The London School of Economics and Political Science

Entry to market of new medicines and medicines treating rare diseases: Issues arising from value assessment processes in the European Union, the United Kingdom and Canada

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Declaration

I certify that the thesis I have presented for examination for the MPhil/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).

I declare that my thesis consists of 77,497 words.

Statement of co-authored work

The first study (chapter 6) was co-authored by Mrs. Erica Visintin (London School of Economics and Political Science) and Dr. Panos Kanavos (primary Ph.D.supervisor at the London School of Economics and Political Science). The study was published in *PharmacoEconomics – Open*. The article was recognised by *PharmacoEconomics – Open* as one of the five most downloaded articles in the journal.

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Authors contribution: AMF conceived the study. AMF and EV collected the data. AMF analysed and interpreted the findings. AMF drafted the paper. EV and PK commented on all versions of the manuscript. All authors read and approved the final manuscript. PK provided guidance throughout the study. AMF is the guarantor.

The second study (chapter 7) was co-authored by Mrs. Bregtje Kamphuis (London School of Economics and Political Science) and Dr. Panos Kanavos (London School of Economics and Political Science). The study has been published in *The European Journal of Health Economics*.

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Authors contribution: AMF conceived the study. AMF and BK conducted the scoping review. AMF and BK designed the Delphi panel and collected the data. AMF analysed and interpreted the findings. AMF drafted the paper. BK and PK commented on all versions of the manuscript. All authors read and approved the final manuscript. PK provided guidance throughout the study. AMF is the guarantor.

The thirst study (chapter 8) was single authored by the Ph.D. candidate. The study was published in *Social Science & Medicine*.

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Authors contribution: AMF conceived the study. AMF collected and analysed the data. AMF interpreted the findings. AMF drafted and revised the manuscript. AMF is the guarantor.

The fourth study (chapter 9) was co-authored by Dr. Panos Kanavos (London School of Economics and Political Science). The study was published in *Value in Health.*

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Authors contribution: AMF conceived the study. AMF collected and analysed the data. AMF designed the regression model and interpreted the findings. AMF drafted and revised the manuscript. PK read and approved the final manuscript. PK provided guidance throughout the study. AMF is the guarantor.

Other relevant work

During my PhD, I co-authored other peer-reviewed articles and reports on pharmaceutical regulations and policies, listed below. Even though these documents are not contributing directly to the main chapters of this thesis, the work is relevant to the broader policy topics presented in this document.

- Kamphuis, B., Fontrier, A.M., Gill, J., Efthymiadou, O., Salyga, H. and Kanavos, P., 2021. Access to medicines in Europe delays and challenges for patient access: delays and challenges for patient access.
- Kamphuis, B., Fontrier, A.M., Haig, M., Politopoulou, K., Salyga, H., Gentilini, A. and Kanavos, P., 2021. Development of policies to increase headroom for innovation in Egypt and the Kingdom of Saudi Arabia.
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Statement on editorial help

I can confirm that my thesis was copy edited for conventions of language, spelling and grammar by my supervisor Panos Kanavos and my friend Olivier Wouters.

Abstract

To achieve access to new medicines within markets, manufacturers need to first receive marketing authorisation and subsequently seek funding from healthcare insurance. In countries where access to healthcare is free, the allocation of finite resources poses substantial challenges. Increasingly in these settings, health technology assessment (HTA) is used to inform funding decisions whilst seeking to promote healthcare financial sustainability and macro- and micro-economic efficiency. Variations in access to medicines can occur as countries implement HTA differently. These variations are further highlighted in medicines used to treat rare diseases, known as orphan medicines. Due to their high prices and high uncertainty about their clinical benefit, some HTA bodies have specialised assessment frameworks for orphan medicines to safeguard equity by considering additional dimensions of value beyond clinical- and/or cost-effectiveness.

In this thesis, I explored how differences in HTA systems and processes may contribute to access variations of new medicines and medicines for rare diseases across settings. First, I outlined a conceptual framework that showed how HTA is operationalised; I also mapped HTA systems across 32 countries. Second, through a Delphi panel of European stakeholders, I identified features of HTA that facilitate access to new medicines. Third, I observed whether the presence of specialised assessment frameworks might translate to more favourable funding recommendations for and timely access to orphan medicines by comparing two settings where these medicines are treated differently. Finally, I evaluated whether HTA recommendations are aligned with funding decisions for orphan medicines in a decentralised healthcare setting where the HTA body has an advisory role.

The main contributions of this thesis are fivefold: (i) it develops a conceptual framework that allows comparisons of HTA systems regardless of how well-developed they are; (ii) it generates evidence on the performance of HTA features, looking at HTA holistically, against different access metrics; (iii) it examines whether efforts to optimise access to orphan medicines across the market access pathway may translate into more favourable reimbursement decisions; (iv) it studies whether HTA recommendations are followed in funding decisions; and (v) it provides recommendations on what features of HTA need improvement to optimise patient access.

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List of acronyms

A	Agree
ANOVA	One-way analysis of variance
ASMR	L'amélioration du service médical rendu
ATC	Anatomical therapeutic chemical
ATU	Temporary authorisation programme
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR-T	Chimeric antigen receptor T cells
CDEC	Canadian Drug Expert Committee
CDF	Cancer Drug Fund
CDR	Common Drug Review
CED	Committee to Evaluate Drugs
CMA	Conditional marketing authorisation
CI	Confidence interval
D	Disagree
DDD	Defined daily dose
DNL	Do not list
EMA	European Medicines Agency
EO	Executive Officer
EPAR	European public assessment report
ERP	External reference pricing
EU	European
EUnetHTA	European network of health technology assessment
F	Funded
FDA	Food and Drug Administrator
FIMEA	Finnish Medicines Agency
GDP	Gross domestic product
HSTP	Highly specialised technologies program
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ID	Identification
IMPACT-HTA	Improved methods and actionable tools for enhancing HTA
INAHTA	The International Network of Agencies for Health Technology Assessment

INESSS	Institut National d'Excellence en Santé et en Services Sociaux
IQR	Interquartile range
IRR	Inter-rater reliability
L	Listed
LwR	Listed with restrictions
MA	Marketing authorisation
MCDA	Multiple-criteria decision analysis
MEA	Managed entry agreement
MHRA	Medicines and Healthcare products Regulatory Agency
N/A	Not applicable
NF	Not funded
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOC	Notice of compliance
NOC/c	Notice of compliance with conditions
OECD	Organisation for Economic Co-operation and Development
OOP	Out-of-pocket
OR	Odds ratio
PACE	Patient and clinician engagement
PAS	Patient access schemes
pCODR	pan-Canadian Oncology Drug Review
pERC	pan-Canadian Oncology Drug Review Expert Committee
PICO	Patient, intervention, comparison, and outcome
PICo	Population/patient/problem, interest/intervention, and context
QALY	Quality-adjusted life years
R&D	Research and development
RCT	Randomised controlled trials
RWE	Real-world evidence
SA	Strongly agree
SD	Strongly disagree
SMC	Scottish Medicines Consortium
SMR	Le service médical rendu
UK	United Kingdom
US	United States
WHO	World Health Organisation

WTP Willingness-to-pay

1 Introduction

Medicines have transformed our lives. When sick, they allow us to fight serious or life-threatening diseases, return to our day-to-day activities and improve our overall health and quality of life. In short, medicines have given us hope. This hope, though, is often associated with high costs due to ever-increasing pharmaceutical prices and is conditional upon many factors that may or may not be within our reach. These include the place we were born and currently reside, our diagnosis, our personal and our country's wealth and the level of medical coverage offered by our healthcare system. For example, spinal muscular atrophy is a rare genetic condition affecting infants or children. Paediatric patients with this condition have moving difficulties, they cannot eat, swallow, or breathe without support (1). Until recently, there was no cure for this disease. Now, all this could change, with just one curative injection. However, this therapy comes with a price tag of GBP 1.79 million (USD 2.1 million) per dose, making it one of the most expensive medicines currently in the pharmaceutical market. Patients in most European countries or Canada may have access to this medicine free of charge due to universal health coverage. However, in the United States (US), where healthcare coverage is not universal and is highly fragmented, patients' families may have to face catastrophic costs (2).

Disparities in access to medicines, namely their availability, affordability and the time they are available within a market, are often seen in the case of rare diseases, which affect approximately less than one individual in 2,000 people of the general population (3). Medicines used to treat rare diseases, known as orphan medicines, are usually associated with very high prices and small patient populations (4,5). Whilst universal health coverage, provided in some settings, can potentially guarantee access to such treatments and give patients hope, it may result in enormous implications for the affordability and the sustainability of the healthcare system.

Direct and indirect measures have been introduced across healthcare systems to (i) control rising pharmaceutical prices and (ii) help decision-makers decide which therapies to offer to patients and be paid for by the system, what the level of cost-sharing should be, if any, and what criteria should inform coverage decisions. Blunt supply-side interventions, such as external reference pricing (which applies a benchmark list price to medicines based on prices of other countries) or one-off price cuts, might seem appealing to local authorities for achieving macro-economic efficiency. However, knock-on effects, such as launch sequencing strategies from manufacturers causing access delays and limiting medicines' availability, have been observed in countries where these measures are in force (6–10). Strict pricing policies have been criticised extensively for not accounting for the value and the potential therapeutic benefit of medicines, and, thus, not adequately rewarding manufacturers for developing innovative new products (8).

