mutations prior to therapy with KEYTRUDA.
Daratumumab	Darzalex®	Janssen-Cilag	L01XC24	DARZALEX is indicated as a monotherapy for the treatment of adult patients with recurrent and refractory multiple myeloma who have already been treated with a proteasome inhibitor and an immune modulator and have shown a disease progression during the last therapy.
Alectinib	Alecensaro®	Hoffmann-La Roche	L01XE36	As monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK) positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
Bortezomib-1	Velcade®	Janssen-Cilag	L01XX32	In combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation
Idelalisib-1	Zydelig®	Gilead	L01XX47	In combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy
Olaparib	Lynparza®	AstraZeneca	L01XX46	monotherapy (alone) for maintenance therapy for ovarian cancer recurrence in patients with a specific mutation, BRCA
Eribulin-1	Halaven®	Eisai	L01XX41	Halaven® with the active substance eribulin is approved as a monotherapy for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapies for the treatment of advanced breast cancer. The pre-treatment regimens should contain an anthracycline and a taxane, unless these treatments were not suitable for the patient.

Palbociclib	Ibrance®	Pfizer	L01XE33	in patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer
Nintedanib-2	Vargatef®	Boehringer Ingelheim	L01XE31	Nintedanib (Vargatef®) is used in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small-cell lung carcinoma (NSCLC) with adenocarcinoma histology after first-line chemotherapy.
Lenvatinib	Lenvima®	Eisai	L01XE29	Lenvima is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).
Ceritinib	Zykadia®	Novartis	L01XE28	for treating adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib
Trametinib	Mekinist®	Novartis	L01XE25	for treatment in combination with dabrafenib (Tafinlar) in malignant melanoma.
Ponatinib	Iclusig®	ARIAD pharmaceuticals	L01XE24	used for the treatment of two types of blood cancer, chronic myeloid leukemia (KML) and Philadelphia chromosomal acute lymphocytic leukemia (Ph + ALL)
Dabrafenib-1	Tafinlar®	GlaxoSmithKline	L01XE23	As monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Regorafenib-2	Stivarga®	Bayer	L01XE21	for use in the treatment of adult patients with advanced colorectal cancer
Axitinib	Inlyta®	Pfizer	L01XE17	Treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine
Crizotinib-1	Xalkori®	Pfizer	L01XE16	Treatment of advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kynase (ALK+) for adult patients previously treated with at least one other lung cancer treatment
Crizotinib-2	Xalkori®	Pfizer	L01XE16	for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults
Blinatumomab	Blincyto®	Amgen	L01XC19	previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia
Pembrolizumab-3	Keytruda®	Merck Sharp & Dohme	L01XC18	First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) without

				activating EGFR or ALK mutations in adults
Pembrolizumab-1	Keytruda®	Merck Sharp & Dohme	L01XC18	KEYTRUDA® is indicated as a monotherapy for the treatment of advanced (non-resectable or metastasizing) melanoma in adults.
Nivolumab-3	Opdivo®	Bristol-Myers Squibb	L01XC17	Kidney Cell Carcinoma (RCC) OPDIVO is indicated as monotherapy in adults for the treatment of advanced renal cell carcinoma after pretreatment.
Nivolumab-1	Opdivo®	Bristol-Myers Squibb	L01XC17	OPDIVO® is indicated as a monotherapy in adults for the treatment of advanced (non-resectable or metastatic) melanoma.
Nivolumab-6	Opdivo®	Bristol-Myers Squibb	L01XC17	OPDIVO® is indicated in adults for the treatment of advanced (non-resectable or metastatic) melanoma in combination with ipilimumab
Obinutuzumab-1	Gazyvaro®	Hoffmann-La Roche	L01XC15	In combination with chlorambucil for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them
Trastuzumab emtansine-1	Kadcyla®	Hoffmann-La Roche	L01XC14	Trastuzumab Emtansin (Kadcyla®) is indicated as a single agent for the treatment of adult patients with HER2-positive, inoperable locally advanced or metastatic breast cancer who previously received, individually or in combination, trastuzumab and a taxane. Patients should either have received prior treatment for locally advanced or metastatic disease, or have developed a recurrence during or within six months after adjuvant treatment.
Brentuximab Vedotin-2	Adcetris®	Takeda	L01XC12	for the treatment of adult patients with relapse or refractory systemic large cell anaplastic lymphoma (sALCL).
Brentuximab Vedotin-3	Adcetris®	Takeda	L01XC12	ADCETRIS® is used for the treatment of adult patients with CD30 + HL with increased recurrence or progressive risk after an ASCT
Ofatumumab	Arzerra®	GlaxoSmithKline	L01XC10	To treat, in combination with chlorambucil or bendamustine, patients with CLS who have not received prior treatment and who are not suitable for fludarabine-based treatment (a type of cellular toxicity) To treat patients with CLL that are no longer suitable by the drugs fludarabine and alemtuzumab.
Carfilzomib	Kyprolis®	Amgen	L01XX45	in combination with either lenalidomide and dexamethasone or dexamethasone alone in comparison

				with the appropriate comparator therapy (ACT) for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.
Pazopanib-1	Votrient®	GlaxoSmithKline	L01XE11	Votrient is indicated in adults for the first-line treatment of advanced renal-cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.
Trifluridine–tipiracil	Lonsurf®	Servier Laboratories	L01BC59	Lonsurf is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents.
Vismodegib	Erivedge®	Hoffmann-La Roche	L01XX43	Erivedge is indicated for the treatment of adult patients with: - symptomatic metastatic basal cell carcinoma - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy
Paclitaxel	Abraxane ®	Celgene	L01CD01	Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.
Cabazitaxel	Jevtana®	Sanofi-Aventis	L01CD04	Jevtana in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
Rituximab-1	MabtheraSC ®	Hoffmann-La Roche	L01XC02	CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin’s lymphoma; · CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma; · CD20 positive, diffuse large B-cell non-Hodgkin’s lymphoma, in combination with chemotherapy.
Ipilimumab-1	Yervoy®	Bristol-Myers Squibb	L01XC11	the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy
Brentuximab Vedotin-1	Adcetris ®	Takeda	L01XC12	Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell

				transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
Pertuzumab-2	Perjeta®	Hoffmann-La Roche	L01XC13	Perjeta®, in combination with trastuzumab and chemotherapy in adult patients, is indicated for the neoadjuvant treatment of HER2-positive locally advanced, inflammatory or early breast cancer with high recurrence risk
Cobimetinib	Cotellic ®	Hoffmann-La Roche	L01XE38	In combination vermurafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation
Ribociclib	Kisqali ®	Novartis	L01XE42	Treating hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults
Obinutuzumab-2	Gazyvaro®	Hoffmann-La Roche	L01XC15	for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen
Nivolumab-2	Opdivo ®	Bristol-Myers Squibb	L01XC17	in adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy.
Nivolumab-4	Opdivo®	Bristol-Myers Squibb	L01XC17	Treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy
Ramucirumab-1	Cyramza®	Eli Lilly	L01XC21	alone or with paclitaxel for advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy
Ramucirumab-2	Cyramza®	Eli Lilly	L01XC21	in combination with docetaxel for treating locally advanced or metastatic non-small-cell lung cancer in adults with disease progression after platinum-based chemotherapy
Everolimus-3	Afinitor®	Novartis	L01XE10	For treatment of post menopausal women with hormone receptor-positive advanced breast cancer in combination with exemestane, after progression or recurrence (failure) on NSAI therapy.
Everolimus-4	Votubia®	Novartis	L01XE10	for patients with growing symptomatic SEGA where it is considered necessary for a treatment, but for which surgery is not appropriate
Vandetanib	Caprelsa®	AstraZeneca	L01XE12	used for the treatment of aggressive and symptomatic thyroid cancer

				(MTC) that can not be operated or spread.
Bosutinib	Bosulif ®	Pfizer	L01XE14	the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options
Vemurafenib	Zelboraf®	Hoffmann-La Roche	L01XE15	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma
Ruxolitinib-1	Jakavi®	Novartis	L01XE18	used for the treatment of myelofibrosis in adults who have enlarged spleen or symptoms related to the disease, such as fever, night sweats, skeletal pain and weight loss. The drug is also used in secondary myelofibrosis
Regorafenib-1	Stivarga®	Bayer	L01XE21	a medicine for the treatment of a type of gastrointestinal cancer called gastrointestinal stromal cell tumors (GIST)
Cabozantinib-1	Cabometyx®	Ipsen ltd.	L01XE26	Treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy
Ibrutinib-1	Imbruvica®	Janssen-Cilag	L01XE27	previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation
Ibrutinib-2	Imbruvica®	Janssen-Cilag	L01XE27	For the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL)
Ibrutinib-3	Imbruvica®	Janssen-Cilag	L01XE27	for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 prior therapy
Aflibercept-5	Zaltrap®	Sanofi-Aventis	L01XX44	Zaltrap® in combination with chemotherapy consisting of irinotecan / 5-fluorouracil / folinic acid (FOLFIRI) is used in adults with metastatic colorectal carcinoma (MCRC) who have undergone under or after an oxaliplatin-containing regimen.
Idelalisib-2	Zydelig®	Gilead	L01XX47	for the treatment of relapsed/refractory follicular lymphoma (FL) that has progressed despite prior treatment with rituximab and an alkylating agent.
Talimogene laherparepvec	Imlygic®	Amgen	L01XX51	IMLYGIC® is indicated for the treatment of adults with non-

				resectable, locally or remotely metastatic melanoma (stage IIIB, IIIC and IVM1a) without bone, brain, pulmonary or other visceral involvement.
Venetoclax	Venclexta®	AbbVie	L01XX52	treating chronic lymphocytic leukaemia
Enzalutamide-1	Xtandi®	Astellas Pharma	L02BB04	Enzalutamide (Xtandi®) is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease progresses during or after chemotherapy with docetaxel.
Enzalutamide-2	Xtandi®	Astellas Pharma	L02BB04	Enzalutamide (Xtandi®) is indicated for the treatment of adult men with metastatic castration-resistant prostate carcinoma with asymptomatic or mild symptomatic course after failure of androgen withdrawal therapy, in which chemotherapy has not yet been clinically indicated.
Abiraterone Acetate-2	Zytiga®	Janssen-Cilag	L02BX03	Treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated
Abiraterone Acetate-1	Zytiga®	Janssen-Cilag	L02BX03	In combination with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate carcinoma in adult men whose disease is progressive during or after docetaxel-containing chemotherapy.
Pomalidomide	Imnovid®	Celgene	L04AX06	In combination with dexamethasone, phlalidomide (IMNOVID®) is indicated for the treatment of recurrent and refractory multiple myeloma in adult patients who have received at least two previous therapies, including lenalidomide and bortezomib, and have shown a progression under the last therapy.

10.3 Appendix 3: Differences in the number (%) of uncertainties and SVJs raised/ considered between LWC and LWCMEA coverage decisions across countries and their respective statistical significance (Pearson's x^2, p-value).

HTA criteria	England (n=59)	Scotland (n=54)	Australia (n=50)	Sweden (n=23)
Clinical evidence	0% vs. 100% (.69, .40)	**0% vs. 100% (3.68, .04)** †	26% vs. 74% (1.18, .27)	33% vs. 67% (.059, .80)
Clinical benefit	**0% vs. 100% (4.98, .026)** †	3% vs. 97% (1.38, .240)	31% vs. 69% (.099, .75)	36% vs. 64% (.471, .493)
Clinical comparator	0% vs. 100% (.605, .437)	9% vs. 91% (.329, .566)	25% vs. 75% (.005, .94)	67% vs. 33% (2.139, .144)
Study design	0% vs. 100% (1.483, .223)	4% vs. 96% (.353, .552)	24% vs. 76% (.007, .93)	25% vs. 75% (.068, .795)
Population generalisability	0% vs. 100% (.983, .321)	6% vs. 94% (.021, .885)	14% vs. 86% (.460, .49)	100% vs. 0% (2.39, .122)
Clinical practice	0% vs. 100% (1.126, .289)	5% vs. 95% (.019, .891)	25% vs.75% (.002, .96)	33% vs. 67% (.014, .907)
Modelling	**0% vs. 100% (5.65, .017)** †	3% vs. 97% (2.09, .148)	24% vs. 76% (.003, .95)	44% vs. 56% (1.371, .242)
Cost	0% vs. 100% (1.59, .207)	0% vs.100% (1.00, .316)	22% vs. 88% (.167, .68)	33% vs. 67% (.032, .858)
Utilities	0% vs. 100% (2.317, .128)	0% vs. 100% (1.58, .20)	**0% vs. 100% (3.10, .028)** †	50% vs. 50% (.396, .529)
Cost-effectiveness	**0% vs. 100% (8.98, .003)** †	**0% vs. 100% (3.97, .046)** †	**11% vs. 89% (5.02, .025)** †	37% vs. 63% (1.24, .26)
Economic comparator	0% vs. 100% (.233, .629)	0% vs. 100% (1.724, .189)	0% vs. 100% (.676, .411)	0% vs. 100% (1.509, .219)
Rarity	0% vs. 100% (.233, .629)	14% vs. 86% (1.168, .280)	37% vs. 63% (.875, .350)	50% vs. 50% (1.46, .226)
Severity	0% vs. 100% (.650, .420)	4% vs. 96% (.217, .543)	25% vs. 75% (.001, .980)	25% vs. 75% (2.139, .144)
Unmet need	0% vs. 100% (2.734, .098)	7% vs, 93% (.813, .367)	25% vs. 75% (.007, .935)	36% vs. 64% (.350, .554)
Innovation	0% vs. 100% (2.513, .113)	5% vs. 95% (.021, .885)	**0% vs. 100% (3.10, .028)** †	*
Administration advantage	0% vs. 100% (.233, .629)	5% vs. 95% (.021, .885)	0% vs. 100% (2.21, .136)	*
Impact on society	0% vs. 100% (.115, .734)	6% vs. 94% (2.09, .688)	20% vs. 80% (.061, .805)	*
Impact on QoL	0% vs. 100% (.983, .321)	6% vs. 94% (.019, .891)	27% vs. 73% (.059, .807)	*
Special considerations	0% vs. 100% (2.734, .098)	5% vs. 95% (.227, .634)	100% vs. 0% (3.15, .076)	31% vs. 69% (.002, .968)

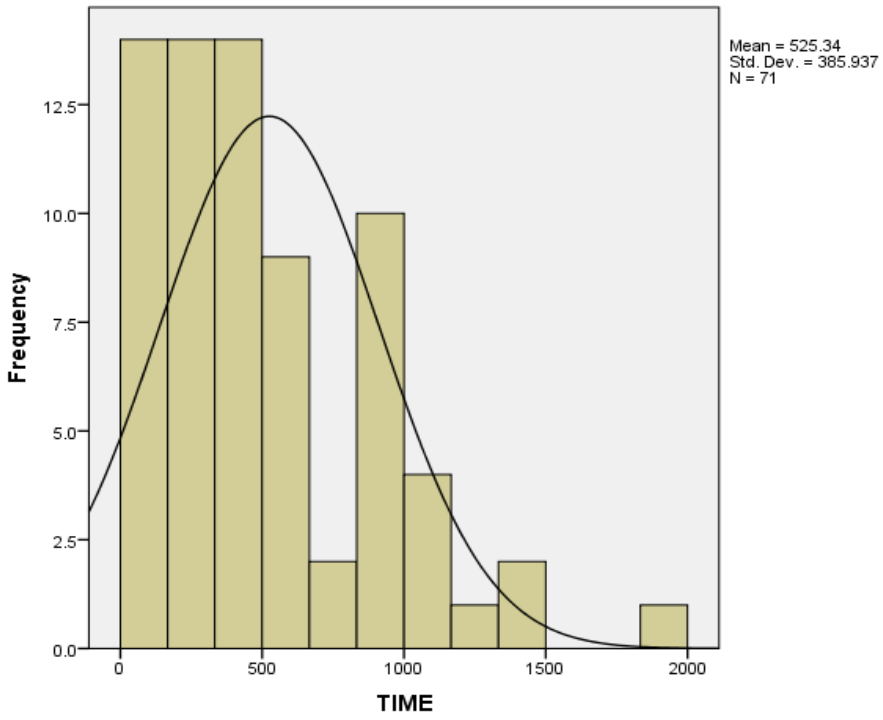
Key: *No statistics are computed because variable is a constant.

† Bold highlighted results denote statistical significance for the respective country in question

Note: LWC: List With Conditions, LWCMEA: List With Conditions, including a Managed Entry Agreement. SVJs: Social Value Judgements, QoL: Quality of Life.

10.4 Appendix 4: Probability distribution for the dependent variable "time to final funding decision"

Appendix Figure 5. Probability distribution for the dependent variable of "time to final funding decision".



Key: The variable "TIME" represents average days elapsed from first submission to final funding decision.

Note: Mean: average time to final funding decision across all sample, N: sample size, Std. Dev: Standard deviation.