1.1 Health technology assessment

The international network of agencies for health technology assessment (INAHTA) has described health technology assessment (HTA) as "*a tool to review technologies and provide evidence of the value these technologies can deliver to patients and their families, health system stakeholders, and to society more broadly"* (11). HTA has been introduced in numerous high-income countries, and, more recently in middle-income countries (12). HTA allows payers and decision-makers to make informed, evidence-based decisions on what therapies are worth funding using public budgets, and it provides a valuable reimbursement tool for healthcare insurance bodies during pricing negotiations with manufacturers. HTA targets both macro and micro-economic efficiency and further covers both the supply- and the demand-side of medicines by identifying parts of the population that will benefit the most from using certain treatments (13).

Funding recommendations published by HTA bodies are usually based on whether new medicines offer a therapeutic benefit in comparison to alternative treatments and are good value for money (13). Unlike other pricing and reimbursement policies, HTA is able to account for other socioeconomic factors, such as high unmet need and disease rarity (14). In addition, HTA allows multiple key stakeholders such as healthcare providers, manufacturers, clinicians, and patients, to be involved in the HTA process and/or in decision-making (15). In this way, HTA can capture different value dimensions beyond the clinical- and/or cost-effectiveness of a product while accounting for the input of all involved parties.

As with every other policy intervention, HTA comes with some limitations. Timely access to medicines can be seriously impacted by potentially long evaluation processes. And differences in HTA practices including discrepancies in the accepted evidence or the model followed by the HTA body can lead to access variations across settings (16). Differences in the way HTA is operationalised, where HTA lies within the healthcare system and the organisation of the healthcare system itself (i.e.: whether decisions are made at national, regional or provider level or how budgets are allocated) can further impact the extent to which HTA recommendations are used in funding decision-making (15,17,18).

To mitigate some of these limitations, efforts are being made both at national and supranational levels to improve and harmonise HTA processes within and across settings. For instance, the European Commission has stated its intention to implement a new HTA regulation, which will join clinical benefit assessments across European (EU) member states. This new regulation aims to improve access to innovative medicines and eliminate duplication of efforts (19). However,

evidence is limited on how HTA can be improved in a holistic way and whether efforts such as the new HTA regulation can be successful in improving access to innovative medicines.

Access issues and inequalities caused by variations in HTA processes are especially prominent for certain therapies, such as medicines for life-threatening conditions or medicines targeting areas of high unmet need (16,20,21). Some countries assess medicines of high-societal impact as any other medicine, while others have in place specially designed assessment frameworks or criteria to allow explicit consideration of additional dimensions of value beyond clinical- and cost-effectiveness (e.g.: the end-of-life criteria applied to medicines offering an extension to life or the highly specialised technologies program which evaluates medicines treating very rare conditions, both implemented by the English HTA body).

Nowhere have these tensions been felt more acutely than in the orphan medicine space. As the example of the curative treatment of spinal muscular atrophy demonstrates, orphan medicines are not only carrying high price tags but are often associated with high clinical uncertainty due to small sample sizes and lack of comparative treatments (5,13,22–24). Therefore, at HTA level, orphan medicines do not always meet established cost-effectiveness thresholds, especially when other societal dimensions are not routinely considered during value assessment processes, which could potentially allow for the acceptance of higher uncertainty, leading to unfavourable recommendations of funding. Nevertheless, the presence of dedicated funds for highly innovative medicines and medicines of high unmet need in some settings makes the association between HTA recommendations and funding of orphan medicines more complex to understand.

1.2 Thesis objectives

Focusing on market access to medicines, rather than patient access which may depend on many other factors that are not easily quantified and controlled for, this PhD thesis aimed to better understand three broad policy questions: (i) How does the implementation of HTA differ across settings and how these variations are reflected in access to medicines? (ii) Considering finite budgets, should very expensive treatments, whose costs run in the millions of dollars and have potentially significant clinical benefits, be funded at public expense? and (iii) Should decision- and policymakers treat orphan medicines differently than non-orphan medicines to optimise their access within markets?

To explore these overarching issues, this thesis focused on the use of HTA as an approach to resource allocation. It further explored whether differences in HTA systems and processes translate into variations of new medicines and medicines for rare diseases across settings. It is important to highlight that this thesis studies access to better medicines defined as treatments with

better clinical- and cost- effectiveness in comparison to current available treatments and/or therapies that address an unmet need, rather than access to more medicines regardless of their value.

My research objectives were to (i) understand how differences in the way HTA systems are set up and operationalised within settings can influence the relationship between HTA and funding decisions; (ii) identify features of HTA that facilitate access to improved medicines within markets; (iii) explore whether specialised assessment frameworks for orphan medicines may improve market access, and; (iv) test whether HTA recommendations translate into funding decisions in a decentralised healthcare system where HTA has only an advisory role, meaning that the uptake of HTA into funding decision-making is unclear.

To note, this thesis does not aim to prove causality in any of the included studies. Due to the nature of pharmaceutical policy and the numerous factors that shape it, the thesis places a greater emphasis on descriptive and qualitative analyses aiming to gain a better understanding of the multifaceted nature of HTA and its role in the market access pathway.

1.3 Structure of the thesis

Chapter 2 sets the scene for this thesis by providing relevant information about current trends in the healthcare and pharmaceutical sector.

Chapter 3 presents the scoping review of the relevant literature to this thesis. In this chapter, evidence from the literature is summarised against the study endpoints. These include the definition and metrics of access to medicines, the regulatory pathway that medicines follow to reach markets, HTA-related drivers of access variations and information on how processes along the access pathway differ for orphan medicines in certain settings.

Chapter 4 identifies gaps in the current literature and outlines the research objectives of this thesis along with an analytical framework showcasing how each paper addresses the research questions.

Chapter 5 summarises the methods used for data collection and data analysis throughout the thesis.

Chapters 6 to 9 present the four main studies of this thesis. In brief each chapter includes the following: Chapter 6 studies the similarities and differences in HTA systems across 32 countries by designing an analytical framework which enables systematic comparisons. Chapter 7 uses the Delphi technique to elicit opinions and perspectives of key European stakeholders on what features of HTA can facilitate or impede access to clinically- and cost- effective medicines. Chapters 8 and 9 focus on access to orphan medicines within markets. Specifically, chapter 8 examines HTA recommendations and time to market access for medicines treating rare diseases

in two settings (Canada and Scotland), where these medicines are treated differently both in MA and HTA levels. Chapter 9 studies the agreement of HTA recommendations and outcomes of pricing negotiations with funding decisions for orphan medicines in the Canadian province of Ontario.

Chapter 10 summarises the main contributions of this thesis, discusses broader policy implications and suggests areas for future research.

2 The healthcare and pharmaceutical sector

Every country faces tough decisions on how annual budgets should be allocated across different sectors, public services, and programmes. If annual spending exceeds the projected budget this might lead to public debt and budget deficit, and, ultimately, can threaten the sustainability of the system (25). Deciding how budgets are allocated across different sectors can be very challenging and may vary based on the policy objectives the country is trying to achieve. Budget allocation decisions account for the long-lasting values the country believes in but also reflect worldwide policy goals. For instance, initiatives targeting environment protection, low carbon emissions and climate change prevention have been increasingly discussed across high-income countries, with many wealthy countries making this their first policy priority (26). Even though the protection of our environment is essential to ensure the continuation of humankind, for some low- and middle-income countries, these issues might seem like "rich country problems". The COVID-19 pandemic brought once again into the spotlight that health is what all nations have in common, regardless of how high or low their gross domestic product (GDP) is. With mortality rates skyrocketing, national health services struggling to cope and local economies plunging into recession with lockdowns and other measures restricting economic growth, COVID-19 became a global invisible enemy (27–29).

Despite the outbreak of the pandemic, health is undeniably an area of massive importance and high priority worldwide. A healthy nation is a wealthy nation as Nduka Obaigbena once said (30). According to the World Health Organisation (WHO), health is a human right and countries should ensure without discrimination *'the right to the highest attainable standard of health'* to their population (31). This means that countries are legally bounded to ensure access to timely, acceptable, and affordable health services of high quality through the allocation of '*maximum available resources'* (31).

Universal health coverage, as outlined in the WHO's 2030 agenda for sustainable development, is one way to ensure that all people regardless of their age, race or income have access to essential healthcare services and medicines (32). Universal health coverage provides access free of charge or at a low cost without leaving patients to suffer financial hardships (32). Canada, Australia and EU member states offer their citizens the right to universal health in the spirit of equal access despite individual socioeconomic profiles (33).

Unlike, other healthcare systems which rely on out-of-pocket spending and private health insurance coverage, allocation of budgets in systems with universal health coverage, usually relying on taxes or social insurance contributions, should be thoroughly orchestrated. As healthcare budgets are set prospectively, they aim to control spending, reduce the financial risks of the

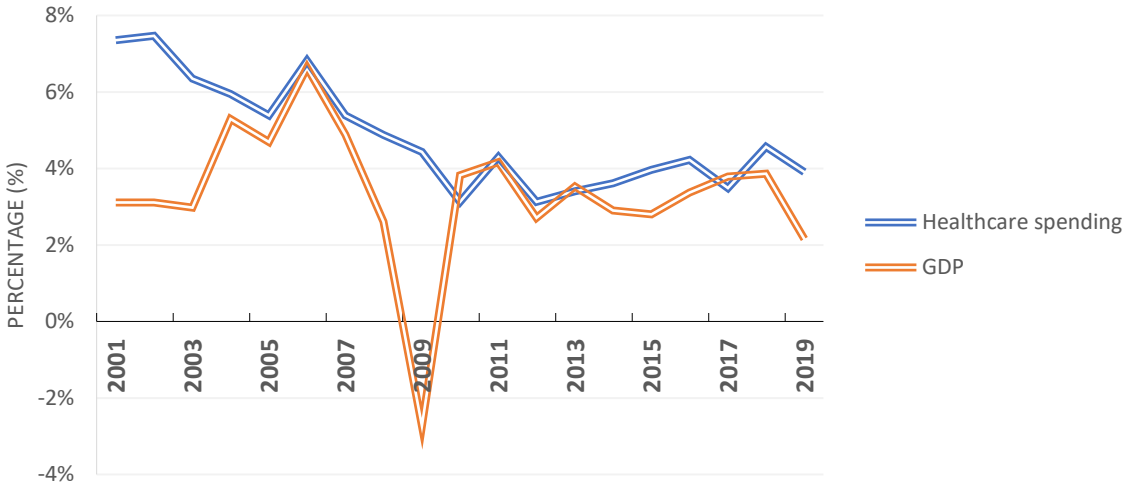
healthcare system, and promote fiscal and economic sustainability (34). Depending on the organisation of the healthcare system, budgets can be national or regional and sometimes can be disease-specific or product-specific (34). Regardless of their scope, setting up budgets in healthcare is usually accompanied by other demand- and supply-side measures which aim to promote efficiency and wise allocation of resources.

The objective of this chapter is to describe expenditure trends in the healthcare and pharmaceutical sector and discuss the main drivers of pharmaceutical spending. It highlights the need for policy tools, such as HTA, which optimise the allocation of finite resources, ensure the 'right' treatments are available to patients, and contribute to a sustainable healthcare environment.

2.1 Healthcare spending

According to the Organisation for Economic Co-operation and Development (OECD), the amount of money nations spend on healthcare each year fluctuates with time due to variations in the growth of the nation's economy and of the health spending (35). Figure 1 shows that annual growth in healthcare spending was not always proportional to the annual GDP growth, at least across OECD members[1].

Figure 1: Annual growth in per capita health spending and annual growth in per capita GDP (PPP, current international USD) in OECD members



Source: *Data were extracted by the World Bank database (2022). (Accessed on 8 August 2022).*

[1] OECD includes 38 members: Australia, Austria, Belgium, Canada, Chile, Columbia, Costa Rica, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, South Korea, Latvia, Lithuania, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States. In this thesis, all the countries of interest are a member of OECD.

Over recent years, before the pandemic outbreak, the ratio of healthcare spending to GDP in OECD members was stable with average spending of 8.8% of countries' GDP. US and Germany had the highest ratio of healthcare expenditure to GDP followed by France, Canada, and the United Kingdom (UK), amongst others, which spent more than 10% of their GDP on healthcare (35).

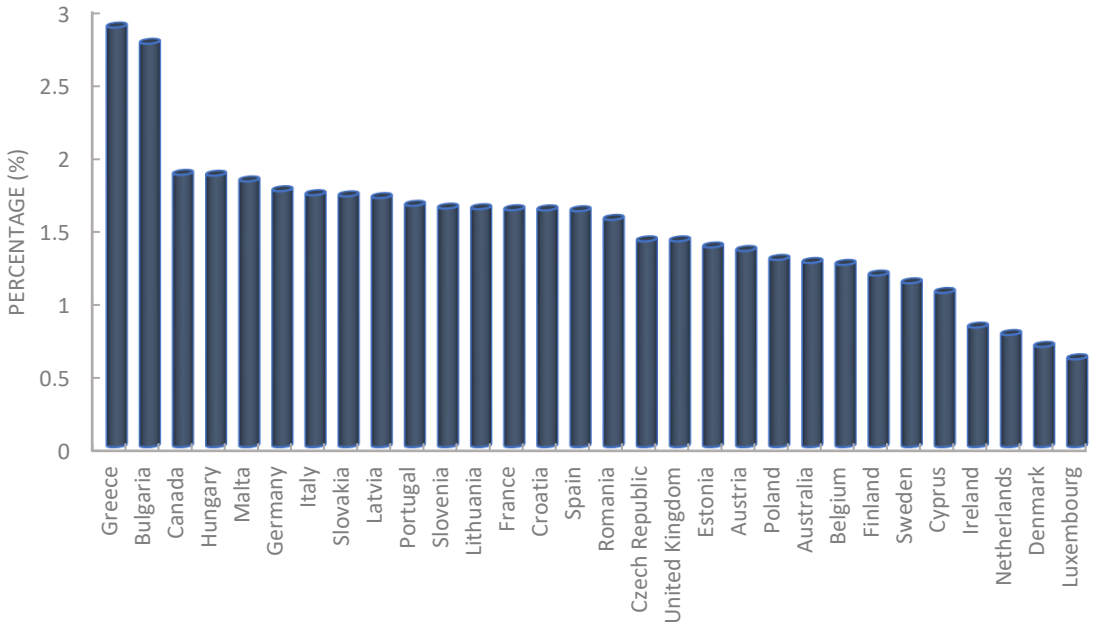
The most common reported drivers of rising healthcare spending in high-income countries are advances and innovation in medical technologies, the ageing of the population, the rise of non-communicable diseases as well as higher expectations of patients from the health services provided by local healthcare systems (33,36,37). Evidence has shown that there is a positive association between public spending, lower mortality rates and increased life expectancy (38).

2.2 Pharmaceutical spending

Across OECD countries, in 2019, financing of retail medicines was made predominantly by public budgets collected either through general taxation or social insurance schemes. Public budgets have covered up to 56% of total spending in some countries while in others, such as France, the percentage rose to 80% (39). On average, OECD countries have spent 1.8% of their total GDP on retail pharmaceuticals including prescription medicines and over-the-counter products and spends on average USD 589 per capita (39). However, OECD classifies costs of inpatient medicines under the inpatient care indicator, therefore, the ratio of the actual pharmaceutical spending, including inpatient medicines in relation to GDP might be much higher. Figure 2 shows the total retail pharmaceutical spending as a percentage of countries' GDP based on 2020 data across EU member states, the US, the UK, Canada, and Australia. Large disparities were seen, with countries such as Greece and Bulgaria spending almost 3% of their GDP on retail pharmaceuticals while others, such as Denmark and the Netherlands, spent less than 1% of their GDP. These disparities might be explained due to differences in their regulatory environment, variations in the implemented supply- and demand-side measures to control increasing pharmaceutical prices, differences in the country's negotiating power and divergent levels of generic medicines' uptake.[2]

[2] A generic medicine has the same active substance, quality, safety, and efficacy as an already authorised branded medicine after loss of its patent.

Figure 2: Total pharmaceutical spending as a share of GDP in 2020 across EU member states, the UK, US, Australia, and Canada



***Note**: Data for Australia and Malta are from 2019 since data from 2020 were not available.*

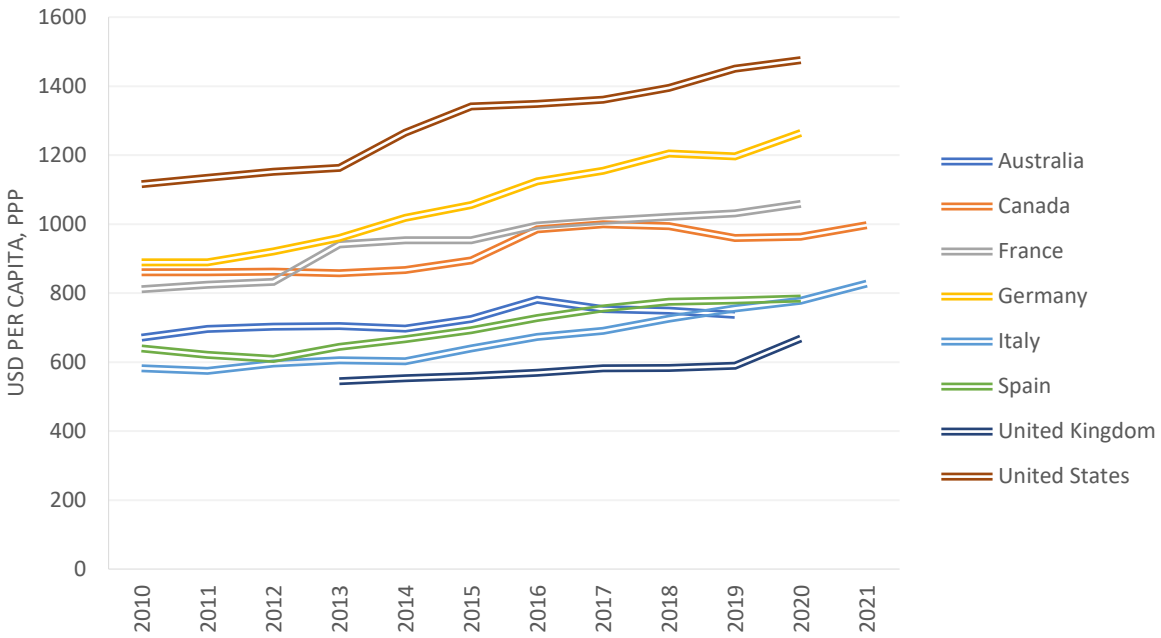
***Source:** OECD (2022), Pharmaceutical spending (indicator). DOI: 10.1787/998febf6-en (Accessed on 18 July 2022).*