10.5 Appendix 5: Study molecules for Research Article III

National Competent Authority	Molecule name	Brand name	Manufacturer	ATC classification	Indication under review (as per EMA)
NICE	Ipilimumab-1	Yervoy®	Bristol-Myers Squibb	L01XC11	Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy
NICE	Bevacizumab-1	Avastin®	Hoffmann-La Roche	L01XC07	In combination with carboplatin and paclitaxel for 'the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer
NICE	Eribulin-1	Halaven®	Eisai	L01XX41	Halaven® with the active substance eribulin is approved as a monotherapy for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapies for the treatment of advanced breast cancer. The pre-treatment regimens should contain an anthracycline and a taxane, unless these treatments were not suitable for the patient.
NICE	Paclitaxel	Abraxane®	Celgene	L01CD01	Abraxane® in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.
NICE	Pomalidomide	Imnovid®	Celgene	L04AX06	In combination with dexamethasone, phlalidomide (Imnovid®) is indicated for the treatment of recurrent and refractory multiple myeloma in adult patients who have received at least two previous therapies, including lenalidomide and bortezomib, and have shown a progression under the last therapy.
NICE	Cabazitaxel	Jevtana®	Sanofi-Aventis	L01CD04	Jevtana® in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
PBAC	Osimertinib	Tagrisso®	AstraZeneca	L01XE35	In patients with non-small cell lung cancer whose cancer is advanced or has spread and has a particular mutation called T790M. The mutation is a change in the gene of the protein epidermal growth factor receptor, EGFR
PBAC	Idelalisib-1	Zydelig®	Gilead	L01XX47	In combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy
PBAC	Olaparib	Lynparza®	AstraZeneca	L01XX46	Monotherapy (alone) for maintenance therapy for ovarian cancer recurrence in patients with a specific mutation, BRCA
PBAC	Eribulin-1	Halaven®	Eisai	L01XX41	Halaven® with the active substance eribulin is approved as a monotherapy for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapies for the treatment of advanced breast cancer. The pre-treatment regimens should contain an anthracycline and a taxane, unless these treatments were not suitable for the patient.
PBAC	Palbociclib	Ibrance®	Pfizer	L01XE33	In patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer

PBAC	Nintedanib-2	Vargatef®	Boehringer Ingelheim	L01XE31	Nintedanib (Vargatef®) is used in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small-cell lung carcinoma (NSCLC) with adenocarcinoma histology after first-line chemotherapy.
PBAC	Lenvatinib	Lenvima®	Eisai	L01XE29	Lenvima® is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).
PBAC	Axitinib	Inlyta®	Pfizer	L01XE17	Treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine
PBAC	Blinatumomab	Blincyto®	Amgen	L01XC19	Previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia
PBAC	Pembrolizumab -3	Keytruda®	Merck Sharp & Dohme	L01XC18	First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) without activating EGFR or ALK mutations in adults
PBAC	Nivolumab-3	Opdivo®	Bristol-Myers Squibb	L01XC17	Renal Cell Carcinoma (RCC); Opdivo(r) is indicated as monotherapy in adults for the treatment of advanced renal cell carcinoma after pretreatment.
PBAC	Nivolumab-1	Opdivo®	Bristol-Myers Squibb	L01XC17	Opdivo® is indicated as a monotherapy in adults for the treatment of advanced (non-resectable or metastatic) melanoma.
PBAC	Nivolumab-6	Opdivo®	Bristol-Myers Squibb	L01XC17	Opdivo® is indicated in adults for the treatment of advanced (non-resectable or metastatic) melanoma in combination with ipilimumab
PBAC	Obinutuzumab-1	Gazyvaro®	Hoffmann-La Roche	L01XC15	In combination with chlorambucil for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them
PBAC	Trastuzumab emtansine-1	Kadcyla®	Hoffmann-La Roche	L01XC14	Trastuzumab Emtansin (Kadcyla®) is indicated as a single agent for the treatment of adult patients with HER2-positive, inoperable locally advanced or metastatic breast cancer who previously received, individually or in combination, trastuzumab and a taxane. Patients should either have received prior treatment for locally advanced or metastatic disease, or have developed a recurrence during or within six months after adjuvant treatment.
PBAC	Brentuximab Vedotin-2	Adcetris®	Takeda	L01XC12	For the treatment of adult patients with relapse or refractory systemic large cell anaplastic lymphoma (sALCL).
PBAC	Brentuximab Vedotin-3	Adcetris®	Takeda	L01XC12	Adcetris® is used for the treatment of adult patients with CD30 + HL with increased recurrence or progressive risk after an ASCT
PBAC	Pazopanib-1	Votrient®	GlaxoSmithKline	L01XE11	Votrient® T is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC).
PBAC	Cabazitaxel	Jevtana®	Sanofi-Aventis	L01CD04	Jevtana® in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
PBAC	Ribociclib	Kisqali ®	Novartis	L01XE42	Treating hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults
PBAC	Nivolumab-2	Opdivo®	Bristol-Myers Squibb	L01XC17	In adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy.
PBAC	Nivolumab-4	Opdivo®	Bristol-Myers Squibb	L01XC17	Treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy
PBAC	Everolimus-3	Afinitor®	Novartis	L01XE10	For treatment of post menopausal women with hormone receptor-positive advanced breast cancer in combination with exemestane, after progression or recurrence (failure) on NSAI therapy.

PBAC	Ruxolitinib-1	Jakavi®	Novartis	L01XE18	For the treatment of myelofibrosis in adults who have enlarged spleen or symptoms related to the disease, such as fever, night sweats, skeletal pain and weight loss. The drug is also used in secondary myelofibrosis
PBAC	Enzalutamide-2	Xtandi®	Astellas Pharma	L02BB04	Enzalutamide (Xtandi®) is indicated for the treatment of adult men with metastatic castration-resistant prostate carcinoma with asymptomatic or mild symptomatic course after failure of androgen withdrawal therapy, in which chemotherapy has not yet been clinically indicated.
PBAC	Pomalidomide	Imnovid®	Celgene	L04AX06	In combination with dexamethasone, phlalidomide (Imnovid®) is indicated for the treatment of recurrent and refractory multiple myeloma in adult patients who have received at least two previous therapies, including lenalidomide and bortezomib, and have shown a progression under the last therapy.
PBAC	Ponatinib	Iclusig®	ARIAD pharmaceuticals	L01XE24	For the treatment of two types of blood cancer, chronic myeloid leukemia (KML) and Philadelphia chromosomal acute lymphocytic leukemia (Ph + ALL)
PBAC	Dabrafenib-1	Tafinlar®	GlaxoSmithKline	L01XE23	As monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
PBAC	Crizotinib-1	Xalkori®	Pfizer	L01XE16	Treatment of advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kynase (ALK+) for adult patients previously treated with at least one other lung cancer treatment
PBAC	Ipilimumab-1	Yervoy®	Bristol-Myers Squibb	L01XC11	Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy
PBAC	Brentuximab Vedotin-1	Adcetris®	Takeda	L01XC12	Adcetris ® is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
PBAC	Ibrutinib-1	Imbruvica®	Janssen-Cilag	L01XE27	Previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation
PBAC	Idelalisib-2	Zydelig®	Gilead	L01XX47	Treatment of relapsed/refractory follicular lymphoma (FL) that has progressed despite prior treatment with rituximab and an alkylating agent.
SMC	Daratumumab	Darzalex®	Janssen-Cilag	L01XC24	Darzalex® is indicated as a monotherapy for the treatment of adult patients with recurrent and refractory multiple myeloma who have already been treated with a proteasome inhibitor and an immune modulator and have shown a disease progression during the last therapy.
SMC	Olaparib	Lynparza®	AstraZeneca	L01XX46	Monotherapy (alone) for maintenance therapy for ovarian cancer recurrence in patients with a specific mutation, BRCA
SMC	Crizotinib-1	Xalkori®	Pfizer	L01XE16	Treatment of advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kynase (ALK+) for adult patients previously treated with at least one other lung cancer treatment
SMC	Nivolumab-3	Opdivo®	Bristol-Myers Squibb	L01XC17	Renal Cell Carcinoma (RCC): Opdivo® is indicated as monotherapy in adults for the treatment of advanced renal cell carcinoma after pretreatment.
SMC	Nivolumab-1	Opdivo®	Bristol-Myers Squibb	L01XC17	Opdivo® is indicated as a monotherapy in adults for the treatment of advanced (non-resectable or metastatic) melanoma.
SMC	Paclitaxel	Abraxane®	Celgene	L01CD01	Abraxane® in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

SMC	Cabazitaxel	Jevtana®	Sanofi-Aventis	L01CD04	Jevtana® in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.
SMC	Ipilimumab-1	Yervoy®	Bristol-Myers Squibb	L01XC11	Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy
SMC	Pertuzumab-2	Perjeta®	Hoffmann-La Roche	L01XC13	Perjeta®, in combination with trastuzumab and chemotherapy in adult patients, is indicated for the neoadjuvant treatment of HER2-positive locally advanced, inflammatory or early breast cancer with high recurrence risk
SMC	Everolimus-3	Afinitor®	Novartis	L01XE10	For treatment of post menopausal women with hormone receptor-positive advanced breast cancer in combination with exemestane, after progression or recurrence (failure) on NSAI therapy.
SMC	Bosutinib	Bosulif®	Pfizer	L01XE14	Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options
SMC	Vemurafenib	Zelboraf®	Hoffmann-La Roche	L01XE15	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma
SMC	Aflibercept-5	Zaltrap®	Sanofi-Aventis	L01XX44	Zaltrap® in combination with chemotherapy consisting of irinotecan / 5-fluorouracil / folinic acid (FOLFIRI) is used in adults with metastatic colorectal carcinoma (MCRC) who have undergone under or after an oxaliplatin-containing regimen.
SMC	Abiraterone Acetate-1	Zytiga®	Janssen-Cilag	L02BX03	In combination with prednisone or prednisolone for the treatment of metastatic castration-resistant prostate carcinoma in adult men whose disease is progressive during or after docetaxel-containing chemotherapy.
SMC	Pomalidomide	Imnovid®	Celgene	L04AX06	In combination with dexamethasone, phlalidomide (Imnovid®) is indicated for the treatment of recurrent and refractory multiple myeloma in adult patients who have received at least two previous therapies, including lenalidomide and bortezomib, and have shown a progression under the last therapy.
TLV	Vismodegib	Erivedge®	Hoffmann-La Roche	L01XX43	Erivedge® is indicated for the treatment of adult patients with: - symptomatic metastatic basal cell carcinoma - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy
TLV	Vemurafenib	Zelboraf®	Hoffmann-La Roche	L01XE15	Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma
TLV	Cabozantinib-1	Cabometyx ®	Ipsen ltd.	L01XE26	Treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy
TLV	Enzalutamide-1	Xtandi®	Astellas Pharma	L02BB04	Enzalutamide (Xtandi®) is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease progresses during or after chemotherapy with docetaxel.
TLV	Enzalutamide-2	Xtandi®	Astellas Pharma	L02BB04	Enzalutamide (Xtandi®) is indicated for the treatment of adult men with metastatic castration-resistant prostate carcinoma with asymptomatic or mild symptomatic course after failure of androgen withdrawal therapy, in which chemotherapy has not yet been clinically indicated.

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Determinants of Managed Entry Agreements in the context of Health Technology Assessment: a comparative analysis of oncology therapies in four countries

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Abstract

Background. Managed Entry Agreements (MEAs) are increasingly used to address uncertainties arising in the Health Technology Assessment (HTA) process due to immature evidence of new, high-cost medicines on their real-world performance and cost-effectiveness. The literature remains inconclusive on the HTA decision-making factors that influence the utilization of MEAs. We aimed to assess if the uptake of MEAs differs between countries and if so, to understand which HTA decision-making criteria play a role in determining such differences.
Methods. All oncology medicines approved since 2009 in Australia, England, Scotland, and Sweden were studied. Four categories of variables were collected from publicly available HTA reports of the above drugs: (i) Social Value Judgments (SVJs), (ii) Clinical/Economic evidence submitted, (iii) Interpretation of this evidence, and (iv) Funding decision. Conditional/restricted decisions were coded as Listed With Conditions (LWC) other than an MEA or LWC including an MEA (LWCMEA). Cohen's κ-scores measured the inter-rater agreement of countries on their LWCMEA outcomes and Pearson's chi-squared tests explored the association between HTA variables and LWCMEA outcomes.
Results. A total of 74 drug-indication pairs were found resulting in $n = 296$ observations; 8 percent ($n = 23$) were LWC and 55 percent ($n = 163$) were LWCMEA. A poor-to-moderate agreement existed between countries ($-.29 < \kappa < .33$) on LWCMEA decisions. Cross-country differences within the LWCMEA sample were partly driven by economic uncertainties and largely driven by SVJs considered across agencies.
Conclusions. A set of HTA-related variables driving the uptake of MEAs across countries was identified. These findings can be useful in future research aimed at informing country-specific, "best-practice" guidelines for successful MEA implementation.

Background and Objectives

Over the past decade, the continuous market entry of new therapies, which are either high volume—for treating many patients (i.e., antidiabetic agents) or high cost—for a single treatment course (i.e., oncology therapies), has escalated pharmaceutical spending (1). It was recently reported that pharmaceutical spending accounts for almost 20 percent of the total health expenditure in OECD countries, and because funding from governments and social insurance schemes plays the largest role in pharmaceutical purchasing, this rise bears significant implications for the budget of health systems (2).

The growing healthcare expenditure poses pressures for pharmaceutical manufacturers to demonstrate real-world value for money beyond that of safety and efficacy and simultaneously for national healthcare payers to engage in strategic pricing and reimbursement policies that ensure patients' access to new therapies while optimizing budget impact (3;4). Although most new products are assessed as part of Health Technology Assessment (HTA) processes in many countries, the data available on the cost-effectiveness of high-cost therapies, particularly in oncology, are severely lacking at the time of product launch (5). Uncertainties arise due to the often immature evidence available from controlled trials on the real-world clinical outcomes of newly launched pharmaceuticals, meaning that the benefits of a new product cannot be fully estimated at drug launch; uncertainties may be present around treatment eligibility of patient subgroups, generalizability of trial results to clinical practice, the use of surrogate outcome measures instead of "hard" end points and subsequent transferability of surrogate outcomes used in trials to real-world studies (6). As these challenges can lead to delayed reimbursement decisions and patient access, manufacturers and payers are seeking ways to collaboratively manage the market entry of new pharmaceutical products and mitigate risks related to premature evidence (7;8); one way to achieve this has been through the introduction of contractual arrangements

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between the two parties, referred to as Managed Entry Agreements (MEAs) or Risk Sharing Agreements (RSAs).

MEAs are used in many countries worldwide and primarily in Europe, in accordance with country-specific governance and preferences around evidence requirements and evaluation for new medicines (9). Cross-country differences in HTA assessment requirements have led to a well-documented disparity in the respective risk-sharing practices followed by countries (6). A review of MEAs in the EU showcased that only for two drug-indication pairs in the whole sample, an MEA was applied to all six study countries, and even between these, there was variation in the type of MEAs applied (10).

Despite the growing interest of healthcare systems and manufacturers in the use of MEAs over the past decade, there is still a knowledge gap in the drivers of this variation, partially due to a lack of transparency in the negotiation from both parties (11).

Even though the literature has concluded that countries indeed differ in their MEA implementation practices, with MEAs being highly specific to the HTA decision-making context in which they operate, the current body of relevant literature arises mainly from secondary evidence and remains largely descriptive in nature (8;12–14). Therefore, we aimed to (i) make a methodological contribution to existing research on determining whether the uptake of MEAs differs between countries and (ii) if so, to understand whether specific HTA decision-making uncertainties and considerations play some role in determining such differences.

Methods

Sample Selection

A retrospective analysis of HTA appraisals on all oncology drugs (i.e., all L01 molecules, based on the Anatomical Therapeutic Chemical classification) which obtained regulatory approval by the European Medicines Agency (EMA) and by the Therapeutic Goods Administration (TGA) in Australia between 1 January 2009 and 15 June 2018 (at the drug-indication pair level) in Australia (AUS), England (ENG), Scotland (SCOT), and Sweden (SE). Oncology was selected as our study therapeutic class because it has been documented to be the therapeutic class with the largest proportion (38 percent) of implemented MEAs; it is also the therapeutic class where MEAs continue to be increasingly implemented (6). Study countries were selected because they all implement MEAs, they all have long-established HTA policies and processes to guide their coverage decisions, they have both a publicly available list of MEAs and publicly available HTA reports that provide a sufficient level of information for the purposes of this analysis, and they use similar criteria in their decision-making processes (i.e., clinical and/or cost-effectiveness), allowing for comparability across agencies (15).

The sample used for this analysis comprises a small part of a larger sample of drugs studied for a different, broader project on HTA. Nevertheless, the aim/scope of that project is not related to that of our study and neither is the methodology we used for data analysis and management. The only common aspects between the two studies relate to the overarching framework used for data collection, as well as the classification and validation of dimensions studied, as described below.

Methodological Framework for Data Collection

The methodology underpinning the data collection process was based on the literature (15;16) where it is suggested that the final outcome of an HTA appraisal is driven by (i) the clinical and cost-effectiveness evidence submitted (i.e., clinical trial design and end points, safety, economic models, and comparators) and (ii) the interpretation of this evidence, influenced by the perception of uncertainty around this evidence, by setting-specific preferences on risk and other social value considerations.