Interestingly, a report by IQVIA focusing on medicines' expenditure of both retail and hospital products in relation to healthcare spending from 1995 to 2020 in 11 large pharmaceutical markets[3] reported that spending on medicines was on average only 15% of the total healthcare spending with this percentage being stable for most of the last 20 years (40). However, pharmaceutical spending per capita has increased in OECD countries in recent years as seen in Figure 3. New data from OECD indicated a significant growth in pharmaceutical spending in 2020 compared to data from 2019 (39), while data from the 2000s showed that pharmaceutical spending was increasing at a steady rate.

Evidence on whether rising pharmaceutical spending has a direct impact on health outcomes is conflicting: Earlier studies showed that pharmaceutical spending compared to non-pharmaceutical one improved health outcomes to a greater extent (41,42) while a more recent study failed to confirm this (43).

[3] These included: Australia, Brazil, Canada, France, Germany, Italy, Japan, South Korea, Spain, the UK, US.

Figure 3: Total pharmaceutical spending per capita (PPP, current international USD) between 2010 to 2021 in selected OECD countries



Source: *OECD (2022), Pharmaceutical spending (indicator). DOI: 10.1787/998febf6-en (Accessed on 18 July 2022).*

Belloni et al. (2016) discussed that growth in pharmaceutical spending depends, first, on market dynamics which represent the supply of and demand for medicines, and second, on regulatory policies used to control pharmaceuticals' prices and help with reimbursement decisions that can either contain or exploit these dynamics (6). As previously mentioned, advances in the pharmaceutical sector and the introduction of highly innovative treatments were other key contributing factors to increasing pharmaceutical spending seen in recent years (33,36,37,40). These are discussed in the sub-section below.

2.3 Innovation as a driver of pharmaceutical spending

Healthcare innovation is achieved when new services and health technologies have a clear clinical benefit in comparison to existing ones (44). Pharmaceutical innovation is not only limited to new active substances but also includes treatments that offer a new route of administration that is more comfortable for patients (45). Theoretically, innovation in healthcare and the pharmaceutical sector not only improves the health of the population but improves the quality of life of patients, their families and carers and has the potential to increase life expectancy (45). The advantages novel therapies could bring can contribute to savings for the healthcare system and provide additional benefits to society by decreasing the use of healthcare resources and reducing disease-related direct and indirect costs (45).

Despite the potential advantages of innovation, concerns remain amongst policymakers about restrictive budgets, increasing demand for medicines and rising associated costs with research and development (R&D). Evidence showed that the development of a new active substance may take up to 15 years of research and can cost up to USD 2.7 million (46). DiMasi et al. (2016) reported a sharp increase in the cost of bringing a new active substance to market, from an average of USD 1.1 billion in 2003 to an average of USD 2.8 billion in 2013 (46). A more recent study reported, using publicly available data, that the estimated median capitalised R&D cost per product was USD 1.1 billion for products approved by the US Food and Drug Administration (FDA) from 2009 to 2018 (47). Looking at these figures, one can wonder whether these high R&D costs of novel therapies are justifiable (6,48,49), whether financial incentives offered to manufacturers for R&D purposes are fair as well as whether R&D costs can explain the high price tags seen in novel therapies (6,48–51).

In the literature, the financial strain of novel therapies has been widely reported. Evidence has shown that the entry of new and innovative high-cost therapies has contributed significantly to the growth of pharmaceutical spending (6,36,39,52–55). An OECD study from 2016 outlined how innovative therapies were expected to increase pharmaceutical spending by 50 to 100% in the upcoming years due to increasing availability and high associated costs (6). Another study highlighted that in only one year, with the entry of two new novel treatments for hepatitis C in the US, the net real spending for hepatitis C medicines only increased by USD 7 billion and accounted for about 40% of the total increase in all US pharmaceutical spending in 2014 (52). Earlier evidence on cancer care treatments from Europe showed that the high number of patients suffering from cancer and the price of innovative medicines have driven public expenditure on cancer treatments to around 6 to 8% of the total healthcare budget (56). In 2017, global spending on cancer medicines rose to USD 133 billion compared to USD 96 billion in 2013. Interestingly, cancer spending was heavily concentrated on 35 medicines which were mostly used by fewer than 10,000 cancer patients (57). Finally, increasing concerns have been raised regarding the affordability of healthcare systems when providing funding for the new chimeric antigen receptor T cells (CAR-T) therapies, which cost up to USD 350,000 per infusion, despite their ground-breaking results in the treatment of relapsed or refractory B-cell malignancies (58,59).

2.3.1 Orphan medicines

In theory, spending on orphan medicines should be low in proportion to national pharmaceutical spending, however, recent therapeutic advances coupled with incentives for manufacturers to invest in R&D of orphan medicines substantially has increased this ratio (60). According to data from the annual reports of the European Medicines Agency (EMA), the proportion of orphan

medicines approved compared to total MA approvals was about 20.7% in 2021 and 22.7% in 2020 (61,62).

A study which looked at shares of public spending in eight European countries showed that there was an increase in the proportion of expenditure on orphan medicines, ranging from 2.0% to 6.2% in 2013 and from 2.5% to 6.9% in 2014 (63). A more recent study which looked at data over time across different countries confirmed that there has been a substantial growth in national spending on orphan medicines (64). Another study reported that spending on orphan medicines as a proportion of GDP was not higher in lower-income European countries compared to the ones with higher income, although the authors highlighted that the high-income European countries showed better access to these medicines (63).

Evidence has shown that revenues generated by manufacturers of some orphan medicines can be over USD 1 billion a year (65–68). For example, Hollis (2019) studied the case of two orphan medicines indicated for the treatment of cystic fibrosis and reported that their manufacturer was expected to earn substantial profits as a return on investment which were as high as USD 21.1 billion (65).

Overall, prices of medicines with an orphan designation can be much higher compared to prices of medicines indicated for non-rare diseases. When comparing the prices per defined daily dose, orphan medicines had a median price of EU 138.56 compared to the median price for non-orphan medicines which was EU 16.55 (69). In the US, in 2014, the average list price per person for an orphan medicine was almost USD 119,000, compared to USD 23,000 for non-orphan medicines (70).

Therefore, with very high prices and the fact that more and more companies are increasingly developing therapies for rare diseases, healthcare efficiency issues have been brought into the spotlight (5,6,64,71).

2.4 Summary

Increases in healthcare and pharmaceutical spending are mainly driven by the entry of novel therapies and medicines for rare diseases. And they are further intensified by market dynamics and regulatory policies. Even though increased healthcare expenditure has been associated with better health outcomes, the association between rising pharmaceutical spending and improved health outcomes has not been yet established. This signals the need for implementation of efficient and effective supply and demand side measures to control the entry of novel therapies and containment of increasing pharmaceutical prices and costs. To achieve these objectives, reward innovation and ensure a sustainable and efficient healthcare system, implementation of policy interventions, such

as HTA, which assess whether the clinical benefit of a new technology outweighs the associated costs while considering additional value dimensions, is paramount (72).

3 Scoping review

Despite issues around limited budgets and increasing healthcare and pharmaceutical spending, we cannot deny that the pharmaceutical sector has changed our lives over time. However, access to medicines is far than equal across countries. Variations are not only observed in countries with different socioeconomic profiles but also in countries that share similar ones. Through a scoping review of the recent literature, the aim of this chapter was to identify evidence of market access variations in Australia, Canada, EU member states and the UK, and explore the reasons why these variations are observed with a focus on HTA systems. Specifically, the objectives of the scoping review were the following:

1. Explore how access to medicines has been defined in the current literature;
2. Identify different regulatory stages in-patent medicines undergo to achieve market access, after their development and before they reach patients;
3. Explore how HTA processes and procedures can contribute to access variations;
4. Observe differences in the presence of orphan medicine regulations and dedicated value assessment frameworks across the study countries and explore their implications on access to orphan medicines.