For the purposes of our analysis, a simplified methodological framework was adopted based on the assumption that the impact of the clinical and economic evidence submitted (Stage 1) on the final decision outcome (Stage 4) is captured through the respective uncertainties that this evidence has raised or not raised (Stage 2). Therefore, the final HTA outcome (Stage 4) is a function of the uncertainties raised (Stage 2) and other social value and system-specific considerations (Stage 3) (Figure 1).

The HTA process was divided in four different stages corresponding to: (1) *the evidence submitted and appraised* (e.g., trial type, clinically meaningful end points; response rate/disease progression/safety end points, comparators, Incremental Cost-Effectiveness Ratio (ICER) range and economic model used), (2) *the interpretation of this evidence/uncertainties raised* (i.e., clinical and economic evidence-related uncertainties around clinical benefit and study/research design and those around economic modeling and cost-effectiveness, respectively), (3) *Social Value Judgments (SVJs) and HTA system-specific considerations* (i.e., additional dimensions of societal value that a new technology adds, beyond its clinical evidence/benefit and cost-effectiveness such as the innovation and administration advantage it offers, value dimensions specific to the disease area the technology addresses, such as its severity, rarity, and unmet need, or whether it is a condition toward the end of life, where the benefit of a treatment is valued more highly, and/or system-specific considerations such as the use of a single or multiple technology appraisal (MTA) in England that shape decision-making processes for each study country), and (4) *the final decision outcome,* classified as (i) L = List (i.e., positive HTA recommendation), (ii) LWC = List with conditions, where the technology has been accepted with restrictions but which are not classified as MEAs (e.g., a product should be used in a subpopulation of its licensed indication, and/or it should be used in a second line or higher line of therapy, and/or it should be used in a specific dose only, and/or it requires monitoring, and/or it requires prescription by a specialist), (iii) LWCMEA = Listed with conditions/restrictions including, among others (if any), at least one classified as an MEA (e.g., simple discount, free stock, rebate, patient access scheme, commercial access agreement coverage with evidence development and/or additional data collection), and (iv) DNL = Do not list (i.e., negative HTA recommendation). We preferred a four-category outcome variable over the three-outcome variable traditionally used in the HTA literature (i.e., listed, listed with conditions, rejected) as it better reflects the multiple coverage options available when studying conditional/restricted HTA decisions. As L and DNL decisions would, by definition, not lead to some kind of a condition/restriction, for the purposes of this analysis, we studied only those drug-indication pairs with a conditional/restricted recommendation decision (i.e., LWC or LWCMEA).

Data Collection

SVJs and uncertainties were classified and defined based on the literature (Supplementary Appendix, Table 1) (12;15;17;18), and the classification was also discussed and validated between the authors and external referees. Data on the above stages per

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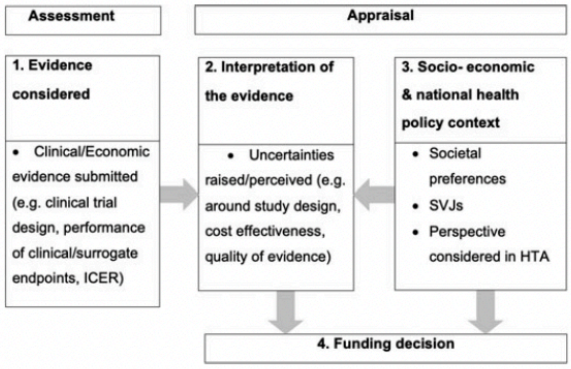

Figure 1. Methodological framework on the analysis of the HTA process and variables included therein. *Note*: ICER, Incremental Cost-Effectiveness Ratio; SVJs, Social Value Judgments. *Source*: The authors based on the literature (15;16).

drug-indication pair in all study countries were extracted only from the official, publicly available HTA appraisals, which were published in the Web sites of the respective HTA bodies (i.e., PBAC (AUS), NICE (ENG), SMC (SCOT)), TLV (SE)) (Supplementary Appendix, Table 2); other relevant sources of data, such as the county councils' group on new drug therapies (NLT) in Sweden were not searched. Where needed, searches were conducted in local languages (English and Swedish) to improve the accuracy and comprehensiveness of the extraction. The data extracted were fed into a database stratified by an HTA agency to describe and classify MEAs across the respective HTA bodies and ultimately facilitate data analyses. Data collection was undertaken between June and November 2018 and only the final HTA recommendation reports available for the drug-indication pairs studied were used for data collection (Supplementary Appendix, Table 3).

Data Analysis

For the first part of our hypothesis (i.e., determining whether the uptake of MEAs differs between countries), Pearson's chi-squared (χ^2) test of independence was used to test for differences in the restricted outcome (LWC or LWCMEA) between agencies. Cohen's kappa scores (κ) of cross-country agreement levels were also measured as an additional robustness check.

Agreement between agencies was measured based on whether conditional/restricted HTA outcomes across agencies included a form of MEA as a condition (or not); this allowed a comparison of the observed inter-rater agreement with the agreement expected by chance, ranging from poor ($\kappa = 0$) to perfect ($\kappa = 1$), with negative values of κ corresponding to cases where the inter-rater agreement was even less than that expected by chance (19).

Finally, for the second part of our research question (i.e., understand whether specific HTA decision-making uncertainties and considerations play some role in driving divergent LWCMEA decisions between countries), variables under the HTA appraisal (Figure 1) were initially analyzed by means of descriptive statistics, including percentages and crosstabulations (Excel® 2013). Assuming that all categories of uncertainties and SVJs were applicable to all drug-indication pairs studied, these were treated and coded as binary variables based on whether they have been raised and considered (or not), respectively, in the HTA report for each drug-indication pair. As such, bivariate analyses were also performed, using Pearson's chi-squared (χ^2) test of independence, to identify which of these variables drive differences between the LWC and LWCMEA sample overall, and across agencies. For the former comparison, where uncertainty and SVJ dimensions had small sample sizes (i.e., five or less observations), the Fisher's exact test was also performed as a robustness check. The SPSS® (v.24.0) was used to perform statistical tests and measure inter-rater agreement.

Results

Sample Characteristics

A total of 74 molecules were studied across the four countries, corresponding to a total sample of $n = 296$ drug-indication pairs. Of these, 7 percent ($n = 21$) were Listed (L), 9.5 percent ($n = 28$) were Not Listed (DNL), and 63 percent ($n = 186$) were Listed with at least one type of condition/restriction (LWC or LWCMEA). Other outcomes included drug-indication pairs that were "Not Assessed" (10 percent, $n = 29$), "Not submitted" (4 percent, $n = 12$), or formed only an "Advice or Health Economic Report" (6.5 percent, $n = 20$) (Table 1).

Of the conditional/restricted HTA outcomes ($n = 186$), 88 percent ($n = 163$) were LWCMEA overall, but only 17 percent ($n = 32$) were LWCMEA across all countries for the same molecules. This was further emphasized by the Cohen's kappa scores measuring the level of inter-rater agreement between agencies across their LWCMEA outcomes. The scores ranged from −.29 to .33 (Table 2), demonstrating a poor-to-moderate agreement. More precisely, it was shown that only SCOT and SE had a moderate agreement, whereas the rest of the countries had a poor or even negative agreement between them. Cross-country differences in MEA utilization were further strengthened by results of the χ^2 test, which showed statistically significant differences between the study countries in terms of their LWCMEA recommendation decisions ($P < .05$).

Clinical and Economic Uncertainties

Among all clinical uncertainties raised, those that seemed to differ distinctly in proportion between LWC and LWCMEA were population generalizability (13% vs. 31%, respectively), followed by relevance to clinical practice (22% vs. 37%) and study design (35% vs. 51%) (Table 1). Uncertainties around all other clinical evidence aspects were raised at a nearly equal proportion between the LWC and LWCMEA sample, for example, clinical evidence submitted (48% vs. 47%, respectively), clinical benefit (65% vs. 72%), and clinical comparator (35% vs. 29%). Overall, it was shown by χ^2 tests, and where applicable, by the Fisher's exact test, that there were no statistically significant differences between LWC and LWCMEA groups in terms of clinical uncertainties (Table 1).

Clinical uncertainties did not drive any statistically significant differences between countries within the LWC sample. Nevertheless, in the LWCMEA sample, agencies differed significantly in raising clinical uncertainties around *study design* ($P < .05$), *clinical comparator* ($P < .05$), *population generalizability* ($P < .001$), and *relevance to clinical practice* ($P < .0001$) (Figure 2).

Differences between the LWC and LWCMEA groups were more prominent when studying economic uncertainties. Those that underpinned significant differences included *utilities* (4% vs. 42%, $P < .0001$; Fisher's exact significance), followed by

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Table 1. Differences in HTA variables studied between conditional/restricted recommendation decisions (LWC and LWCMEA) and their respective *P* values

All recommendation decisions (*n* = 296)		
List (L)	21 (7%)	
List with conditions		
LWC	23 (8%)	
LWCMEA	163 (55%)	
Do not list (DNL)	28 (9.5%)	
Not assessed	29 (10%)	
Not submitted	12 (4%)	
Economic report	20 (6.5%)	
Conditional/Restricted recommendation decisions (*n* = 186)		
Number of assessments per country (**P* < .05)		
	LWC	LWCMEA
England (NICE)	1 (4%)	58 (36%)
Australia (PBAC)	12 (52%)	38 (23%)
Scotland (SMC)	3 (13%)	51 (31%)
Sweden (TLV)	7 (31%)	16 (10%)
Social Value Judgments		
	LWC	LWCMEA
Rarity (*P* = .07)		
Considered	7 (30%)	25 (15%)
Not considered	16 (70%)	138 (85%)
Disease severity (*P* = .33)		
Considered	7 (30%)	67 (42%)
Not considered	16 (70%)	96 (59%)
Unmet need (*P* = .33)		
Considered	13 (56.5%)	109 (67%)
Not considered	10 (43.5%)	54 (33%)
Administration advantage (**P* < .01)		
Considered	2 (9%)	54 (33%)
Not considered	21(91%)	109 (67%)
Innovation (**P* < .001)		
Considered	2 (9%)	86 (53%)
Not considered	21 (91%)	77 (47%)
Special Considerations (i.e., end-of-life criteria) (**P* < .05)		
Considered	7 (30%)	92 (56%)
Not considered	16 (70%)	71 (43%)
Clinical uncertainties		
	LWC	LWCMEA
Clinical benefit (*P* = .47)		
Raised	15 (65%)	118 (72%)
Not raised	8 (35%)	45 (28%)
Study design (*P* = .14)		
Raised	8 (35%)	83 (51%)
Not raised	15 (65%)	80 (49%)
Relevance to clinical practice (*P* = .14)		
Raised	5 (22%)	61 (37%)
Not raised	18 (78%)	102 (63%)
Population generalizability (*P* = .08)		
Raised	3 (13%)	50 (31%)
Not raised	20 (87%)	113 (69%)
Clinical comparator (*P* = .60)		
Raised	8 (35%)	48 (29%)
Not raised	15 (65%)	115 (71%)
Clinical evidence (*P* = .95)		
Raised	11 (48%)	77 (47%)
Not raised	12 (52%)	86 (53%)
Economic uncertainties		
	LWC	LWCMEA
Cost-effectiveness (**P* < .01)		
Raised	9 (39%)	117 (72%)
Not raised	14 (61%)	46 (28%)
Utilities (**P* < .01)		
Raised	1 (4%)	68 (42%)
Not raised	22 (96%)	95 (58%)
Costs (*P* = .31)		
Raised	8 (35%)	75 (46%)
Not raised	15 (65%)	88 (54%)
Modeling (*P* = .95)		
Raised	13 (57%)	118 (72%)
Not raised	10 (43%)	45 (28%)
Model type (*P* = .90)		
Raised	1 (4%)	8 (5%)
Not raised	22 (96%)	155 (95%)
Economic comparator (**P* < .05)		
Raised	0 (0%)	35 (22%)
Not raised	23 (100%)	128 (78%)

Note: LWC, Listed With Criteria; LWCMEA, Listed With Criteria, including an MEA; NICE, National Institute of Clinical Excellence; SMC, Scottish Medicines Consortium; PBAC, Pharmaceutical Benefits Advisory Committee; TLV, The Dental and Pharmaceutical Benefits Agency.

economic comparator (0% vs. 22%, $P < .01$; Fisher's exact significance) and *cost-effectiveness* (39% vs. 72%, $P < .01$) (Table 1).

Furthermore, uncertainties around *utilities* ($P < .0001$), *economic comparator* ($P < .01$), *cost-effectiveness* ($P < .01$), *modeling* ($P < .0001$), *model type* ($P < .05$), and *costs included* ($P < .0001$) also drove differences between agencies within the LWCMEA group (Figure 2). Finally, only *cost-effectiveness* ($P < .05$) generated statistically significant differences among the agencies within the LWC sample.

Social Value Judgments

There was no statistical difference in the likelihood that most categories of SVJs were considered for drugs that were listed on the

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Table 2. *K* scores (*k*, [95 percent CI]) of inter-rater agreement in the commonly assessed and conditional/restricted HTA outcomes across countries

	England (NICE)	Scotland (SMC)	Australia (PBAC)	Sweden[a] (TLV)
England (NICE)	–	−.03 [−.07;.01]	−.05 [−.14;.04]	−.12 [−.32;.08]
Scotland (SMC)	–	–	−.05 [−.14;.04]	.33 [−.17;.83]
Australia (PBAC)	–	–	–	−.29 [−.51; −.07]
Sweden (TLV)	–	–	–	–

Note: NICE, National Institute of Clinical Excellence; SMC, Scottish Medicines Consortium; PBAC, Pharmaceutical Benefits Advisory Committee; TLV, The Dental and Pharmaceutical Benefits Agency.
[a]Scores were generated only with the mutual drug-indication pairs that were both commonly assessed and listed with conditions (LWC or LWCMEA) among all study countries (i.e., 15 molecules commonly assessed between England, Scotland, Australia, and Sweden and 34 molecules commonly assessed and listed with conditions between England, Scotland, and Australia.

basis of LWC versus LWCMEA. Exceptions to this were *innovation* (9% vs. 53%, $P < .0001$; Fisher's exact significance), *administration advantage* (9% vs. 33%, $P < .05$; Fisher's exact significance), and *special considerations* (30% vs. 56%, $P < .05$) (Table 1). In contrast, within the LWCMEA sample, statistically significant differences were observed across countries in the likelihood of considering most SVJs, including *unmet need* ($P < .0001$), *special considerations* ($P < .0001$), *impact on society* ($P < .01$), *impact on Quality of Life (QoL)* ($P < .0001$), *impact on emotional and functional burden* ($P < .0001$, respectively), *severity of disease* ($P < .0001$), *innovation* ($P < .0001$), and *administration advantage* ($P < .0001$) (Figure 2). Finally, only the last three SVJs seemed to drive statistically significant ($P < .05$) cross-country differences in the LWC sample too.

Discussion

We demonstrated significant disparities in the conditional/restricted recommendations across all cancer drugs appraised by four HTA agencies between 2009 and 2018. More precisely, we demonstrated a poor level of agreement in MEA implementation across countries as indicated by the kappa scores. Our results suggest that the countries followed different strategies in dealing with the risk/uncertainty arising from the respective evidence submitted by manufacturers on new oncology therapies.

Diverging MEA outcomes between countries were influenced heavily by economic evidence uncertainties including those around cost-effectiveness, utilities, and costs included in the economic model, highlighting agency-specific preferences on cost-effectiveness thresholds and evidentiary requirements for economic modeling. Similar findings around the importance of economic considerations, and notably, the criterion of cost-effectiveness in determining the final HTA recommendation, have been described elsewhere (19–21).

Clinical evidence uncertainties were less influential than economic toward listing a drug with an MEA; this was not surprising because in many cases it has been demonstrated that uncertainties around the strength of clinical evidence and benefit often lead to rejections commonly across agencies, without allowing any

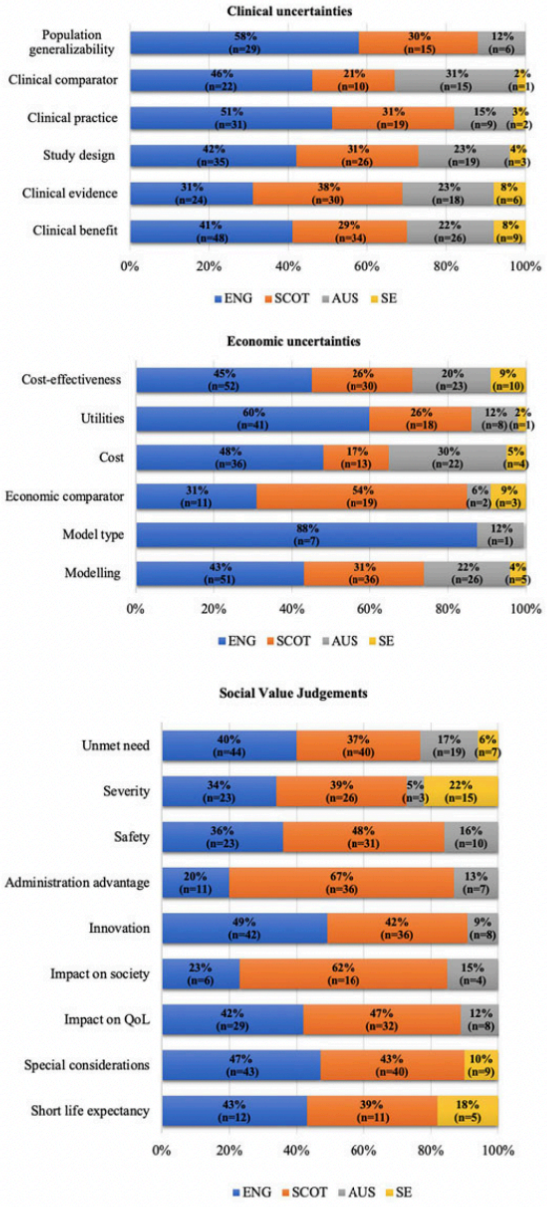

Figure 2. Cross-country variation in clinical/economic uncertainties and SVJs raised and considered respectively by HTA agencies for drug-indication pairs approved with MEAs. *Note*: ENG, England; SCOT, Scotland; AUS, Australia; SE, Sweden; QoL, Quality of Life. *Source*: The authors.

flexibility for conditions or funding negotiations (15;19). However, clinical uncertainties related to setting-specific characteristics (i.e., relevance of the technology in question and of the clinical comparator to the country/region-specific clinical practice, and/or the generalizability of trial population to the setting-specific population) were found to play a role in cross-country

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variation within the LWCMEA sample. This finding confirms that some agencies might place a greater emphasis on evidence related to clinical practice and trial population compared with other agencies (15). It follows that uncertainties around these factors may also play a role in the uptake of risk-sharing negotiations across specific countries.

In terms of SVJs, our findings suggest that most social value considerations determined cross-country differences within the LWCMEA group only, with the exception of innovation, administration advantage, and severity of disease, which underpinned variation within the LWC group too. This observation highlights that considerations around innovation and burden of disease might be crucial in allowing greater flexibility toward funding with conditions/restrictions in general, whereas considerations around impact on QoL, societal impact, emotional/functional burden, as well as other special considerations (i.e., end-of-life criteria) could be influential specifically toward funding with an MEA as a restriction.

Indeed, the HTA literature has recognized that factors such as the burden of disease the treatment addresses, aspects of the treatment's innovation level, but also the wider socioeconomic implications of the treatment largely affect the perceived value of new medical technologies (22). Similarly, a number of setting-specific decision modulators (e.g., the SMC modifiers, the NICE's end-of-life criteria, and the human dignity principle for TLV) can contribute to a greater flexibility toward the acceptance of uncertainty or higher and uncertain ICERs (18). Nevertheless, as shown in Figure 2, the extent to which the above factors are considered across countries in their LWCMEA recommendation decisions can fluctuate significantly, whereas even in countries where these factors are taken into account, they are not necessarily reported in their assessment processes.

Ultimately, this links to discussions about the role of MEAs in the implementation of Value-Based Pricing (VBP) policies through negotiations that enable weight-adjustment of cost-effectiveness thresholds for new medicines that tackle diseases with a higher burden, demonstrate greater therapeutic innovation, and/or have wider societal benefits, such that they reflect any of these additional elements. For example, experience from TLV has shown that in Sweden, risk-sharing agreements indeed complement the VBP system for out-patient drugs and enable stakeholders to mitigate different types of uncertainty (23). Of course, greater clarity on the long-term outcomes of MEAs is also key to understanding the feasibility of MEA negotiations as a tool for the efficient enactment of VBP policies.

To the best of our knowledge, this is the first systematic analysis that confirms cross-country differences in the uptake of MEAs and provides an understanding of the HTA decision-making variables that might influence such differences. Similar, largely descriptive studies have also identified differences in the design and implementation of MEAs across countries but still lack an in-depth analysis and transparency around the HTA determinants of MEAs (6;8;11;13;24). To date, there have been no best-practice guidelines in MEA implementation, and only a few scientific papers suggest some related principles, such as the proposal by KCE in Belgium for good practice in (performance-based) MEAs (25). As such, results from this analysis contribute to shedding light on the rationale/strategies behind the implementation of MEAs across countries and, therefore, facilitate policy relevant research on the creation of implementation guidelines and/or regulations on "risk-sharing" policies. Finally, providing a transparent, evidence-based description of the HTA decision-making variables that can typically influence an approval with MEAs could be applied in practice by policy makers to facilitate/accelerate HTA decision making and, therefore, allow for more timely reimbursement decisions and consequently more timely access to new, high-cost medicines.

Limitations

This research contributes to an improved understanding of the potential factors that drive conditional/restricted HTA recommendations with versus without an MEA and why these two outcomes might differ significantly between countries for the same drug, presenting with similar clinical evidence across countries. Nevertheless, our findings should be interpreted with caution, because there are certain limitations in our analysis that have hindered the accuracy and robustness of our results.

Firstly, variables under Stage 1 of the HTA process (Figure 1), such as the type of clinical evidence submitted or the ICER submitted, have not been included in this analysis based on the assumption that their influence on determining an LWC or LWCMEA outcome will be captured through their respective uncertainties and whether these were raised or not in the decision-making process. Because variables under both stages have been found to have an impact on the final HTA recommendation (15;23), future analyses could include these variables as a robustness check.

Additionally, as budget impact is taken into account only by the Pharmaceutical Benefits Advisory Committee (PBAC), a budget impact-specific uncertainty was not considered due to the lack of comparability across countries. Nevertheless, any budget impact-related concerns raised by the PBAC would have already been reflected in the "cost"- and "modeling"-related uncertainties.

Furthermore, as the calculation of the κ scores required the assumption of paired observations to be met, we performed the calculation only on those drug-indication pairs that were assessed by all four agencies, thus reducing the available sample size significantly. As these analyses could have been more robust if the sample size was increased, it is suggested that a future replication of this study augments the sample size through the inclusion of molecules from additional therapeutic areas. Similarly, as our analysis covered medicines reimbursed only at the national level, future analyses could also account for technologies negotiated at the hospital level.

Finally, advanced statistical modeling was not used at this stage, as our aim was to understand which of the variables play at least some role in driving key differences in the conditional/restricted HTA recommendation decisions between countries. However, in subsequent analyses, the key variables identified herein can be included in a multinomial logistic regression model to also understand their level of impact on divergencies between the conditional/restricted HTA recommendation decisions and the types of MEAs in place across countries.

Overall, it is important that the findings reported here are interpreted with caution, given that the data collected and analyzed were sourced from publicly accessible reports that may, in some instances, represent amended versions of the assessment process to preserve manufacturers' commercial sensitivities and as such, may not present an absolute reflection of the committee's considerations.

Conclusions and the Way Forward

MEAs are implemented globally and particularly in oncology, to address uncertainties arising from the high cost and simultaneous

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immature clinical evidence of new, innovative pharmaceuticals. We showed that the uptake of MEAs across countries for the same drugs might differ substantially, and it is subject to setting-specific evidentiary requirements on economic modeling, the comparators, costs, and utilities included therein but primarily also subject to preferences on social value considerations, such as the socioeconomic and QoL impact of the treatment appraised, as well as setting the specific burden of disease. A better understanding of the criteria that determine MEA utilization across countries is fundamental for future research aimed at informing country-specific, "best-practice" guidelines for successful MEA negotiations.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0266462321000039.

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10.7 Appendix 7: Published version of Research Article II

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ORIGINAL PAPER

Health technology assessment criteria as drivers of coverage with managed entry agreements: a case study of cancer medicines in four countries

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Abstract

Background Managed entry agreements (MEAs) continue to emerge in health technology assessment (HTA)-based decision-making, to address evidentiary uncertainties arising therein. Evidence on the HTA criteria that influence MEAs' uptake remains scarce. This study explores the HTA criteria that determine (i) if an HTA funding decision will be listed with conditions (LWC) other than a MEA, or with a MEA as a condition (LWCMEA), and ii) the MEA type implemented (i.e., financial, outcomes based, or combination).

Methods HTA reports of all oncology medicines approved since 2009 in Australia, England, Scotland, and Sweden were searched to capture the clinical/economic evidence uncertainties raised in the decision-making process, the Social Value Judgements (SVJs) considered therein and the final coverage decision. Binary and multinomial logit models captured the probability (odds ratio (OR)) of a coverage decision being LWCMEA vs. LWC, and of the MEA being financial, outcomes based, or combination, based on the HTA criteria studied.

Results 23 (12%) LWC and 163 (88%) LWCMEA decisions were identified; 136 (83.4%) comprised financial, 10 (6.2%) outcomes based and 17 (10.4%) combination MEAs. LWCMEA decisions were driven by economic model utilities' uncertainties ($7.16 < OR < 26.7$, $p < .05$), and the innovation ($8.5 < OR < 11.7$, $p < .05$) SVJ. Outcomes based contracts were influenced by clinical evidence ($OR = 69.2$, $p < .05$) and relevance to clinical practice ($OR = 26.4$, $p < .05$) uncertainties, and rarity ($OR = 46.2$, $p < .05$) and severity ($OR = 23.3$, $p < .05$) SVJs. Financial MEAs were influenced by innovation ($8.9 < OR < 9.3$, $p < .05$) and societal impact ($OR = 17.7$, $p < .0001$) SVJs.

Conclusions This study provides an empirical framework on the HTA criteria that shape payers' preferences in funding with MEAs, when faced with uncertainty.

Keywords Managed entry agreements · HTA decision-making · Conditional reimbursement · Risk-sharing · Discounts

Background and objectives

The rapid progress of therapeutic innovation and the respective introduction of new, high-cost, therapies might be favourable from the patient's perspective, but from the payer's perspective, it poses challenges in managing the market entry and long-term affordability of these therapies [1]. To mitigate these pressures, countries are developing policies to facilitate decision-making about the reimbursement of novel, high-cost pharmaceuticals, such as the cost-effectiveness appraisal of these technologies. In many countries worldwide, these evaluations take the form of health technology assessment (HTA), a process where the clinical and cost-effectiveness of these products is assessed by national competent authorities, to understand if these products demonstrate the "value-for-money" profile required by different healthcare systems to enable coverage [2, 3]. In the HTA process, challenges may arise due to evidentiary uncertainties generated by the immature or early phase evidence submitted by manufactures for appraisal. The uncertainties facing decision-makers have been classified into three broader categories including (i) clinical (e.g., the applicability of study endpoints and treatment population to the actual clinical practice in the country of interest),

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(ii) financial (e.g., the actual number of doses and treatment duration required in real-world practice and the respective aggregate budget impact) and (iii) utilisation uncertainties (e.g., the appropriate prescribing of the product for the patient population in which it is deemed to be cost-effective) [2, 4]. To address uncertainties arising in the HTA-based decision-making, managed entry agreements (MEAs) between payers and manufacturers are increasingly being employed in many countries as part of the process. Depending on the type of uncertainty to be addressed, literature has classified MEAs in two broader categories, namely outcome- and financial-based agreements depending on whether they aim to mitigate uncertainties related to drug performance or not respectively, while combination agreements with financial and outcome-based aspects have also been observed [2, 5, 6]. Literature has shown that even in cases where countries implemented a MEA for the same medicine-indication pair, often presenting with similar uncertainties, there was still variation in the types of agreements implemented and the respective objective targeted by these agreements [7–9]. Descriptive studies have suggested that health system-specific considerations and perceptions of "risk" across settings might play a role in explaining such differences [4, 8, 10]. Furthermore, a descriptive, comparative analysis of MEAs for cancer medicines in different settings, found that cross-country differences may arise chiefly due to payers' preferences on social value considerations, such as the socioeconomic and Quality of Life (QoL) impact of the treatment appraised, followed by setting-specific requirements on the economic model, and the comparators, costs, and utilities included in the model [11].

Despite the growing utilisation of MEAs, quantitative, empirical research on the HTA factors that have an impact on the uptake of MEAs across settings remains scarce [12, 13]. This has significant implications for the transparency of "best-practice" guidelines on MEA negotiation and implementation processes across and within countries [6, 13]. To address this literature gap, this paper provides a quantitative assessment of the key HTA criteria that have been suggested by previous, descriptive research as potential determinants of MEAs. Ultimately, the objective of this analysis is twofold: first, to identify the relative importance of these criteria in comparison to each other towards shaping decision-making under uncertainty and second, using specifically a quantitative approach, to map the HTA criteria that determine coverage with a MEA or not, and if so, the criteria that determine the type of MEA.

Methods

Sample selection

All oncology medicines which obtained regulatory approval by the European Medicines Agency (EMA) in Europe and by the Therapeutic Goods Administration (TGA) in Australia between 1st January 2009 and 15th June 2018 (at the medicine-indication pair level) were studied in Australia (AUS), England (ENG), Scotland (SCOT) and Sweden (SE). Oncology was selected as the study therapeutic class because it has been documented to be the therapeutic class with the largest proportion of implemented MEAs and the therapeutic class where MEAs continue to be increasingly implemented [2]. Study countries were selected because they all implement MEAs, they all have long-established HTA policies and processes to guide their coverage decisions, they have both a publicly available list of MEAs and HTA reports (or publicly available documents where MEAs and other HTA criteria can be inferred from, such as the Public Summary Documents in Australia) and they use similar approaches in their pricing and reimbursement decision-making process (i.e., clinical and cost-effectiveness approach), allowing for comparability across agencies [14].

Data collection

The conceptual framework underpinning data collection operates under the overarching hypothesis that HTA coverage decisions (whether positive, negative or restricted) are primarily shaped by the HTA process itself, including the evidence appraised therein (whether clinical, economic or otherwise), the way this evidence is interpreted/assessed by the decision-makers, and the broader socioeconomic and political context in which the decision-making takes place [11, 14, 15].

Essentially, this framework divides the HTA process and relevant variables of interest in four "buckets" where it is hypothesised that a combination of variables within "buckets" (A), (B) and (C), determine the observed outcome in "bucket" (D) as follows: (A) clinical and economic evidence appraised (e.g., trial characteristics, comparators, Incremental Cost Effectiveness Ratio (ICER) and economic model specifications), (B) interpretation/assessment of this evidence (i.e., clinical and economic evidence related uncertainties raised), (C) societal and system-specific context in which HTA-based decision-making operates (i.e., dimensions of value that a technology adds in the society/setting of interest, such as the unmet need it targets in terms of therapeutic treatment availability, the societal benefit it offers in terms of improved patient QoL, functional ability outcomes, all referred to as Social Value Judgements (SVJs)) and system-specific processes for decision-making (e.g., the use of a single or multiple technology appraisal in England), and (D) coverage decision outcome categorised as: (i) L = List (i.e., positive coverage decision), (ii) LWC = List with one or more conditions which are not classified as MEAs (e.g., dosing restrictions, clinical restrictions relating to treatment eligible sub-population, etc.), (iii) LWCMEA = List with one

or more conditions including at least one restriction classified as MEA and iv) DNL = Do not list (i.e., negative coverage decision).

Data on the above "buckets", per medicine-indication pair in all study countries were extracted from publicly available HTA appraisals published in the respective HTA bodies' websites, namely PBAC (AUS), NICE (ENG), TLV (SE) and SMC (SCOT). A database stratified by HTA agency was built to describe and classify MEAs across the respective HTA bodies and facilitate data analysis.

Data analysis

Restricted HTA outcomes were coded as a binary variable (i.e., LWC vs. LWCMEA), while the type of MEA was coded as a multinomial variable (i.e., financial ("F"), outcomes ("O") based or combination ("C")), based on taxonomies that have been described in the literature [2, 6, 9], with discounts explicitly considered as financial MEAs in this analysis. Finally, assuming that all categories of uncertainties and SVJs were applicable to all drug-indication pairs studied, these were treated and coded as binary variables based on whether they have been raised and considered (or not), respectively, in the HTA-based decision-making process [11]. More specifically, the mention/raise of an uncertainty or SVJ—regardless of its weight/impact on the decision-making process—has been classified as "raised" or "considered", while in cases where there is no mention of a specific uncertainty or SVJ this was classified as "not raised" or "not considered", respectively, for each drug-indication pair.

For the purposes of this analysis, a panel data design was not feasible as the study sample comprised one decision per medicine-indication pair per country in a particular year as opposed to annual decisions; similarly, since the response variables are categorical, they could not be modelled as a linear combination of explanatory variables either [15]. Therefore, the associations studied were described as probabilities, estimated by means of a binary and a multinomial logit model. For the first part of the analysis, binary logistic regression was used to estimate the probability of a technology receiving restricted coverage with at least one restriction in the form of a MEA (as opposed to one or more restrictions without a MEA) based on a set of HTA explanatory variables, hypothesised to influence HTA-based decision-making [14, 16]. Additionally, as a robustness check, Pearson's Chi-squared tests were performed to identify which HTA criteria determine statistically significant differences between LWC and LWCMEA coverage decisions for each study country. Finally, for the second part of the analysis, multinomial logistic regression was used to model the probability of an implemented MEA taking one of the three outcomes "F", "O" or "C" given a set of HTA criteria/ explanatory variables associated with the medicine-indication pair in question.