3.1 Methods

A modified version of the PICO (patient, intervention, comparison, and outcome) framework was used to develop the broader research objective of the scoping review (73,74). According to the modified version (known as PICo), the questions of the scoping review were designed following the below PICo (population/patient/problem, interest/intervention, and context) criteria.

Table 1: PICo criteria followed in the scoping review

Population/patient/problem	***Interest/intervention***	***Context***
Access including access metrics, focusing predominately on market access	▪ Regulatory stages of a medicine's access pathway ▪ HTA ▪ Regulations and dedicated assessment frameworks for orphan medicines	Australia, Canada, EU member states and the UK

The timeline of the scoping review was set from January 2012 until July 2022 to identify recent literature but also capture changes in pharmaceutical policies and regulations over the last decade. The scoping review included both peer-reviewed papers, identified through MEDLINE via

PubMed database, and reports from the grey literature identified from the websites of the WHO, OECD, the United Nations, and the European Commission. The search was limited to the English language and the following keywords were used to search through titles and abstracts: *'access'; 'availability'; 'health technology assessment'; 'HTA'; 'value assessment'; 'appraisal'; 'assessment; 'regulatory process';' marketing authorisation'; 'market approval'; 'pricing'; 'reimbursement'; 'fund'; 'funding'; 'listing';' coverage'; 'risk sharing'; 'managed entry'; 'managed access'; 'market entry'; 'specialised pathways'; 'specialised process'; 'dedicated process'; 'rare disease'; 'orphan'*. The search keywords did not include initially any country-specific restrictions to ensure that search results from a wide geographical range would have been identified. However, evidence from Australia, EU member states, the UK and Canada was included. These countries were prioritised since they were studied in the main chapters of this thesis.

The initial screening of the search results was completed through a review of titles and abstracts. Papers and reports were included when at least one of the above terms used as keywords was mentioned and evidence was from the studied countries. Literature focusing on medicines was included, while evidence on medical devices and other health technologies was excluded. Subsequently, search results were screened in full text to identify evidence that was relevant to the scoping review objectives (1-4), mentioned above. Other relevant articles identified from the reference lists of the identified papers were included in the scoping review. Finally, additional searches were conducted on the websites of relevant competent authorities, including regulatory agencies, HTA agencies and local ministries of health.

The initial search resulted in 125,555 references. To minimise the initial search results, the search was limited to papers/reports on medicines and to the study countries only which led to 1,096 references. Full text was available for 1,070 references. No duplicates were detected. These references were screened in their titles and abstracts for relevance. The final number of relevant references used in this scoping review was 177. The evidence was summarised in a narrative way for each of the following endpoints: (i) access to medicines; (ii) stages of medicines' access pathway; (iii) HTA variations and their impact on access; (iv) orphan medicine regulations and dedicated assessment frameworks for medicines treating rare diseases and their implications for access.

3.2 Access to medicines

Various definitions and metrics of access exist, however, all of them focus on common dimensions that need to be accomplished to ensure better health of the population and sustainability of healthcare systems.

3.2.1 Definition of international organisations

According to WHO, access to medicines is an essential step to achieving universal health coverage. In WHO's definition, access to medicines is considered successful when access is affordable and the medicines are safe, of high quality and effective (75). In the United Nation's Sustainable Development Goal 3, the importance of access to medicines was raised using similar metrics to the ones used by the WHO (76). A study by the European Parliament highlighted that successful access to medicines is not only limited to broader availability and affordability of medicines but through the availability of the "right" products to patients (i.e.: medicines with a considerable added value compared to existing treatments), especially in an era when market dynamics are driven by commercial interests (77). While the resolution adopted by the European Parliament in 2017 on 'EU options for improving access to medicines', suggested that Europe should "*guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies"* to achieve a sustainable system and encourage innovation (78).

3.2.2 Definition in peer-reviewed literature

In the peer-reviewed literature, access to medicines usually focused on (i) availability of medicines within markets in terms of marketing authorisation (MA) and (ii) access to medicines that were publicly reimbursed, looking at HTA recommendations (79–82). Successful access was defined as *"the enabling of individuals in their financial and physical ability to obtain and receive relevant care",* which is highly dependent on national pricing and reimbursement policies (80–83). The Lancet's Commission on Essential Medicines Policies discussed five areas of focus for optimal access to medicines: (i) public reimbursement of essential medicines; (ii) affordable medicines; (iii) use of safe and high-quality medicines; (iv) quality use of medicines; and (v) development of medicines in areas of unmet need (84). Timely access to medicines, defined as the time between MA and publication of HTA recommendation or HTA submission, has also been studied (79,85,86). However, the majority of these studies focused on the time dimension only, rather than looking at access in a holistic way.

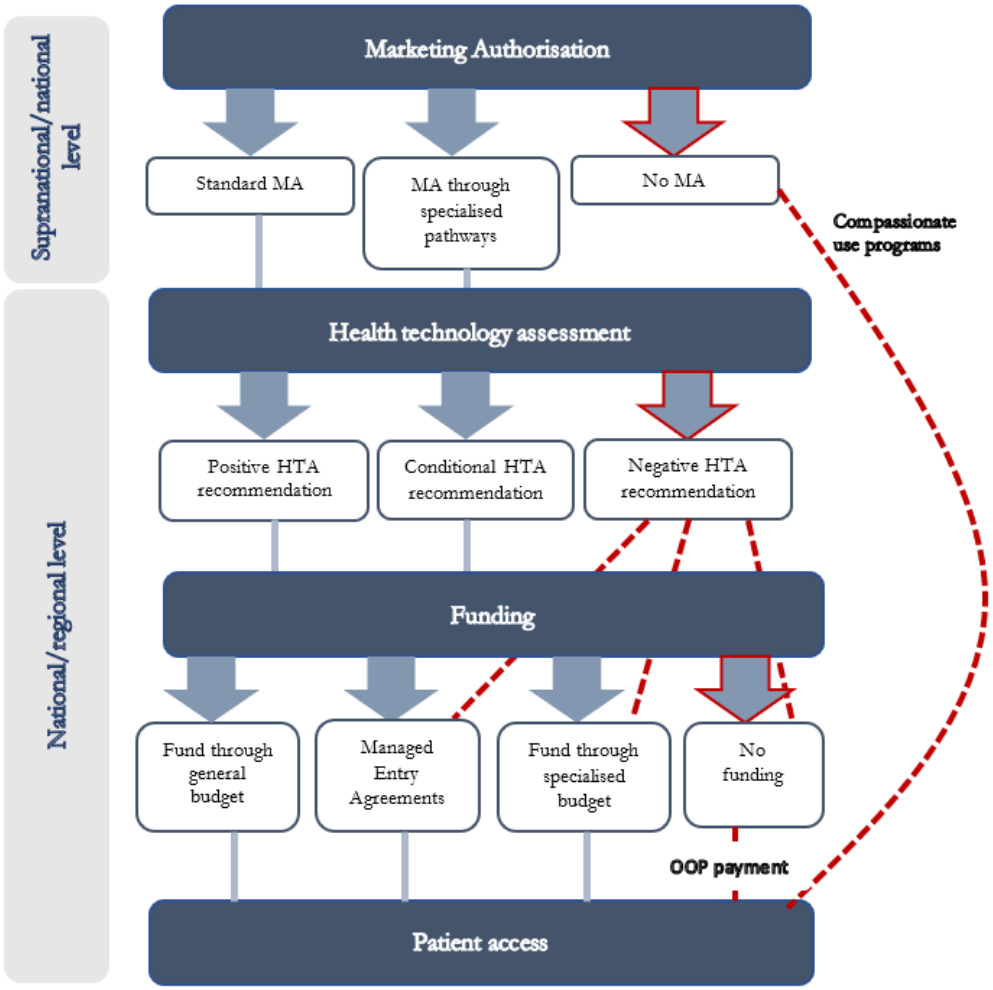
Various endpoints related to both supply- and demand-side policies have been explored to identify barriers to access to medicines in high-income countries. These include, but are not limited to, issues around regulatory processes for MA, pricing and reimbursement policies, health technology assessment systems, the structure of the healthcare system, delivery of healthcare services, supply chain of medicines, physicians' prescribing patterns and patients' co-payments (82,83,87–93).

3.3 The access pathway of medicines

There are multiple stages that in-patent medicines undergo before they reach patients: manufacturers need to apply for a MA, then national healthcare systems usually assess the value of the medicine, and national or regional healthcare insurances decide whether they will reimburse the medicine through public funds (77). All these stages need to be successful to ensure that patients have timely access to the 'right' treatments (77,85,87,92).

Figure 4 showcases the main stages of a medicine's access pathway in systems with universal health coverage and at which level they occur. The stages discussed below predominately relate to access to improved medicines within markets, which is the focus of this thesis. It is important to note that patient access may further depend on other system-related factors such as prescribing practices and supply chain and distribution, which were not captured in the figure below.