Results

235 coverage decisions were studied, of which 88% ($n=207$) were favourable (with or without restrictions) and 12% ($n=28$) non-favourable across all countries. The majority of favourable coverage decisions were LWCMEA (78.7%, $n=163$), 11.1% ($n=23$) were LWC and 10.2% ($n=21$) were L. In England, 93% (n = 54) of MEAs were financial, 96% ($n=49$) in Scotland, 76.3% ($n=29$) in Australia and 27% ($n=4$) in Sweden. Outcome-based schemes were mostly implemented in Sweden (47%, $n=7$) and combination schemes primarily used in Australia (21%, $n=8$) (Table 1).

LWC vs. LWCMEA coverage decision

Of the restricted coverage decisions studied (n = 186), 88% (n = 163) were LWCMEA and 12% (n = 23) were LWC. A number of binary logit models were performed to ascertain the effects of different HTA criteria on the likelihood of receiving a LWCMEA as opposed to a LWC coverage decision. The statistically significant models with the best predictability rate are presented below (Table 2). Values highlighted in bold correspond to the effect size/ likelihood (*i.e.*, OR) and the respective *p*-value of the HTA criteria that were found to be of statistical significance within the different models.

The first model ($\chi^2=47.7$, $p<0.0001$) explained 43% (Nagelkerke R^2) of the variance in restricted coverage decisions and correctly classified 92% of cases. Medicine-indication pairs with utility and cost-effectiveness related uncertainties were approximately 27 (OR=26.731, $p<0.05$) and 4 (OR=3.926, $p<0.05$) times, respectively, more likely to receive a LWCMEA instead of a LWC coverage decision. The SVJs of innovation and rarity were associated with an increased (OR=8.504, $p<0.05$) and decreased (OR=.147, $p<0.05$) likelihood of a LWCMEA (as opposed to LWC) coverage decision, respectively.

The second model ($\chi^2=51.3$, $p<0.0001$) explained 46% (Nagelkerke R^2) of the variance in restricted outcomes and correctly classified 91% of cases. Medicine-indication pairs with utility and cost-effectiveness related uncertainties were approximately 21 (OR=20.97, $p<0.05$) and 4.5 (OR=4.361, $p< 0.05$) times respectively, more likely to receive a LWCMEA instead of a LWC coverage decision. The SVJs of innovation and rarity were associated with an increased (OR=10.632, $p<0.05$) and decreased (OR=.165, $p<0.05$) likelihood of a LWCMEA (as opposed to LWC) coverage decision, respectively.

Table 1 Study sample characteristics, including, number of favourable decisions (with or without MEA) per country, and the respective types of MEAs implemented (where applicable)

Oncology medicine-indication pairs assessed by the study HTA agencies (*n*, %)					
	England (NICE) (*n* = 68)	Australia (PBAC) (*n* = 64)	Scotland (SMC) (*n* = 61)	Sweden (TLV) (*n* = 42)	All sample (*n* = 235)
List (L)	2 (3%)	1 (1.5%)	4 (6.5%)	14 (33.4%)	21 (8.9%)
List with conditions (LWC)	1 (1.4%)	12 (18.8%)	3 (4.9%)	7 (16.6%)	23 (9.8%)
LWC w/ MEA (LWCMEA) Of which	58 (85.3%)	38 (59.3%)	51 (83.6%)	16 (38%)	163 (69.3%)
Financial	54 (93%)	29 (76.3%)	49 (96%)	4 (27%)	136 (83.4%)
Outcomes	2 (3.5%)	1 (2.6%)	0%	7 (47%)	10 (6.2%)
Combination	2 (3.5%)	8 (21%)	2 (4%)	5 (26%)	17 (10.4%)
Do not list (DNL)	7 (10.3%)	13 (20.3%)	3 (5%)	5 (12%)	28 (12%)

n/a not applicable for the HTA agency of interest, *DNL* do not list, *L* list, *LWC* list with conditions, *LWCMEA* list with conditions including a MEA, *MEA* managed entry agreement, *NICE* National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee, *SMC* Scottish Medicines Consortium, *TLV* The Dental and Pharmaceutical Benefits Agency

The third model ($\chi^2 = 18.25$, $p < 0.0001$) explained 30% (Nagelkerke R^2) of the variance in restricted coverage decisions and correctly classified 88% of cases. Medicine-indication pairs with utility and economic comparator related uncertainties were approximately 7 (OR=7.169, $p<0.01$) and 4 (OR=4.147, $p<0.05$) times, respectively, more likely to receive a LWCMEA instead of a LWC coverage decision. The SVJ of innovation was associated with an increased (OR=11.727, $p<0.01$) likelihood of a LWCMEA (as opposed to LWC) coverage decision.

Finally, the fourth model ($\chi^2 = 19.45$, $p < 0.001$) explained 19% (Nagelkerke R^2) of the variance in restricted outcomes and correctly classified 87% of cases. Medicine-indication pairs with cost-effectiveness related uncertainties were approximately 3 (OR=3.24, $p<0.05$) times more likely to be classified as LWCMEA instead of LWC. The SVJs of special considerations and rarity were associated with an increased (OR=3.014, $p<0.05$) and decreased (OR=.254, $p<0.05$) likelihood of a LWCMEA (as opposed to LWC) coverage decision, respectively.

Country-specific outcomes

Pearson's chi-squared tests were also performed to identify any HTA criteria that determine statistically significant differences between LWC and LWCMEA coverage decisions for each study country. Cost-effectiveness uncertainties determined statistically significant differences between the LWC and LWCMEA groups for England ($\chi^2 = 8.98$, $p = 0.003$), Scotland ($\chi^2 = 3.97$, $p = 0.046$) and Australia ($\chi^2 = 5.02$, $p = 0.025$). Additionally, uncertainties around the economic model used and the utilities included in the model highlighted statistically significant differences between LWC and LWCMEA coverage outcomes in England ($\chi^2 = 5.65$, $p = 0.017$) and Australia ($\chi^2 = 3.10$, p = 0.028), respectively. Finally, uncertainties around clinical evidence and clinical benefit, and the SVJ of innovation, underscored statistically significant differences between LWC and LWC-MEA groups for Scotland ($\chi^2 = 3.68$, $p = 0.04$), England ($\chi^2 = 4.98$, $p = 0.026$) and Australia ($\chi^2 = 3.10$, $p = 0.028$), respectively (Online resource 1).

Type of MEA

163 MEAs were identified, of which 83.4% ($n = 136$) were "F", 6.2% (n = 10) were "O" and 10.4% ($n = 17$) were "C". A number of multinomial logit models were performed to identify the sets of HTA criteria, including clinical/economic uncertainties and SVJs, that best predicted the likelihood of a MEA in place for the study medicine-indication pairs being "F", "O" or "C" (Table 3, Fig. 1). Values highlighted in bold correspond to the effect size/likelihood (*i.e.*, OR) and the respective p-value of the HTA criteria that were found to be of statistical significance within the different models.

The first model ($\chi^2 = 38.61$, $p < 0.0001$) explained 42% (Nagelkerke R^2) of the variance in MEA types. Medicine-indication pairs with uncertainties raised around relevance to clinical practice (OR=.072, $p< 0.05$ and OR=.056, $p<0.05$) and social value considerations around rarity (OR=.073, $p<0.05$ and OR=.04, $p<0.05$) were more likely to be funded with an "O", as opposed to a "F" and a "C" agreement respectively. On the contrary, the social value consideration of innovation was as associated with an approximately 9.5 (OR=9.346, $p<0.05$) times higher likelihood of a "F" as opposed to an "O" agreement.

The second model ($\chi^2 = 41.79$, $p < 0.0001$) explained 45% (Nagelkerke R^2) of the variance in MEA types. Medicine-indication pairs with uncertainties raised around clinical evidence (OR=.066, $p<0.05$) and relevance to

Table 2 Binary logit models, predicting the likelihood (odds ratio (OR)) of a coverage decision being restricted with vs. without MEA, based on the different sets of HTA criteria studied

HTA criteria	Model 1		Model 2		Model 3		Model 4	
	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Clinical uncertainties								
Population generalisability	1.859	.506	2.112	.430	.444	.505	2.352	.219
Study design	1.861	.359	1.977	.319	.535	.464		
Clinical comparator	.585	.459	.594	.477	.835	.361		
Relevance to clinical practice	.415	.241	.493	.349				
Clinical evidence					.292	.589		
Clinical benefit							.791	.688
Economic uncertainties								
Economic modelling	.695	.612	.579	.463	.386	.535	1.264	.672
Cost-effectiveness	**3.926**	**.034**	**4.361**	**.029**	**6.700**	**.010**	**3.240**	**.022**
Utilities	**26.731**	**.018**	**20.970**	**.028**	**7.169**	**.007**		
Model type	1.198	.898	1.954	.653				
Costs	.906	.878	.846	.796				
Economic comparator			13.204	.997	**4.147**	**.042**		
Social Value Judgements								
Rarity	**.147**	**.024**	**.165**	**.040**	3.443	.064	**.254**	**.017**
Special considerations	.553	.452	.478	.359	.361	.548	**3.014**	**.040**
Severity	2.683	.148	2.326	.208	.160	.689		
Unmet need	.905	.880	.834	.789	.003	.956		
Innovation	**8.504**	**.029**	**10.632**	**.026**	**11.727**	**.001**		
Administration advantage	4.721	.160	4.709	.184	2.506	.113		
Impact on society	.292	.356	.259	.316	.035	.852		
Impact on QoL	1.038	.962	.993	.993	.084	.772		
Impact on emotional burden	19.047	.998	16.154	.998				
Impact on functional burden	1.245	.893	.392	.612				
Constant	1.819	.291	1.898	.259	3.667	.000	2.686	.033
Model statistics	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*
Likelihood ratio test	47.659	.000	51.297	.000	18.25	.000	19.45	.003
Hosmer and Lemeshow test	12.348	.136	7.289	.506	.279	.870	5.97	.543
Predictability (%)	92%		91%		87%		87%	

OR odds ratio, *p p* value, *QoL* quality of life, χ^2 Chi-squared value

clinical practice (OR=.084, $p<0.05$), and social value considerations around rarity (OR=.061, $p<.05$) were more likely to be funded under an "O" as opposed to a "F" agreement. Similarly, medicine-indication pairs with social value considerations around rarity were more likely (OR=.034, $p<0.05$) to lead to an "O" as opposed to a "C" agreement. On the contrary, medicine-indication pairs with social value considerations around innovation and impact on society were associated with an approximately 9 (OR=8.999, $p<0.05$) and 18 (OR=17.732, $p<0.0001$) times higher likelihood of coverage with a "F" as opposed to an "O" agreement.

The third model ($\chi^2 = 47.94$, $p < 0.0001$) explained 50% (Nagelkerke R^2) of the variance in MEA types. Medicine-indication pairs with uncertainties raised around clinical evidence (OR=69.221, $p<0.05$) and relevance to clinical practice (OR=26.4, $p< 0.05$), and social value considerations around rarity (OR=46.207, $p<0.05$) and severity (OR=23.349, $p<0.05$), had a higher likelihood of coverage with an "O" instead of a "F" agreement. Additionally, medicine-indication pairs with social value considerations around innovation (OR=.038, p<0.05) and special considerations (OR=.148, p<0.05) were associated with a higher likelihood of coverage with a "F" instead of a "C" agreement.

Table 3 Multinomial logit models, predicting the likelihood (odds ratio (OR)) and respective statistical significance (*p*) of a MEA being financial or outcomes based or a combination of both, based on the different sets of HTA criteria studied

HTA criteria	Model 1				Model 2			Model 3				
	Financial vs. outcomes[a]		Combination vs. outcomes[a]		Financial vs. outcomes[a]		Combination vs. outcomes[a]	Combination vs. financial[a]			Outcomes vs. financial[a]	
	OR	*p*	OR	*p*	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Clinical evidence	0.097	0.080	0.233	0.332	**0.066**	**0.045**	0.153	0.234	5.262	0.078	**69.221**	**0.023**
Cost-effectiveness	3.033	0.437	0.663	0.800	3.793	0.379	0.691	0.828	0.327	0.207	0.310	0.460
Innovation	**9.346**	**0.042**	0.276	0.412	**8.999**	**0.047**	0.188	0.331	**0.038**	**0.013**	0.072	0.085
Rarity	**0.073**	**0.032**	**0.040**	**0.048**	**0.061**	**0.029**	**0.034**	**0.046**	0.977	0.986	**46.207**	**0.041**
Clinical practice	**0.072**	**0.043**	**0.056**	**0.044**	**0.084**	**0.047**	0.065	0.070	0.786	0.779	**26.400**	**0.046**
Clinical benefit	4.830	.177	16.491	.059	1.000	0.264	1.000	0.110				
Clinical comparator	0.726	0.776	0.627	0.736								
Impact on society					**17.732**	**0.000**	18.416	[b]				
Modelling									0.662	0.641	0.685	0.768
Special considerations									**0.148**	**0.047**	0.139	0.212
Utilities									1.719	0.575	0.257	0.365
Severity									3.490	.278	**23.349**	**0.049**
Intercept		0.011		0.124		0.006		0.056		0.426		0.012

OR odds ratio, *p p* value

[a]Reference category of the multinomial model

[b]No statistics are computed because variable is a constant

Discussion and policy implications

This paper explored the sets of HTA criteria, including clinical/economic uncertainties and SVJs, that might contribute to a higher likelihood of restricted HTA recommendations including a MEA as part of the restriction or not, and subsequently identified the HTA-relevant criteria that determine the respective type of a MEA in place (Fig. 1). This is the first study to date to model the HTA criteria that determine both the utilisation and the typology of MEAs in oncology therapies across countries.

Coverage with a MEA was predominantly driven by uncertainties around the utilities of the economic model, and the SVJ of innovation. Outcome-based contracts were primarily influenced by uncertainties on the clinical evidence and relevance to clinical practice, followed by the rarity and severity of the condition. Financial MEAs were influenced by the SVJs of innovation and societal impact of the technology in question. Similar findings arise from the limited and largely descriptive evidence available in the relevant literature. A recent review of outcome-based MEAs in the OECD countries concluded that these may indeed be more common for products with orphan indications, while a case study presented therein concluded that outcome-based schemes in England mostly tried to address uncertainty around the magnitude of long-term clinical benefit, and concerns around the duration of therapy in routine clinical practice [17]. It has also been suggested that outcome-based contracts typically aim to address uncertainties around efficacy or effectiveness in the general population, long-term clinical evidence on clinically significant endpoints (i.e., clinical rather than surrogate markers), as well as safety, and numbers likely to be treated in real-world practice [6]. Finally, using a theoretical model, Antonanzas et al. (2011) analysed situations in which payers will prefer a MEA over non-MEA and concluded that payers' decisions will depend on monitoring costs, marginal production costs, and the utility patients will derive from treatment [18].

Beyond its empirical study design, another strength of this analysis is the holistic approach considered in the HTA criteria driving MEAs, accounting for the interconnected impact of both uncertainties and SVJs on the final HTA/MEA outcomes, as opposed to the existing literature that has primarily studied the impact of uncertainties. This is important because the emphasis placed on HTA criteria differs between HTA stakeholders across or even within countries; some countries focus on disease severity and drug efficacy, others concentrate on cost-effectiveness, whereas in some countries, payers and HTA stakeholder experts have different preferences on the HTA process and hence, divergent views on which criteria are the most significant within their systems [12]. Specifically, for MEAs, it arises that the requirement for an agreement and the type of agreement preferred by payers, is subject to the disease area and other setting and medicine specific, value considerations [19]. Furthermore, despite significant efforts to create good practice guidelines

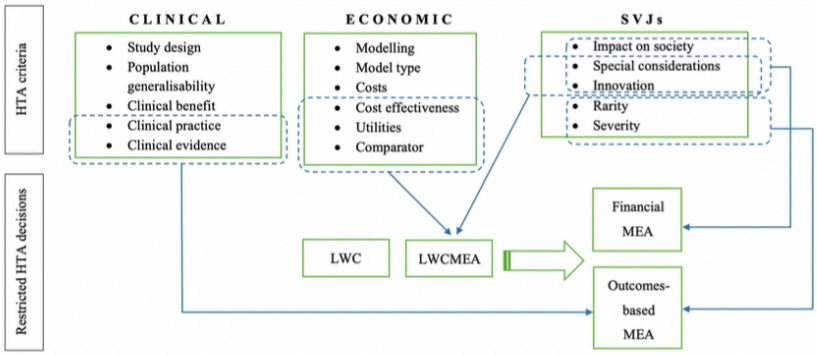

Fig. 1 Analytical framework on the HTA criteria driving restricted coverage decisions with a MEA (LWCMEA) and the respective type of MEA. HTA: Health Technology Assessment, LWC: List with conditions, LWCMEA: List with conditions, including a MEA, MEA: Managed Entry Agreement, SVJs: Social Value Judgements. The categories of the HTA criteria included in this analysis and subsequently used in the above framework are based on previously published relevant research and all respective definitions are described in detail therein [11]. Source: The author; the framework is fully conceptualised by the author, based on background from relevant literature [2, 11, 14]

on the design, implementation, and evaluation of MEAs [6, 20–24], there are still gaps in understanding the conditions that lead to acceptance of proposed MEAs from the payers' perspective. For example, in England, rejections of manufacturer proposed agreements (i.e., Patient Access Schemes (PAS)) are still observed, highlighting that despite existing guidelines on the submission of PAS, we still lack an understanding of the considerations that render a MEA successful from the point that a company submits a PAS proposal and until this is accepted by NICE [24, 25]. On that front, the findings presented here can enhance transparency in existing guidelines by promoting a shared understanding on the aspects that determine value in MEA negotiations from the payer's' perspective. This can guide both manufacturers—to tailor agreement proposals such that they align with the value perceptions of different payers, and payers—to establish more streamlined processes in decision-making under uncertainty.