Figure 4: The stages of a medicine's access pathway



Notes: *All the stages are described in detail in the sub-sections below.*

OOP payment= out-of-pocket payment by patients.
Compassionate use programs refer to programs that allow the use of medicines that have not been granted a MA and are in development. Patients might be eligible to have access to these products if they suffer from conditions with no alternative treatments or if they cannot participate in clinical trials (94).
Source: *The author.*

3.3.1 Marketing authorisation

Once a new active substance has been successfully developed, manufacturers need to apply for MA approval to the respective regulatory agency for their product to become available within markets (77,95–98). The EMA is the regulatory agency of European Union member states including Iceland, Norway and Lichtenstein, Therapeutic Goods Administration (TGA) is the Australian agency, Health Canada is the Canadian agency, and post-Brexit, the Medicines and Healthcare products Regulatory Agency (MHRA) is the competent authority for MA approvals in the UK. All these regulatory agencies are responsible for assessing the benefit-risk profile of new medicines to ensure that the benefits outweigh the risks based on a product's efficacy and safety profile (77,92,95,96). Whilst submission of robust evidence on the safety profile and the clinical benefit of the assessed medicine is required by regulatory agencies (96), MA assessments do not have to be comparative (i.e.: medicines under evaluation do not have to showcase relative clinical benefit against other available treatments)(99).

3.3.1.1 Specialised pathways for MA

Regulators may face trade-offs between the robustness of submitted clinical evidence at the time of MA assessment and the timely availability of medicines within markets, which is known as the "evidence vs. access conundrum" (100). The level of flexibility on how much uncertainty regulators are willing to accept varies across agencies, resulting in discrepancies in MA decisions across markets (96,101–104). Over the last couple of decades, several changes in the regulations of regulatory agencies have taken place to incentivise manufacturers to develop medicines, especially in areas of high need. Specialised pathways for MA approval have been introduced to expedite the availability of medicines that address high unmet need and/or are intended to treat life-threatening conditions (96,105,106). These pathways were mainly seen in two instances: (i) when additional data were required by the regulatory agency post-marketing approval or in cases when manufacturers were unable to provide comprehensive clinical data, or (ii) when MA assessments were performed in shorter timeframes than standard procedures (34,96,98).

Table 2 summarises the available specialised pathways for MA in the Europe Union, Canada, the UK and Australia.

Table 2: Specialised pathways for MA approval in the European Union, Canada, and the UK

		European Medicines Association (EMA)			Health Canada			Medicines and Healthcare products Regulatory Agency (MHRA)			Therapeutic Goods Administration (TGA)		
		Scheme	***Description***	***Eligible medicines****	***Scheme***	***Description***	***Eligible medicines****	***Scheme***	***Description***	***Eligible medicines****	***Scheme***	***Description***	***Eligible medicines****
Aim of specialised pathway	***Shortened timelines***	Accelerated Assessment	Shorten review for MA	Major public interest Therapeutic innovation Medicines considered as 'priority' based on the PRIME scheme	Priority Review	Shorten review for MA	Serious, life-threatening or severely debilitating diseases: a) there is no alternative therapy b) significant improvement in the benefit/risk profile over existing products.	150-day assessment	MA review and decision are published within 150 days after submission	All high-quality new MA submissions	Priority review	Shorten review for MA	New medicine or with a new indication treating a serious or life-threatening condition. The medicine should show a favourable comparison against existing therapies and a major therapeutic advance.

		European Medicines Association (EMA)			Health Canada			Medicines and Healthcare products Regulatory Agency (MHRA)			Therapeutic Goods Administration (TGA)		
Limited clinical data		Conditional MA	MA for medicines with less limited clinical data than normally required given that additional data will be provided once acquired	Seriously debilitating or life-threatening diseases	Notice of Compliance with conditions (NOC/c)	MA with the condition that the manufacturer will undertake additional studies	Serious, life-threatening or severely debilitating diseases: a) there is no alternative therapy b) significant improvement in the benefit/risk profile over existing products	Conditional MA	MA when comprehensive clinical data are incomplete and expected to be available soon	Same eligibility criteria as the European scheme	Provisional approval	MA based on preliminary clinical data where there is the potential for a substantial benefit to patients.	New medicine or with a new indication treating a serious or life-threatening condition. The medicine should show a favourable comparison against existing therapies and a major therapeutic advance. Manufacturers should indicate a plan to submit comprehensive clinical data
		Exceptional Circumstances	MA when the applicant is unable to provide comprehensive clinical under normal circumstances	Orphan medicines				Exceptional Circumstances	MA, when comprehensive data cannot be produced due to the treated condition being rare or collection of data, is not possible or is unethical	Same eligibility criteria as the European scheme			

Notes: ** Criteria of eligible medicines as seen in the websites of the respective regulatory authorities* (107–113).

Other available pathways exist in Europe, Canada, and the UK to support the development of novel therapies such as the 'rolling review process' for MA in the UK and the PRIME in the EU. Even though these schemes are important to optimise the availability of medicines, they do not necessarily expedite standard assessment timelines or apply different assessment criteria for MA compared to those used in the standard MA assessment. Hence, they were not outlined in the table.

Source: *The author based on publicly available information published by the respective regulatory authorities.*

3.3.1.2 Implications for access to medicines

The presence of specialised pathways for MA seemed to enable the availability of medicines and timely market access (in terms of availability of medicines without accounting for their reimbursement) in some settings (96,102,114). However, discrepancies have been reported on the use of specialised MA pathways for the same medicines across regulatory agencies (20,96,106,115,116). In addition, there has been criticism by policymakers that the presence of these schemes may enable the availability of medicines within markets that only show modest efficacy and low added therapeutic value (99,106,117–119). Despite efforts to facilitate market access to medicines of high unmet need at regulatory level, evidence of the success of these efforts at later stages of a medicine's access pathway (i.e.: positive HTA recommendations and granting funding at the local level) was limited in the current literature (see sub-section 3.4.4 for more information).

3.3.2 Health technology assessment

Once manufacturers receive MA for their products, they need to secure coverage at national or regional level if they want their products to be reimbursed by the public healthcare system. At this stage, medicines may be subject to intense scrutiny by HTA agencies, which often consider clinical and economic evidence to provide recommendations for funding (17,87,92). Currently, all EU member states, Canada and the UK have in place HTA processes to either assist with, or in some cases determine, funding decisions (15).

3.3.2.1 The assessment process

Assessment of the submitted clinical and economic evidence is usually performed either by a separate committee within the HTA body or an independent agency (87). At HTA, unlike the MA stage, manufacturers are required to submit a dossier which showcases the clinical benefit and, depending on the system, the cost-effectiveness of their product against a comparator(s) (87). The comparator(s) might be either chosen by the manufacturer or by the HTA body. Usually, the comparator is the current standard of care within a local healthcare setting, however, if this is not available, a scenario of no treatment or use of best supportive care might be chosen. The requirements and standards of the submitted evidence used during assessment differ across HTA bodies (87): Some HTA bodies might accept only clinical evidence from randomised controlled trials (RCTs) with active comparators and others might be more flexible and accept indirect comparisons or real-world evidence (RWE) from observational studies (120). In terms of economic assessment, cost-utility is the most widely used analysis. It measures the incremental cost-effectiveness ratio (ICER) which accounts for incremental costs and benefits in terms of

quality-adjusted life years (QALYs) (17,121). For a medicine to be deemed worthy of funding through public funds, its ICER should not exceed the maximum willingness-to-pay (WTP) threshold set by the HTA body. Depending on the body, WTP thresholds can be either rigid or flexible (17). However, it is important to note that despite the wide use of the ICER ratio, there has been a lot of criticism about QALY's ability to capture accurately the value of health gains that are important to patients and their families (17,122–124).

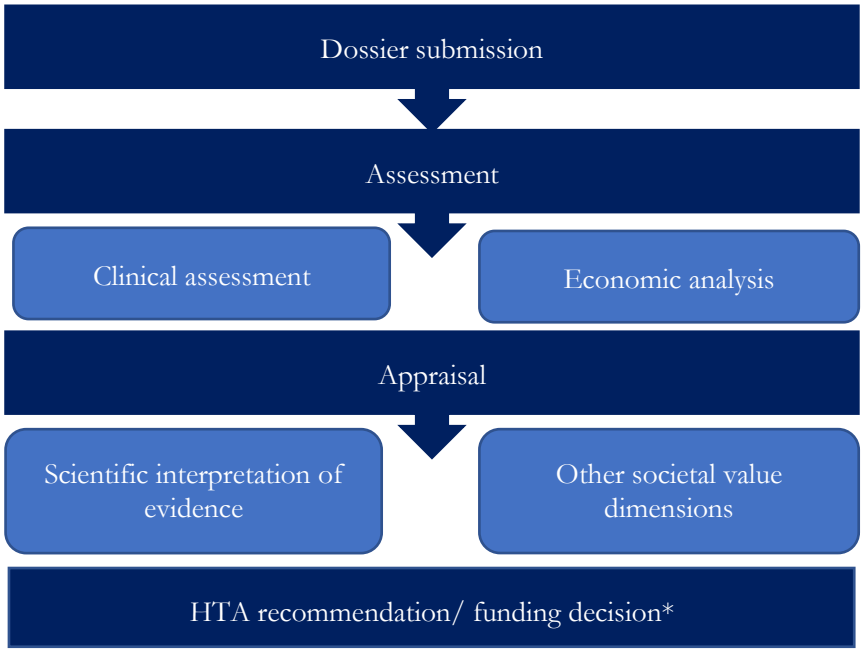
3.3.2.2 The appraisal process

Once the assessment of evidence is complete, an expert committee within the HTA body is responsible to appraise the evidence and form a recommendation, or decision, for funding. During the appraisal process, HTA bodies typically interpret the assessed evidence in the context of the healthcare system (i.e.: local needs and practices); the quality of evidence provided is assessed against the HTA body's evidentiary requirements. And it is further contextualised against other factors that may be of relevance to or reflect the needs and values of the healthcare system (17,87,125–127).

Beyond clinical- and cost-effectiveness, HTA bodies, may take into consideration other socioeconomic factors, such as innovation, the rarity and severity of a disease, and the impact on everyday activities and the quality of life of the patient, when assessing the added value of a medicine. For instance, some HTA bodies consider innovation indirectly using value dimensions such as the novelty of the treatment and unmet need, while others consider the degree of innovation as a separate criterion (128). However, in the context of HTA, finding a balance between rewarding innovation and accounting for the affordability and the sustainability of the healthcare system can be challenging (72,124). Overall, these factors account for potential implications for patients and the broader society (14,17,129). Depending on the HTA body, these value dimensions might be considered routinely or on an ad-hoc basis during the HTA process and decision-making (14,129,130).

Various stakeholders such as clinicians, patients, ethicists, and the pharmaceutical industry might participate at this stage of the HTA process to share their insights and preferences regarding the health technology under assessment. However, there has been limited evidence on what types of stakeholders are involved during HTA and at what point of the process, i.e.: in the assessment process or decision-making. Figure 5 shows schematically the assessment and appraisal process of HTA.

Figure 5: The HTA process



Note: **Depending on the role of the HTA body, HTA recommendations might be binding, therefore, directly translated into funding decisions.*
Source*: The author based on the results of the literature review* (87,125,131).

3.3.2.3 HTA outcomes

In most study countries, except Germany and France,[4] HTA recommendations for funding can be categorised into three main groups (87,129,131,132): First, the HTA body can recommend the unrestricted use of a medicine. Second, a positive recommendation with conditions might be suggested. Conditions might be related to clinical factors, such as the use of the medicine by a smaller part of the population, or when physicians should initiate or discontinue the treatment or dictate who should prescribe the treatment or where the treatment should be administered (i.e.: within a hospital). Suggested conditions can also be economic such as a reduction of the price by the manufacturer or suggested managed-entry agreements (MEAs) between the manufacturer and the healthcare insurance (please see more information in sub-section 3.3.3.1). Third, the HTA body may recommend to the healthcare insurance to not fund the medicine if they deem that no added therapeutic value against the comparator is provided, or its cost-effectiveness cannot be proven (18,86,126,129,131–139).

[4] Both Germany and France follow a comparative clinical benefit assessment model. In France, ratings are given for the actual clinical benefit of the medicine (SMR) and the improvement in clinical benefit compared to existing treatments (ASMR). In Germany, ratings are given to define the magnitude of the added clinical benefit of the medicine and the quality of the clinical evidence used for the assessment.

Recently, another type of HTA recommendation has been introduced by some HTA bodies to mitigate issues around high clinical uncertainty and, in some cases, strengthen collaborations with regulatory agencies. These recommendations provide "conditional" positive HTA recommendations with the requirement that additional clinical evidence will be generated and submitted for review when available (124). In England, for instance, oncology medicines can receive a provisional positive HTA recommendation through the Cancer Drug Fund (NICE, 2016). Similarly, in Scotland, an interim acceptance was introduced for medicines that have been granted conditional MA by the MHRA (140).

3.3.2.4 Implications for access to medicines

Even though manufacturers tend to submit the same clinical evidence across HTA bodies, which is often used during MA assessments, there has been plenty of evidence in the literature that has discussed variations in HTA recommendations for the same medicines across countries (18,86,126,129,131,133–136,138,139,141). As HTA is currently within the remit of each country/system and is not performed at the supranational level, different value assessment criteria and requirements may apply across settings, while interpretation of the assessed evidence during the appraisal process might vary substantially across systems (16,17,77,87,129,131,134,142). Evidence on how HTA systems and processes has impacted access is discussed in detail in sub-section 3.4.

3.3.3 Funding

After manufacturers have granted MA for their product and the HTA body has issued a recommendation, national or regional healthcare payers must decide whether medicines are worth funding through public resources, and at what price (77). At this stage, negotiations between healthcare insurance(s) and manufacturers are taking place to decide whether the medicine will be publicly reimbursed. As discussed earlier, HTA may act as a reimbursement tool during negotiations (92). For instance, in Germany, HTA recommendations, based on the added therapeutic benefit of a medicine, lead the reimbursement negotiations between manufacturers and social healthcare insurance (6). However, except few instances such as that of Germany, it is not clear how HTA recommendations are used during negotiations and to what extent they can impact the final funding decision. In addition, even though current literature accounted for the affordability of the system, most available studies limited their findings only to HTA recommendations rather than the actual funding status of medicines. However, HTA recommendations do not always dictate funding, especially in healthcare systems where HTA recommendations are not binding (see sub-section 3.4.5 for more information).

3.3.3.1 Managed entry agreements (MEAs)

When high clinical uncertainty or incomplete data on the therapeutic value and/or uncertainty on the cost-effectiveness of medicine exist, conditional funding might be granted through the implementation of MEAs (92). Through MEAs, healthcare insurance bodies can ensure access to new and innovative medicines while avoiding incurring very high costs (132,143). MEAs can take two main forms: financial- and health-outcome-based agreements (144). Financial-based MEAs might include agreed discounts on the price of the medicine or price-volume agreements, while health-outcome MEAs provide conditional reimbursement subject to re-assessment of the medicine or temporary funding conditional to additional evidence generation or provision of RWE (144). Depending on the geographic setting, MEAs might not only be suggested during reimbursement negotiations but might be suggested directly by the HTA body or by the manufacturer through their HTA dossier submission to avoid access delays (143).

3.3.3.2 Specialised funds

Specialised funds are available in some settings as an alternative source of government funding and a risk-sharing measure. These funds are dedicated to certain medicines (144) . For example, the Cancer Drug Fund (CDF) in the UK grants conditional funding to oncology medicines with incomplete evidence while additional data are collected, and provides interim funding to new oncology medicines approved by the English HTA body to ensure early and timely patient access (145). In the Canadian province of Ontario, new and expensive injectable in-patient cancer medicines are funded through the New Drug Funding Program (146). In Scotland, specialised funds are available for medicines treating inherited metabolic disorders and medicines for patients suffering from haemophilia and rare bleeding disorders (147). While specialised funds for orphan medicines are available in many countries (more information can be found in sub-section 3.5).

3.3.3.3 Implications for access to medicines

Both MEAs and specialised funds may enable patient access, however, they come with some limitations. MEAs have raised transparency concerns across policymakers as agreed reimbursement prices are not officially disclosed due to confidentially clauses (92) In addition, as funding decisions remain within the remit of local healthcare systems and payers, variations in the use and implementation of MEAs have been documented across countries. Rarely, two or more countries have implemented an MEA for the same medicine (6,144,148–150).Variations seen in the HTA recommendations have had a knock-on effect on the use of MEAs as they were closely interrelated (132). Criticism has also been raised on whether agreed conditions through MEAs are followed. For instance, an older study which focused on the multiple sclerosis patient access

scheme (PAS) in England, that offered access to eligible medicines subject to additional monitoring of cost-effectiveness data, concluded that price reductions were not offered by manufacturers as agreed even though worse than expected cost-effectiveness data were seen during the monitoring period of the agreement (151).

Whilst specialised funds can grant access to treatments that would not have been otherwise covered by the healthcare system, equity concerns have been raised for targeting only specific disease areas and populations (152). More importantly, a study looking at the old CDF in England found that medicines available through the old fund had largely a minimal clinical benefit (153). And another study concluded that the old English CDF did not "*deliver meaningful value to patients with cancer and may have exposed them to toxic side effects of drugs*" (154).

Finally, evidence is lacking on what proportion of eligible medicines with a positive or a negative HTA recommendation are covered through general healthcare budgets or specialised funds.

3.4 HTA and its impact on access to medicines

Despite the advantages HTA has brought as a reimbursement and negotiation tool for payers and decision-makers, access hurdles and delays have been attributed to its processes due to its highly fragmented nature (18). Salient features of HTA including its role, scope, procedures, and evaluation methods can all inherently affect the uptake of HTA recommendations in reimbursement decision-making but also lead to divergent HTA outcomes for the same medicines across settings. These variations might have contributed to unequal access to medicines not only across countries but also across different regions in decentralised healthcare systems such as that of Spain, Italy, and Canada(18,155). Policymakers and researchers have extensively discussed the reasons why variations in HTA outcomes exist and how they are attributed to different HTA processes employed in different settings (18,129,131,133,134,138,139,141). The key areas that have directly affected access to medicines can be categorised into four main groups: (i) Differences in the way healthcare systems are organised and how HTA systems are set up within the healthcare system; (ii) Differences in HTA procedures; (iii) Variations in HTA evaluation processes including evidentiary requirements and the assessment model followed, and; (iv) How HTA recommendations inform funding. Beyond these key areas, evidence has also shown misalignment in efforts to optimise market access across stages of a medicine's access pathway, highlighting the lack of collaboration and information exchange between regulatory agencies and HTA bodies.