Limitations

Despite the empirical contribution of this study in the field of MEA research, the results presented herein should be interpreted with caution due to certain methodological discrepancies that possibly undermine the robustness of the study.

First, country-specific policies, purchasing framework and context in which pricing and reimbursement decision-making operates have not been incorporated in the analysis per se. It is believed that their potential confounding effect has been captured through criteria around HTA system-specific considerations such as SVJs. Of course, even though the SVJ classification used in this analysis is largely applicable to all important SVJs considered across countries [11, 14], SVJs still remain highly subjective and dependent on the setting-specific context in which they are considered. Therefore, the SVJ variables included in this analysis might not be entirely representative of all the system-specific considerations that are of "weight" in HTA-based decision-making across the study countries. In addition, reference in the literature has been made on the impact of the overall country-specific healthcare and welfare characteristics on HTA-based decision-making, such as healthcare spending per capita, societal willingness-to-pay and the structure of the healthcare system [26]. As such, to enhance accuracy of the results, these factors should be explicitly included in future studies modelling the uptake of MEAs.

Second, based on the methodology followed in this analysis, whether an uncertainty has been resolved or not reflects the impact of the implemented MEA, while the mention/raise of an uncertainty during the appraisal (whether resolved or not following the proposed MEA) reflects a potential determinant/reason behind the implementation of a MEA as a funding modality. On that front, this specific analysis does not differentiate between resolved/unresolved uncertainties; it aims to capture all the uncertainties raised (as per the HTA reports/public summary documents) to understand which of these had a greater impact in determining LWCMEA coverage decisions. However, it is of critical importance to conduct further analyses to capture the uncertainties that remain following the proposed MEA, as an evaluation of its impact.

Finally, the limited sample size studied hinders the overall power, sensitivity and specificity of the models. Future replication of these models would benefit from a larger study

sample, possibly by including coverage decisions of medicines in other therapeutic areas too, although caution should be exercised to account for potential comparability issues arising from differences in the value that different SVJs reflect for payers in different disease areas. Overall, due to setting-specific nuances in HTA-based and reimbursement decision-making, the criteria and their relative weight in the decision-making process, as identified in this analysis, are not necessarily generalisable across settings and should be interpreted on an individual basis and adapted to the respective setting-specific context in question.

Conclusions

The growing interest in MEAs and their increased implementation across countries globally, necessitates an enhanced transparency on the aspects that determine value in MEA negotiations. On that front, the findings of this study provide a better understanding on the decision-making criteria that shape payers' preferences in coverage with a MEA or not. Empirical research on the HTA criteria driving MEAs is key to encourage a transparent, cross-country learning on how MEAs can be tailored to align with payers' perceptions on "value" and ultimately, promote more efficient MEA negotiations and increased opportunities for coverage through MEAs. There are still barriers to overcome for MEAs to be implemented more widely and efficiently, such as their increased administrative burden, the absence of standardised processes to evaluate their outcomes and the confidentiality around the final prices and discounts negotiated under these agreements.

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Declarations

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Impact of Managed Entry Agreements on availability of and timely access to medicines: an ex-post evaluation of agreements implemented for oncology therapies in four countries

Olina Efthymiadou* and Panos Kanavos

Abstract

Background: Despite the increased utilisation of Managed Entry Agreements (MEAs), empirical studies assessing their impact on achieving better access to medicines remains scarce. In this study we evaluated the role of MEAs on enhancing availability of and timely access to a sample of oncology medicines that had received at least one prior rejection from reimbursement.

Methods: Funding decisions and their respective timelines for all oncology medicines approved between 2009 and 2018 in Australia, England, Scotland and Sweden were studied. A number of binary logit models captured the probability (Odds ratio (OR)) of a previous coverage rejection being reversed to positive after resubmission with vs. without a MEA. Gamma generalised linear models were used to understand if there is any association between time to final funding decision and the presence of MEA, among other decision-making variables, and if so, the strength and direction of this association (Beta coefficient (B)).

Results: Of the 59 previously rejected medicine-indication pairs studied, 88.2% ($n=45$) received a favourable decision after resubmission with MEA vs. 11.8% ($n=6$) without. Average time from original submission to final funding decision was 404 (± 254) and 452 (± 364) days for submissions without vs. with MEA respectively. Resubmissions with a MEA had a higher likelihood of receiving a favourable funding decision compared to those without MEA ($43.36 < OR < 202$, $p < 0.05$), although approval specifically with an outcomes-based agreement was associated with an increase in the time to final funding decision ($B = 0.89$, $p < 0.01$). A statistically significant decrease in time to final funding decision was observed for resubmissions in Australia and Scotland compared to England and Sweden, and for resubmissions with a clinically relevant instead of a surrogate endpoint.

Conclusions: MEAs can improve availability of medicines by increasing the likelihood of reimbursement for medicines that would have otherwise remained rejected from reimbursement due to their evidentiary uncertainties. Nevertheless, approval with a MEA can increase the time to final funding decision, while the true, added value for

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patients and healthcare systems of the interventions approved with MEAs in comparison to other available interventions remains unknown.

Keywords: Risk sharing agreements, Managed entry agreements, Reimbursement, Access delays, Impact assessment

Background

The restricting cost containment environment in which healthcare systems are required to operate, introduces challenges on policy decisions about the coverage of highly priced pharmaceuticals. These challenges often arise as the evidence presented by manufacturers is not always sufficient to estimate the real-life budget impact, clinical and cost-effectiveness of these high-cost pharmaceuticals. More importantly, the uncertainties posed by the immature evidence submitted by manufacturers may prevent or delay healthcare payers from reaching conclusions on coverage decisions, thus affecting patient access [1].

Against this background, there is an interest from healthcare payers and manufacturers to collaboratively manage the entry of new pharmaceuticals in the market by linking price and reimbursement levels to real-world performance or utilization of medical products with the aim of sharing the risk surrounding the introduction of new technologies with uncertain evidence on their clinical and/or cost-effectiveness profiles. Prices can be linked to future outcomes and/or volumes and the specific conditions of the negotiations are drawn up into product listing agreements usually summarised as Risk Sharing Agreements (RSAs), Managed Entry Agreements (MEAs) or Patient Access Schemes (PAS) [2–4]. The main types of these agreements are financial-based and health outcomes-based agreements, or occasionally combination of both types. The former includes agreements at the population level (e.g., simple discounts or price–volume agreements) or at the patient level (e.g., utilisation, time, or cost capping schemes), and the latter includes performance-linked schemes (e.g., conditional treatment continuation, outcome guarantee and coverage with evidence development) [5].

It has been suggested that MEAs can improve access to innovative medicines by addressing decision-making related uncertainties and hence, preventing rejection from reimbursement due to uncertain clinical and cost-effectiveness evidence [6–8]. Nevertheless, these agreements have not yet gained widespread acceptance primarily because their sustainability is unclear and their effectiveness in meeting their objectives has yet to be evaluated [9]. Key issues around the efficiency of MEAs relate to the often lengthy or stalled MEA negotiations causing access delays, and the risk for a product reimbursed with a MEA being delisted following expiry of the agreement thus, impeding patient access [5]. Another area of concern in the implementation of MEAs relates to the administrative burden they are often associated with [7], especially for agreements that require advanced infrastructure systems to support new data generation [10].

Despite the significant attention placed on the implementation of MEAs, the body of evidence on the performance of MEAs to date is weak, as there is still little information on their real-life impact on patients and healthcare systems [11, 12]. The main body of literature attempting to evaluate MEAs is based on theoretical models that assess the economic impact of MEAs [13–18]. Additionally, the role of MEAs in achieving a meaningful impact on key policy objectives such as cost containment, improved access and reward of innovation, has been discussed in the literature chiefly in the context of describing their "strengths and weaknesses" [3, 7, 19]. The key challenge in conducting empirical impact assessments for MEAs arises due to the confidentiality and limited information available on the specific negotiating terms and operational details of these agreements (i.e., timeframe, patient eligibility, indicators used to monitor outcomes etc.) [3, 11]. Only a few empirical studies exist on the real-life impact of implemented MEAs on pharmaceutical expenditure [20, 21], list prices [11], faster access to cancer medicines [22] and on the ability of outcomes-based schemes to collect meaningful, long-term outcomes data for patients [23, 24]. Additionally, existing empirical literature primarily reflects case studies within one specific setting/country and hence, comprehensive evidence about the broader effectiveness of MEAs in meeting their anticipated objectives remains scarce [9, 25, 26]. For example, Russo et al., (2010) [22] assessed the impact of MEAs on access delays only from the Italian healthcare system perspective and concluded that the impact of MEAs remains equivocal due to diverse health system priorities, different assessment criteria, different market access/purchasing strategies and market sizes across different countries. Other studies concluded that despite MEAs' potential to improve access, there is no consensus on which MEA types and implementation strategies are the most effective in optimising reimbursement decision-making [13].

Drawing more robust conclusions about the pragmatic impact of MEAs is paramount to understand if these agreements represent a sustainable policy tool

for improved coverage across countries. This could also help purchasers to identify the most efficient MEA negotiation practices by understanding which situations call for the use of one type of MEA instead of another, and what trade-offs are involved in choosing different contracts [13]. To that end, structured ex-post evaluations of MEAs are essential to assess the impact of existing schemes on a number of key policy goals such as access to medicines, budget control and encouragement of innovation [4, 8, 27]. In practice, these evaluations can take the form of quantitative models that enable the outcomes of these agreements to be compared with those in situations without them [9, 11].

We are not aware of any other empirical studies that involve direct comparisons of MEAs to understand how these agreements influence the level of and/or speed of access to medicines across countries. Therefore, the objective of this study was to contribute evidence around the impact that completed agreements or resubmissions with an agreement have had on a) the levels of access (*i.e.*, resulting in more "listing" recommendations) and b) the time taken to the final decision outcome. These objectives were selected for impact assessment because first, they reflect a key policy goal targeted by health systems across borders [28] and second, because of relevant data availability that ensures feasibility of the required data analysis.

Methods

Sample selection

This study was based on a retrospective analysis of HTA appraisals for all oncology medicines which obtained regulatory approval by the European Medicines Agency (EMA) in Europe and by the Therapeutic Goods Administration (TGA) in Australia between 1st January 2009 and 15th June 2018 (at the medicine-indication pair level) in Australia, England, Scotland and Sweden. Oncology was the therapeutic area of choice because it has been documented to be the therapeutic class with the largest proportion of implemented MEAs, while also being the therapeutic class where MEAs continue to be increasingly implemented [3].

Study countries were selected because they all implement MEAs, they all have long-established HTA policies and processes to guide their coverage decisions/recommendations, they have both a publicly available list of MEAs and publicly available HTA reports which provide sufficient information for the purposes of this analysis, [29]. Additionally, these countries were selected because, apart from the cost-effectiveness perspective, they also use other, different principles to shape their decision-making around pricing and reimbursement of medicines (e.g., England also considers the national health and personal social services perspective and Sweden also takes into account the human value and solidarity principle (further information about the study HTA agencies and their respective HTA perspective is provided in supplementary material; see Appendix Table 1). Therefore, countries were selected such that they would allow for comparability across agencies, while reflecting the diversity in HTA coverage decisions/recommendations and the respective HTA determinants of access across settings [29].

Variables of interest

From the sample described above, all medicine-indication pairs with a resubmission following an HTA rejection and all medicine-indication pairs with a resubmission following completion/expiry of a previously agreed MEA identified and isolated separately for analysis; none of the respective MEAs were implemented across multiple indications of a specific molecule and/or were part of a Multi-Year Multi-Indication (MYMI) agreement. Further information about the medicine-indication pairs studied is provided in supplementary material (see Appendix Table 2). Among these medicine-indication pairs, three main categories of variables were collected and studied for the purposes of this study. These included:

(1) *Previous and final funding decision outcome (i.e.,* prior to and following a resubmission with and without a MEA) classified as (i) favourable recommendation/ decision, including "List" (L) without restrictions/criteria, "List with criteria" (LWC) and "LWC with MEA as part of the listing criteria" (LWCMEA), and (ii) non-favourable or "do not list" (DNL) HTA funding recommendation/decision.
(2) *HTA decision-making determinants,* based on a conceptual framework described elsewhere [29, 30] dividing the HTA appraisal and assessment processes in three main stages and respective variables therein, corresponding to (i) the evidence submitted (*e.g.,* trial characteristics and endpoints used, size of clinical benefit and existence or not of a MEA), (ii) the interpretation of this evidence (*i.e.,* clinical and economic evidence related uncertainties raised), and (iii) Social Value Judgements (SVJs) and system-specific considerations (*i.e.,* dimensions of value that a technology adds, beyond its clinical evidence/ benefit and cost-effectiveness such as innovation, the severity, rarity and unmet need of the targeted disease or process specific characteristics, as well as type of HTA system.
(3) *Time* from previous submission to resubmission with vs. without MEA and to final decision outcome.

Data on the above variables per medicine-indication pair in all study countries were extracted only from the official, publicly available HTA appraisals, which were published in the websites of the respective HTA bodies, namely the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, the National Institute for Health and Care Excellence (NICE) in England, the Scottish Medicines Consortium (SMC) in Scotland and the Dental and Pharmaceutical Benefits Board (TLV) in Sweden. Other relevant sources of data, such as the county councils' group on new drug therapies in Sweden were not searched. Data collection was undertaken between June and December 2018 and data extracted was put in a database stratified by HTA agency.

Data analysis

Funding decision outcome was coded as a binary variable (*e.g.,* positive and negative reimbursement decision), uncertainties and SVJs were coded as binary variables based on whether they have been raised and considered (or not) respectively in the decision-making process, and variables around the evidence submitted were treated as binary (*i.e.,* existence of MEA or not), continuous (*i.e.,* time to final funding decision) or categorical (*i.e.,* type of MEA, type of endpoint etc.) depending on their specification.

For the first part of the analysis Pearson's chi-squared and where applicable, *t*-tests were performed for all HTA decision-making determinants, and the variables driving significant differences between positive and negative funding decision outcomes, were selected for further analysis. Subsequently, we examined the probability of a previously negative funding decision being reversed to positive following a resubmission, based on the key HTA variables of significance identified, including existence/non-existence of MEA (as a proxy for the impact of MEAs on enhancing availability of medicines). As the dependent variable for the first part of the analysis is categorical, a non-linear, cumulative logit model was chosen, namely a binary logit model, to model the probability (P) of a previously rejected technology receiving a favourable funding decision after resubmission ($y_i = 1$) (as opposed to remaining rejected), based on a set of explanatory variables (x_i), under the following Eq. (1):

$$P(y_i = 1 | x_i) = \frac{exp(x_i \beta)}{1 + exp(x_i \beta)} \quad (1)$$

where:

- y is a binary response variable with:
  - $y_i = 1$ if the resubmission resulted in a positive funding decision
  - $y_i = 0$ if the resubmission resulted in a negative funding decision
- $x = (x_1, x_2, \ldots, x_k)$ is a set of HTA explanatory variables hypothesised to influence HTA decision-making, and a distinct explanatory variable on presence of a MEA (or not) as part of the resubmission whereby:
  - x_i is the observed value/outcome of the respective explanatory variables tested and
  - β is a vector of parameters to be estimated and presented as Odds Ratio (OR) (*e.g.,* a one-unit change in the jth variable, x_j, is associated with the OR, $exp(\beta_j)$ [31].

For the second part of the analysis we captured the relationship between the time to final funding decision and existence of a MEA (including both resubmissions with MEA following a previously negative funding decision and resubmissions following expiry of a MEA), as a proxy for the impact of MEAs on market access delays. First, Mann–Whitney U and Kruskal–Wallis (where applicable) tests were performed to assess if there is a statistically significant association between any of the HTA predictors (including presence of a MEA or not) and the average time to final funding decision. Subsequently, given the non-normally distributed, exponential (*i.e., gamma)* distribution of the average time to final funding decision, a gamma generalised linear model with log link function was performed to identify the strength and direction of the above association. This model was employed as the best fit of a regression model for a non-Gaussian distribution, and is described by the following Eq. (2):

$$g(\mu_i) = \boldsymbol{X_i}^{\mathrm{T}} \boldsymbol{\beta} = \beta_0 + \sum_{j=1}^{P} x_{ij} \beta_j \quad (2)$$

where:

- $\mu_i = \mathbb{E}(Y_i)$ is the expected value of the response Y_i given the predictors
- $g(\cdot)$ is a smooth and monotonic link function that connects μ_i to the predictors
- $\mathbf{X}_i^T = (x_{i0}, x_{i1}, \ldots, x_{ip})$ is the i-th observation's known predictor vector with $X_{i0} = 1$ and
- $\boldsymbol{\beta} = (\beta_0 \beta_1, \ldots, \beta p)^{\mathrm{T}}$ is the unknown vector of regression coefficients.

A log-link function was applied in the above to exponentiate the linear predictors as follows:

$$ln(\mu) = \beta_0 + \beta_1 X \Rightarrow \mu = \exp(\beta_0 + \beta_1 \mathrm{X}),$$

where μ is the predicted value of Y given X, $\exp(\beta_0)$ is the effect on the mean of μ when $\mathrm{X} = 0$.

and $\exp(\beta_1)$ is the multiplicative effect on the mean of Y for a one-unit increase in X.

The SPSS® (v.24.0) was used to perform the econometric models and statistical tests, and Excel® 2013 to generate descriptive statistics, where relevant.

Results

Impact of MEAs on reimbursement decisions

Descriptive statistics

Of the 59 resubmissions studied, 1.7% ($n=1$) were reversed to L, 8.5% ($n=5$) were reversed to LWC, 76.3% ($n=45$) reversed to LWCMEA, and 13.5% ($n=8$) remained rejected. Overall, of the 59 previously rejected medicine-indication pairs 86.5% ($n=51$) received a positive reimbursement decision after resubmission and of these, 88.2% ($n=45$) achieved so with a MEA vs. 11.8% ($n=6$) without (see Appendix Table 3). Furthermore, χ^2 tests were also performed to assess if there is any statistically significant association between any of the HTA predictors and/or molecule specific characteristics and the final funding decision following a resubmission. It was demonstrated that a statistically significant difference between positive and negative decisions following resubmission is underscored by the existence or not of a MEA ($p<0.001$) and existence or not of cost effectiveness uncertainties ($p<0.05$) (see Appendix Table 3). All descriptive statistics on the final funding decision outcomes after resubmission and statistical significance (p) of their HTA determinants are provided in supplementary material (see Appendix Table 3).

Binary logit model

According to the χ^2 tests presented above, only the existence or not of a MEA ($p<0.001$) and existence or not of cost effectiveness uncertainties ($p<0.05$) were shown to play a role in determining the funding decision outcome following resubmission of evidence for a previously rejected medicine-indication pair. A number of binary logit models were performed to ascertain the effects of the above variables, in consideration with a combination of other HTA predictors, on determining the likelihood of a previously non-favourable coverage decision being reversed to favourable.[1] The models with the best predictability rate are presented below (Table 1).

[1] The effects of the two variables found by the χ^2 tests to be statistically significant in determining the funding decision outcome following resubmission of evidence for a previously rejected medicine-indication pair (*i.e.,* resubmission with vs. with MEA and resubmission with vs. without cost effectiveness uncertainties) could not be studied together in the same model due to violation in the assumption of multicollinearity Therefore, their relevant effects were studied by including only one of the two variables in different models and subsequently, comparing their contribution and significance between the respective models.

The first model was statistically significant ($\chi^2=30.84$, $p=0.002$), it explained 75.3% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified 94.8% of cases. In this model, a resubmission with a MEA was the only positive predictor of receiving a favourable funding decision instead of non-favourable (OR = 43.36, $p=0.017$). Other HTA parameters included in the model did not have a statistically significant effect in the overall model.

The second model was statistically significant ($\chi^2=30.84$, $p=0.001$), it explained 74.8% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified 94.8% of cases. Resubmission with a MEA was the only positive predictor of a previously negative coverage decision being reversed to positive, although the positive effect was stronger (OR = 63.35, $p=0.012$) compared to the previous model. Additionally, resubmission with a surrogate endpoint was a negative predictor (OR = 0.017, $p=0.03$) of a previous rejection being reversed to a favourable funding decision.

The third model was statistically significant ($\chi^2=25.7$, $p=0.004$), it explained 69.5% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified 94.6% of cases. Resubmission with a MEA was the only positive predictor of a previously negative coverage decision being reversed to positive, and the positive effect was the strongest (OR = 202, $p=0.007$) compared to the previous models. Additionally, in this model there were two negative predictors in achieving a positive reimbursement decision, namely the use of a surrogate instead of clinical outcome and the presence of clinical benefit uncertainties in the resubmitted evidence, with the former being a slightly stronger negative predictor (OR = 0.019, $p=0.042$) compared to the latter (OR = 0.021, $p=0.044$).

The fourth model was statistically significant ($\chi^2=28.73$, $p=0.001$), it explained 70.8% (Nagelkerke R^2) of the variance in the funding decision outcomes and correctly classified 94.8% of cases. In this model, a resubmission without a MEA was a negative predictor (OR = 0.005, $p=0.004$) of a non-favourable decision being reversed to favourable. Additionally, resubmission without clinical benefit uncertainties in the evidence submitted was the strongest positive predictor (OR = 53.608, $p=0.024$) of a previously non-favourable decision being reversed to favourable, followed by resubmission with a clinically relevant endpoint (OR = 50.965, $p=0.037$) as opposed to a surrogate.

Finally, since the presence of cost-effectiveness uncertainties seemed to drive a statistically significant difference between a favourable and non-favourable funding decision outcome following a resubmission (see Appendix Table 3), a number of models were also performed to

Table 1 Binary logit models, predicting the likelihood/ odds ratio (OR) of a previously negative coverage decision being reversed to a favourable funding decision, based on the set of HTA predictors studied in the model

	Model 1		Model 2		Model 3		Model 4[a]		Model 5	
HTA Predictor	***OR***	***p***	***OR***	***p***	***OR***	***p***	***OR***	***p***	***OR***	***p***
HTA agency		.916		1.0						.180
MEA in place	**43.36**	**.017**	**63.35**	**.012**	**202**	**.008**	**.005**	**.004**		
Orphan designation	62.56	.091	91.29	.108	108.5	.178	.004	.065		
Year MA					1.65	.337				
Endpoint										
Surrogate	.024	.063	**.017**	**.030**	**.019**	**.042**	.113	.289	.000	.997
Clinical	.001	.124	.007	.066	.005	.054	**50.96**	**.037**	.000	.997
Study type					2.08	.798	.490	.800		
Uncertainties										
Clinical evidence			2.734	.505	5.67	.367	.403	.567	3.04	385
Clinical benefit	.094	.206	.065	.132	**.021**	**.044**	**53.60**	**.024**	.000	.997
Utilities	.022	.251								
Cost effectiveness									.000	1.0
Social Value Judgements										
Special considerations			.000	.999						
Severity	.731	.905							.477	.705
Unmet need					2.58	.563	.658	.774	.341	.388
Administration advantage	16.39	.998								
Constant	.000	.998	.195	.713	.000	.335	.632	.772	61.4	.999
Model statistics	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*
Likelihood ratio test	31.15	.002	30.84	.001	25.67	.004	28.73	.001	46.53	.000
Hosmer & Lemeshow test[b]	1.76	.972	1.76	.971	5.11	.646	5.76	.568	5.10	.647
Predictability (%)	94.8%		94.8%		94.6%		94.8%		82%	
Nagelkerke R^2	75.3%		74.8%		69.5%		70.8%		54.6%	

[a] Categorical HTA predictors were treated as binary variables taking the outcomes 0 = not raised/not considered/not in place vs. 1 = raised/considered/in place (and 0 = Surrogate vs. 1 = Clinical for the "Endpoint" variable); the second outcome of each HTA predictor was used as a reference category for all models, apart from model 4 where the first outcome was used

[b] The Hosmer–Lemeshow test has been used as a goodness of fit test to indicate how well the data fits each model; it is not provided as a comparison or grading metric between the different competing models, neither it has been used for selecting the best model

HTA Heath Technology Assessment, *MA* Marketing authorization, *MEA* Managed Entry Agreement, *OR* Odds Ratio, *p*: *p*-value

ascertain the effect of the "cost effectiveness uncertainties" variable on reversing previously negative decisions. Only one model (Model 5; Table 1) was found to be of statistical significance ($\chi^2 = 46.538$, $p < 0.001$) but this had a relatively poor predictability and variance explanation (Nagelkerke R^2) rates (82% and 54.6% respectively), compared to the models presented above. Moreover, none of the predictors included in this model, including the "cost-effectiveness uncertainties" variable contributed a statistically significant effect in the model.

Impact of MEAs on time to reimbursement decisions

Descriptive statistics

Medicine-indication pairs with a resubmission following a previously negative funding decision and those with a resubmission/re-evaluation following MEA expiry were studied. Across the 71 re-submissions and re-evaluations studied, 83% ($n = 59$) were resubmissions following a previous rejection and 17% ($n = 12$) were resubmissions/re-evaluations after expiry of a MEA. Average time to final funding decision across all sample was 525 (±386) days, and this was 452 (±364) and 404 (±254) days for medicine-indication pairs approved with vs. without a MEA respectively (Fig. 1; Appendix Table 4).

The Mann–Whitney U and Kruskal–Wallis tests demonstrated that a statistically significant difference in mean time to final funding decision was underscored by the type of HTA agency ($\chi^2 = 23.587$, $p < 0.001$), type of MEA ($\chi^2 = 14.634$, $p = 0.002$) and the SVJs of disease severity ($U = 342.5$, $p = 0.013$) and societal impact ($U = 159.5$, $p = 0.044$). Among the above predictors, the greatest differences in average time to final funding decision existed between the different types of MEAs and

different HTA agencies (see Appendix Table 4). More precisely, in terms of differences underpinned by the different MEA types, it was shown that shortest mean time to final funding decision was 422 (±231) days for medicine-indication pairs with a combination of a financial and outcomes-based schemes, followed by 476 (±407) days for medicine-indication pairs with a financial agreement and amounting up to 957 (±231) days for medicine-indication pairs approved with an outcomes-based agreement (Fig. 1). Finally, in terms of time differences between HTA agencies, the shortest mean time to final funding decision was 342 (±249) days for the Scottish HTA agency, followed by 378 (±242) days for the Australian agency, 837 (±302) days for the Swedish agency and reaching an average of 938 (±559) days for the English agency (Fig. 2). All descriptive statistics on the time (days) elapsed from initial to final funding decision after resubmission, and statistical significance (p) of their HTA determinants are provided in supplementary material (see Appendix Table 4).

Generalised linear models

Gamma generalised linear models were performed to ascertain the effects of several HTA predictors on the average time taken to reach a final funding decision (Table 2).

In the first model, variables with a statistically significant impact on time to final funding decision were HTA agency ($p<0.001$), the use of clinical endpoint in the evidence submitted ($p=0.022$) and the SVJ of societal impact ($p=0.005$). The Australian and Scottish agencies were associated with a reduction in time to final funding decision, as was the use of a clinically relevant endpoint in the evidence submitted. Absence of considerations around the societal impact of the technology in question increased the time to final funding decision, whereas the presence of a MEA did not have a statistically significant contribution in the overall model.

The second model examined the impact of HTA agency and the type of MEA on the average time to final funding decision. Variables with a statistically significant contribution in the model were HTA agency ($p=0.007$), the type of endpoint used in the clinical evidence submitted ($p=0.034$), clinical evidence uncertainties ($p=0.038$) and the SVJ of societal impact of the technology in question ($p=0.002$). Submissions with a clinically relevant endpoint were associated with a reduction in time to decision-making. Raising considerations around the societal impact of the technology in question and raising uncertainties around the clinical evidence submitted had a positive impact (*i.e.*, increase) on time to final funding decision. Finally, the type of MEA did not have a statistically significant contribution in the overall model.

Controlling for HTA agency, the third model examined the role of the type of MEA on time to final decision. Variables with a statistically significant contribution in the model were the type of MEA ($p<0.001$), the HTA agency ($p=0.007$), uncertainties around the study design ($p=0.019$) and the clinical evidence submitted ($p=0.038$), and the SVJ of the societal impact of the technology ($p=0.002$). Submissions with an outcomes-based agreement increased the time to decision-making. Raising considerations around the societal impact of the technology and raising uncertainties around the clinical evidence submitted increased the time to final funding decision, whereas presence of study design uncertainties had a negative impact (*i.e.*, decrease) on time to final funding decision.

Discussion

We conducted an analysis of oncology medicines previously rejected from reimbursement, to understand if any MEAs implemented upon evidence resubmission of the above medicines had an impact on enhancing the availability of and timely access to these medicines. Our results suggest that presence of MEAs has the potential to improve the availability of new oncology therapies, by increasing their likelihood for reimbursement if they have previously been rejected. However, presence specifically of outcomes-based agreements can cause significant time delays in reimbursement decision-making and hence, time to access.

Only a few studies have provided a quantitative evaluation of the impact of MEAs on access to medicines [12, 22, 32–34]. In Italy, it was shown that the introduction of MEAs contributed substantially to an improvement in patients' access to cancer medicines [12, 34], whereas in Finland and South Korea it was estimated that about 20% and 60% of patented medicines respectively were granted reimbursement due to the presence of a MEA, and of the 60% reimbursed in the later, 23% were previously rejected [32, 33]. Similarly, in Australia, MEAs have been implemented as part of the government's plan to enhance access to medicines, estimating that MEA implementation can help achieve coverage for about one-third of new medicine-indication pairs [35].

It has also been suggested that reimbursement with a MEA, regardless of its type, can improve time to patient access [22, 36]. We found that, medicine-indication pairs approved with a MEA exhibited longer average time to final reimbursement decision, although only the presence of an outcomes-based agreement specifically (as opposed to presence of a MEA in general) was associated with a statistically significant increase of about 480 days to final funding decision. Comparable findings have been

Table 2 Generalised linear models, predicting the association between a set of HTA predictors and time to final reimbursement decision

	Model 1		Model 2		Model 3		Model 4	
HTA Predictor	B	*p*	B	*p*	B	*p*	B	*P*
HTA agency[a]		***.000***		***.007***				***.000***
NICE	-.030	*.926*	.245	*.528*			-.018	*.955*
PBAC	**-1.019**	***.001***	-.709	*.053*			**-.986**	***.001***
SMC	**-.815**	***.003***	-.453	*.226*			**-.790**	***.004***
MEA in place	-.179	*.416*						
Type of MEA				*.453*		***.000***		
Financial			-.100	*.706*	-.145	*.569*		
Outcomes-based			.379	*.299*	**.897**	***.008***		
Orphan designation	.088	*.618*			.287	*.132*		
Endpoint		*.054*		*.146*		*.756*		*.085*
Surrogate	-.301	*.205*	-.340	*.132*	-.057	*.815*	-.324	*.143*
Clinical	**-.612**	***.022***	**-.562**	***.034***	-.098	*.690*	**-.559**	***.033***
Uncertainties								
Study design	-.262	*.118*	-.285	*.089*	**-.361**	***.019***	**-.329**	***.043***
Clinical evidence	.247	*.114*	**.336**	***.038***	**.482**	***.002***	.221	*.150*
Clinical benefit	-.212	*.238*	-.189	*.288*				
Cost effectiveness	.050	*.934*	.052	*.929*			.041	*.943*
Social Value Judgements								
Severity	.176	*.378*	.136	*.502*	-.221	*.173*	.136	*.490*
Societal impact	**.623**	***.005***	**.690**	***.002***	**.628**	***.007***	**.603**	***.004***
Constant	17.13	*.841*	-28.67	*.735*	5.62	*.000*	3.54	*.965*
Model statistics	X^2	*p*	X^2	*p*	X^2	*p*	X^2	*p*
Likelihood ratio test	45.30	*.000*	47.01	*.000*	34.70	*.000*	43.43	.000
Deviance (Value/df)	.407		.406		.430		.395	

[a] The "HTA agency" was treated as a multinomial variable taking the outcomes 0 = NICE, 1 = PBAC, 2 = SMC, 3 = TLV, whereby the last outcome (i.e., TLV) was used as a reference category for all models. All other categorical HTA predictors were treated as binary variables taking the outcomes 0 = not raised/not considered/not in place vs. 1 = raised/considered/in place (and 0 = Surrogate vs. 1 = Clinical for the "Endpoint" variable); the second outcome of each HTA predictor was used as a reference category for all models

B Regression coefficient, *df* Degrees of freedom, *HTA*, Heath Technology Assessment, *MEA* Managed Entry Agreement, *p*: *p*-value, PBAC: Pharmaceutical Benefits Advisory Committee, *NICE* National Institute for Health and Care Excellence, *SMC* Scottish Medicines Consortium, *TLV* Dental and Pharmaceutical Benefits Board

reported by a study of oncology medicines in the Italian setting, which showed an increase in the national time to market of about 150 days for medicines approved with an outcomes-based agreement compared to those approved with a financial scheme [34]. This finding is not surprising; the complexity of outcomes-based contracts in comparison to more simple financial schemes, their negotiation process can often be burdensome and time consuming for manufacturers and payers. Additionally, the collection of additional evidence and if required, the future monitoring and re-assessment of the product, as well as the need to align interpretations of the collected and required data between the different stakeholders involved in reimbursement decision-making may introduce further delays [10, 37, 38].

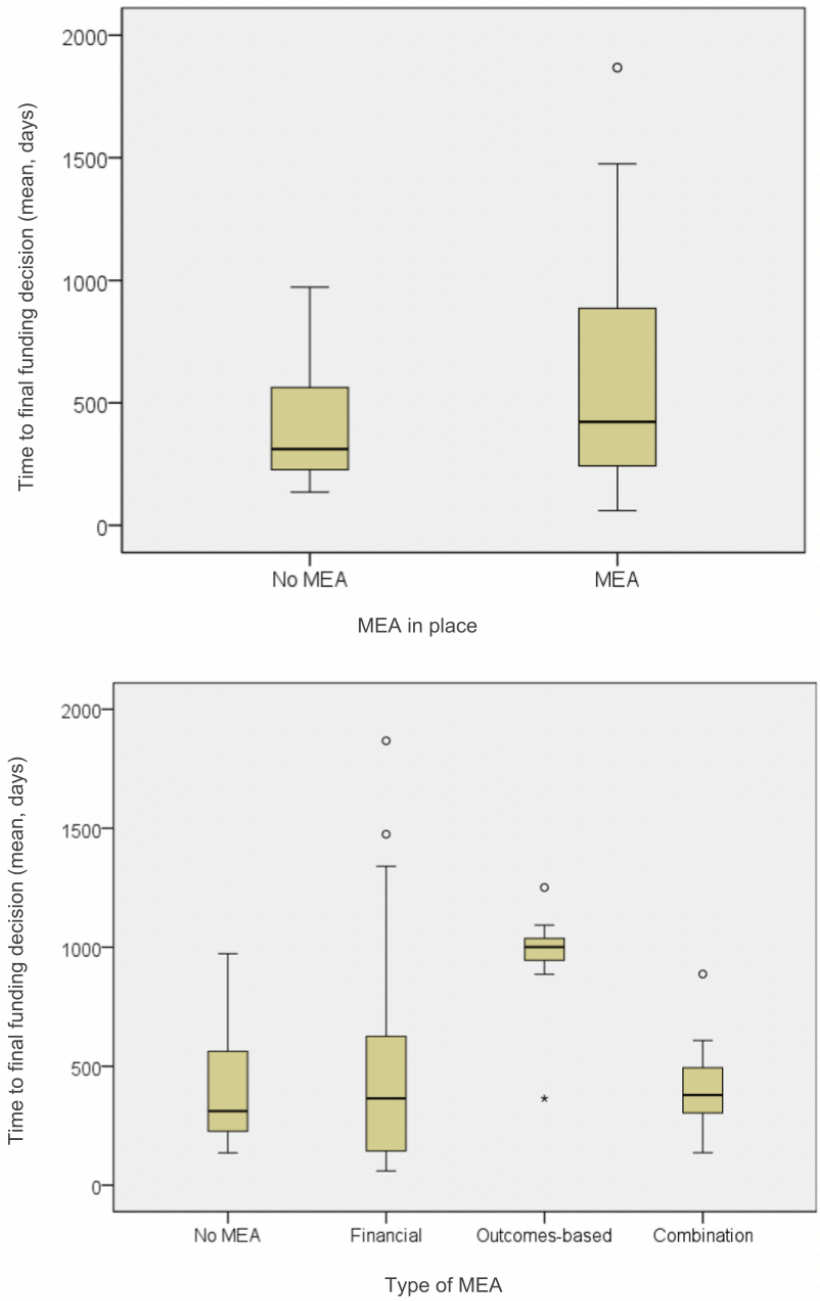

Fig. 1 Average time from initial to final funding decision following resubmission without vs. with MEA, and the respective time exhibited by resubmissions with different MEA types. Key: Time represents average days from first submission to final funding decision after resubmission; Horizontal lines indicate medians; Boxes indicate interquartile range; Single points indicate outliers

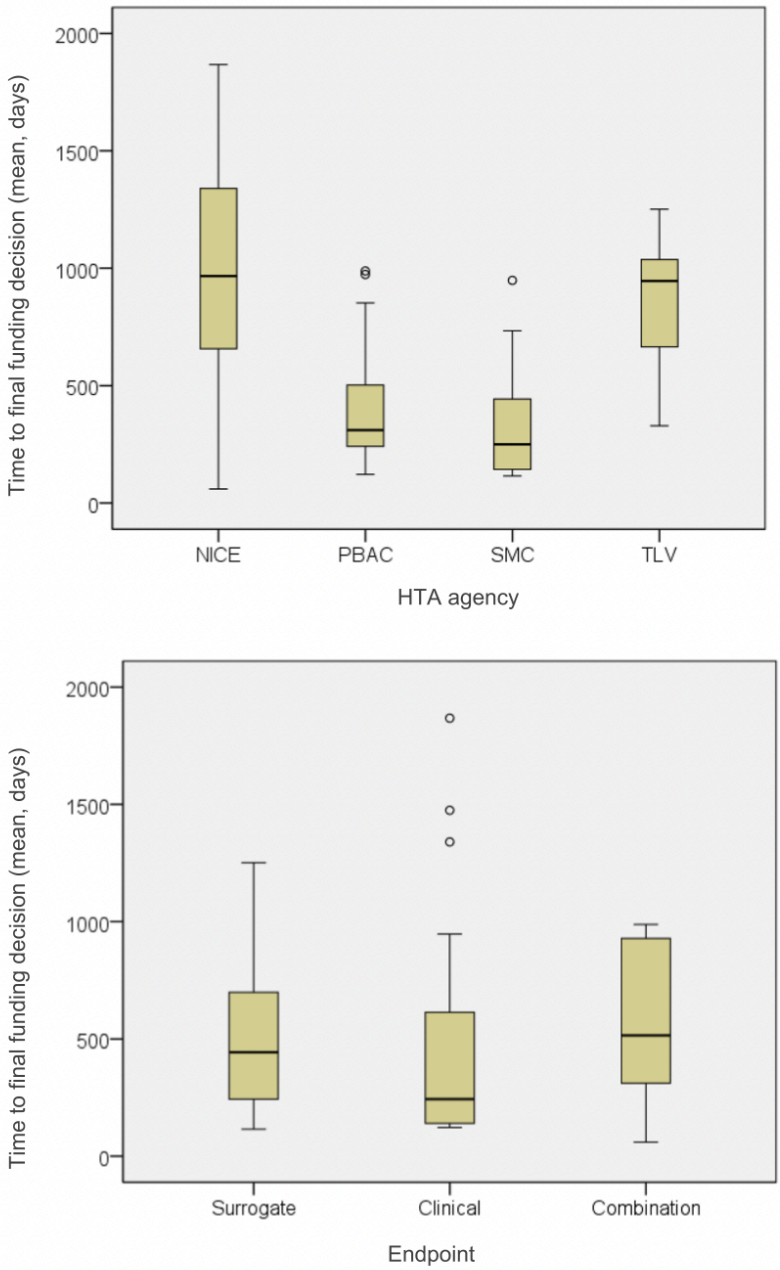

Fig. 2 Average time from initial to final funding decision after a resubmission, between the different HTA agencies and types of endpoints. Key: Time represents average days from first submission to final funding decision after resubmission; Horizontal lines indicate medians; Boxes indicate interquartile range; Single points indicate outliers. Note: PBAC: Pharmaceutical Benefits Advisory Committee (Australia), NICE: National Institute for Health and Care Excellence (England), SMC: Scottish Medicines Consortium (Scotland), TLV: Dental and Pharmaceutical Benefits Board (Sweden)

Discrepancies in the conclusions of existing literature around the impact of MEAs on time to access may be explained on the grounds that regardless of their type, MEAs can only improve time to market access if negotiation processes are well structured and based on sufficient preparation ahead of time such that the proposed schemes have a clear rationale and truly address the uncertainties raised by the competent authorities assessing the technology in question [39]. Growing concerns have been expressed in the literature that MEAs are increasingly used as "an operational tool" to agree on commercial price negotiations and confidential discounts rather than as a tool for managing the actual risk arising from immature data [40]. Therefore, even simple financial schemes need to be implemented such that they meaningfully address the uncertainties that a new therapy presents with, rather than implemented simply as a tool to achieve lower prices. More importantly, when financial schemes are used solely as a cost containment process on top of other cost containment policies, they can add little benefit in terms of outcomes for patients and increase delays in the long term [41]; for example, they might grant access to interventions which might prove cost-ineffective in the long-run with the consequence that these technologies will be delisted after expiry of the agreement and eventually harm patient access, if there is no comprehensive risk management plan in place, in case of delisting [42].

The findings arising from this study suggest that presence of a MEA per se may not always guarantee a favourable funding decision and/or faster access to oncology medicines. There are additional HTA decision-making variables which determine the final reimbursement decision and the time taken to final decision. More precisely, this study highlights that successful and timely access to oncology therapies is also subject to submission of clinical evidence which presents with minimal uncertainties and is primarily based on clinically relevant instead of surrogate endpoints. Literature has also underscored the importance that HTA decision-makers place on submitting evidence with clinically meaningful outcomes relating to mortality, morbidity, and quality of life [43]. Even though the use of surrogate measures in cancer medicines' trials is not associated with an HTA decision to reject a medicine [44], a gap between the surrogate endpoint and the final clinical endpoint creates additional uncertainty for decision-makers. Consequently, in this case, decision-makers often need to engage in additional validation processes to extrapolate findings beyond the submitted evidence to estimate the expected true benefits for patients and health systems, and this translates in further delays on the time required to reach a final reimbursement decision [45, 46].

Additionally, it was demonstrated that uncertainties around the study design had a statistically significant contribution in the model explaining time to final reimbursement decision. This was not surprising given that the trial design is often taken into consideration by some HTA agencies, such as SMC where for example, an active-controlled trial is preferred over a placebo one [47]. In the generalised linear model, the "study design uncertainties" variable was negatively associated with time, potentially demonstrating that this specific type of clinical uncertainty might lead to a confident, outright rejection and thus, shorten time to decision-making. This is in alignment with the results presented elsewhere [30], demonstrating that the presence of clinically relevant uncertainties is not typically associated with the flexibility to enter into negotiations for restricted reimbursement.

Finally, it was demonstrated that time to final funding decision can also be influenced by the HTA agency involved in the decision-making process. In our study, the Australian and Scottish HTA agencies exhibited significantly shorter timelines to final funding decision compared to the Swedish and English agencies. Comparable findings have been reported elsewhere. For example, a study assessing the delays introduced by HTA processes across countries in their coverage decisions for oncology medicines, showed that in England median time from EMA regulatory approval date to NICE decision was 783 days, as opposed to an average of 231 days required for SMC decisions [48]. Similarly, more recent figures estimated the mean length of time from EMA authorization to HTA funding decision for oncology and all products at 436 and 335 days respectively for NICE, compared to for example 389 and 262 days respectively for TLV [49]. Overall, it has been reported that NICE exhibits relatively higher timelines to final funding decision compared to other European HTA agencies [49]. On the contrary, as demonstrated in this study, Australia has been reported to have the fastest median timelines from TGA approval to HTA recommendation at national level (127 days) compared to other jurisdictions, including England (386 days), Scotland (293 days) and Sweden (217 days) [50].

Relevant literature suggests that these differences in time to decision-making are shaped by agency specific characteristics and procedures. Specifically for oncology medicines, evidence demonstrates that divergent HTA methodologies across countries underline differences in the time required for new products to enter the market when considering the average time between date of regulatory approval and date of funding decision [51]. For example, since 2011, the TGA/PBAC parallel process has been introduced in Australia and this played an important role in streamlining the regulatory and

reimbursement processes, leading to a significantly shortened time gap between marketing authorisation and first funding decision [50, 52]. On the contrary, in England, delays may often occur due to NICE specific modalities such as switching to the Cancer Drugs Fund during the review process [53]. Additionally, in England, time delays due to NICE procedures related specifically to MEA implementation processes have been reported. For example, the PAS Liaison Unit (PASLU) process may delay submissions to NICE, whereby specifically for Single Technology Appraisals the existence of a PAS can result in an average time delay of up to four months compared to Multiple Technology Appraisals with a PAS [53, 54]. In other markets, there is greater flexibly in the negotiation of these agreements with the result that this can eventually accelerate the decision-making process [55], such as in Italy where presence of an agreement typically leads to shorter time to patient access [12, 22]. The above further highlights that time delays associated with the presence of MEAs can be attributed to agency specific procedures for the implementation and negotiation of MEAs [56].

This is the first study to date to conduct a post-implementation evaluation of MEAs across countries, to quantify their impact on two key healthcare system policy goals, namely availability of and timely access to medicines. Since the on-going literature debate on the weaknesses of MEAs is primarily generated by the poor and inconclusive evidence as to whether these agreements have managed to meet their objectives, this study addresses important literature gaps on structured, impact assessment studies of MEAs. More importantly, the conclusions arising from this study can facilitate future policy relevant research around the sustainability of MEAs as an effective funding modality that can be applied for greater and faster access to medicines. Another strength of this study is the holistic approach taken in studying the HTA factors that determine coverage decision outcomes and timelines, whereby we accounted for the role of MEAs as well as the interconnected impact of both uncertainties, SVJs and clinical evidence characteristics, as opposed to existing literature that studies the impact of evidentiary uncertainties or MEAs individually.

Our study is not without limitations. First, accuracy of the models performed would have benefited from a larger sample size; although this study provides a good basis for future analyses, it is recommended that replication of similar analyses in the future could increase the sample size, possibly by including assessments of medicines for other therapeutic areas.

Second, we recognize that the cost-effectiveness and "added value" profile of the studied medicine-indication pairs is not equivalent within and across countries and hence, the need to apply a MEA would not always be equally applicable for all medicine-indication pairs studied. To address the limitation of having an unbalanced panel as our study sample, the impact of MEAs on promoting availability was studied only on medicine-indication pairs that were previously rejected, such that a common selection criterion (*i.e.,* previously cost-ineffective profile) would be established for all medicine-indication pairs in the analysis.

Third, accounting for the reversibility of negative to positive funding decisions as a proxy to availability of medicines is an assumption made for the purposes of simplicity in running the binary logit model. This assumption is a potential limitation of the analysis, since a positive reimbursement decision does not always translate in equal availability of the respective medicine; beyond a favourable funding decision other, macro-economic, country specific and healthcare system specific factors determine the actual availability of and patient access to medicines [55]. Similarly, accounting for the time to final funding decision as a proxy to timely access to medicines was an assumption made for simplicity in running the generalised linear model. This is also a potential limitation of our study, given that (as described above) a positive reimbursement decision does not always reflect ready access to the respective medicine, regardless of how promptly the funding decisions might have been reached. Finally, in the above context, it is also important to recognise that binding HTA outcomes (e.g., Sweden) typically correspond to funding decisions, whereas non-binding HTA outcomes (e.g., England, Scotland, Australia) correspond to recommendations, which are not always translated into funding decisions. However, given that the (non-binding) HTA recommendations in England, Scotland and Australia have been found to largely shape the final funding decisions in these countries [57], we treated the HTA outcomes across all study countries as "funding decisions"; based on that, the terms "recommendation", "decision" and "decision outcome" all refer to "funding decisions" and have been used interchangeably throughout the text.

Finally, none of the MEAs included in this analysis were implemented across multiple indications of a specific molecule and/or were part of a MYMI agreement. As such, we acknowledge that in our impact assessment study we do not account for and/or explicitly discuss the potential benefits in patient access arising from the novel approach of applying MEAs across multiple indications and years. This approach arises as an increasingly promising strategy to achieve faster and broader patient access by reducing the administrative burden associated with conducting the same

upfront evaluation process for each indication of the same product, while aligning price to the value that the product offers for each indication without the need for indication-based pricing [58]. Nevertheless, the introduction of MYMI agreements is also subject to country specific legal arrangements which can contribute to unnecessary delays in the negotiation process. Therefore, understanding the extent to which MYMI agreements can enhance the positive impact of traditional MEA mechanisms on greater and more timely access to medicines, especially in oncology, arises as a priority topic for future impact assessment studies on MEAs.

Conclusions

Despite the application of MEAs being heterogenous across countries and often associated with high administrative burden and potential time delays, MEAs can still contribute to enhanced accessibility at the level of individual countries by allowing patient access to medicines that would not be reimbursed otherwise. However, presence of a MEA itself does not necessarily grant a timely and favourable funding decision as other factors such as the quality of clinical evidence submitted, and the type of endpoint used therein are also paramount in shaping the final funding decision and the respective timelines to decision-making. Of course, even though MEAs offer a higher likelihood for positive reimbursement, the question remains on whether the technologies approved with a MEA add true value in outcomes for patients and healthcare systems, whether they truly address the decision-making uncertainties characterising a technology and whether outcomes-based schemes measure meaningful clinical markers from the payers' and patients' perspective. Overall, it arises that only if applied strategically, MEAs can become a mainstay in the future of medicine availability, in reducing the financial burden for healthcare systems and in allowing faster access to new, innovative medicines.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12913-022-08437-w.

Additional file 1: Appendix Table 1. Study countries, their HTA agencies and respective perspective taken into HTA decision- making. **Appendix Table 2.** Information about all medicine-indication pairs (per country) studied in this analysis. **Appendix Table 3.** Descriptive statistics on the final funding decision outcomes after resubmission and statistical significance (p) of their HTA determinants across all sample. **Appendix Table 4.** Time (days) from initial to final funding decision after resubmission, and statistical significance (p) of their HTA determinants across all sample.

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Authors' contributions
OE and PK contributed to the conception of this paper. OE designed the study, conducted the statistical analysis, and wrote the main manuscript text. All authors made substantial contributions to the interpretation of results, reviewed, and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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