3.4.1 HTA system set-up and organization

The way healthcare and HTA systems were organised and set up with the healthcare system and the scope of HTA were all contributed factors for access variations and delays (15,18,20,86,156–158).

3.4.1.1 The organisation of the healthcare system

Evidence from Italy, where HTA assessments are conducted both at national and regional levels, showed inequality in access to new medicines (158). In general, decentralised healthcare systems (i.e.: Italy, Spain, and Canada) can lead to access variations across regions due to divergent HTA recommendations or unclear uptake of HTA outcomes on funding decision-making. These variations may be attributed to regional differences in the methodologies used when assessing technologies and the selection process of technologies undergoing assessment (18,20,86,159).

3.4.1.2 Integrated HTA within local governments

Access hurdles have been observed in countries where HTA is integrated within the government due to a lack of transparency in the HTA process. In Greece, for instance, where the HTA committee is integrated within the ministry of health and the national payer, unclear or non-transparent interactions between the multiple institutions involved resulted in unnecessary delays in funding negotiations (15,157).

3.4.2 HTA procedures

Discrepancies in the HTA procedures employed by HTA bodies, such as whether HTA commences before or after MA, the actual timelines of HTA evaluations, the technologies subject to HTA and whether and/or to what extent stakeholders are involved in the HTA process have all resulted in access variations across settings (16,17,21,85,87,126,160,161).

3.4.2.1 Topic selection

Until recently (January 2022), not all medicines were undergoing assessment by the English HTA body, which was selecting technologies for assessment according to a set of pre-defined criteria. On the other hand, in Scotland and France, all new medicines undergo HTA assessment. The discrepancy in the topic selection can explain differences in the number of medicines having an HTA recommendation across settings (18,126,162).

3.4.2.2 HTA timelines

Timelines between MA and publication of HTA outcomes across countries varied significantly. A study in European countries, showed that Spain had the longest timelines (mean time of 713 days), followed by Italy and Poland (504 and 462 days respectively), while France and Germany were the

fastest, publishing HTA recommendations in 227 days and 199 days on average after MA (86). Similar results were seen in another study where France had the fastest timelines (155 days), and Italy had the slowest ones (375 days) (160). When looking at the median timelines between MA and HTA submission, timelines also differed with seven days seen on average in England, 23 days in Italy, 29 days in France, 42 days in Germany and 49 days in Spain (160). These variations in time were due to different stipulations of HTA procedures. For instance, in Germany, the HTA assessment must be initiated within three months from MA approval according to German law (160). However, in other settings, HTA processes can only be initiated by manufacturers upon dossier submission (163). Stop-the-clock mechanisms which pauses the evaluation process when additional evidence is needed might have further led to longer evaluation processes in some settings (160,164).

3.4.2.3 Stakeholders' involvement

Involvement of HTA stakeholders in the HTA process (i.e.: to select which technologies should be assessed by the HTA body, involved during technology assessment or in the decision-making process) showed to have a positive impact on access to medicines (15,17,156,163,165–167). However, some researchers mentioned that divergent HTA recommendations for the same medicine across HTA bodies could have been attributed to differences in the interpretation of the assessed evidence due to varying levels and types of stakeholders' involvement (87,129,131,163,168).

3.4.2.4 HTA referencing

Evidence looking at HTA systems in Central and Eastern Europe discussed that access hurdles and delays were seen in some countries that relied on HTA decisions of other well-established HTA agencies, such as Bulgaria and Romania. HTA processes in these countries might have been delayed until HTA recommendations were published in the countries they used as a reference (169).

3.4.3 HTA evaluation processes

Evidence in the literature has highlighted that differences in HTA recommendations across countries were mainly due to variations in the assessment and appraisal processes followed by HTA bodies. Specifically, differences in evidentiary requirements, consideration of other value dimensions beyond clinical and cost-effectiveness in decision-making, the model of assessment followed, divergent ways to deal with uncertainty and acceptance of RWE and indirect comparisons, could have all contributed to conflicting HTA outcomes for the same medicines and unequal access to medicines (16–18,21,81,86,87,129,131,136,160,161,170–175).

3.4.3.1 Evidentiary requirements

The divergence of evidentiary requirements of HTA bodies was the most discussed reason for potential access variations due to HTA. These included the choice of the comparator used for assessment, the methods used to synthesise the clinical evidence, the HTA body's criteria for inclusion or exclusion of clinical trials, the methods employed to measure patient's utility, the type of economic analyses and the sources use for direct and indirect costs, among others (16–18,21,81,86,87,129,131,136,160,161,170–174,176,177). However, a study looking at 29 jurisdictions reported that more similarities than differences existed between major methodological aspects used in the HTA processes of the study countries, showing room for better cross-country co-operation (176). Another study reported, though, that manufacturers had to generate local contextualised evidence, including evidence on the local comparator, to meet specific evidentiary requirements of European HTA bodies. Almost 90% of submissions in England incorporated local information such as local standard of care and clinical practice, followed by 82% of the submission in Germany, 80% in Italy, 79% in Spain and 72% in France (160). Both Germany and England were the two countries which required additional local evidence from manufacturers after dossier submission (160). Similarly, another study discussed that country-specific practice-related factors could have explained differences in HTA recommendations across settings (126).

Heterogeneity in HTA recommendations across countries might have also been attributed to differences in the acceptance of evidence from observational studies and indirect comparisons (81,129,136,175,178–180). However, there was contradictory evidence on whether acceptance of RWE might improve access at HTA level. According to a study, setting up registries for RWE generation might contribute to longer access delays (161). While in Bulgaria, manufacturers felt less prepared for HTA dossier submissions due to limited epidemiological data (181).

3.4.3.2 HTA assessment model

The model of assessment employed may have had an impact on HTA recommendations (126,162,163). Across Europe, Greece was an example where assessment focused on the comparative clinical benefit of a medicine. While Germany, beyond the assessment of the clinical benefit, considered the medicines' cost as part of the HTA process but did not require cost-effectiveness analysis (126,163). HTA evaluation in Romania mainly focused on costs and other dimensions of value were not considered (181), while in England value and end-of-life criteria were considered explicitly in the assessment of some medicines, together with recognition of elements such as medical innovation in deliberations on whether to accept higher WTP thresholds (166,182).

3.4.4 MA and HTA

Better cooperation between regulatory and HTA bodies seemed to be crucial for optimal and timely market access, with collaborative processes being implemented in some settings (172,183–186). Despite efforts to expedite assessment processes at regulatory level and harmonise assessment processes at both levels, still, a proportion of approved medicines did not result in positive HTA recommendations, and only in a few cases, HTA bodies seemed to accept a lower quality of evidence which had already been approved by regulatory agencies(18,85,86,134,160,187–189).

3.4.4.1 Parallel review process

Collaborations between MA agencies and HTA bodies were seen in some settings, such as Canada and Australia, with the introduction of parallel review processes. During the parallel review, MA and HTA assessments occur concurrently aiming to optimise time to patient access. In addition, it provides alignment in MA and HTA decisions by allowing an exchange of information while it prepares HTA bodies for any potential issues that might have arisen during MA assessment (18,160,173,190,191).

The introduction of parallel review between MA and HTA has shown to have a positive impact on timely access. However, discrepancies in the timelines were still observed in countries which implement this process: the median overlap between MA and HTA processes was 107 days in Australia while it was only 30 Days in Canada (160). Long timelines in Australia were attributed to the fact that HTA recommendations cannot be made before the publication of MA approval (160).Therefore, even if these processes exist, there is room for improvement in the way they are implemented.

3.4.4.2 Early scientific advice

The presence of early scientific advice from the HTA body to manufacturers before dossier submissions or during the medicine development process is another way to expedite HTA assessments (85,172,173,183–186,192). Provision of early scientific advice has aided manufacturers to generate evidence that meets the standards of both regulatory agencies and HTA bodies, however, according to key stakeholders this initiative had not yet been successful to align regulatory and HTA requirements (85).

3.4.4.3 Specialised MA pathways

Misalignment of MA approvals and HTA recommendations were still being observed: Evidence showed that half of the medicines which granted conditional MA had a subsequent negative HTA

recommendation (193). Other studies showed that medicines with an MA through specialised pathways were not treated differently by HTA bodies: no difference in positive recommendations for medicines with conditional MA and medicines with standard MA were observed (188,194,195). This disagreement stemmed from differences in the evidentiary requirements of MA and HTA bodies that can be also attributed to differences in their remit (i.e.: MA agencies assess the safety and the clinical efficacy of the therapy, while HTA bodies assess the comparative clinical benefit of the medicine against a comparator and, usually, its comparative cost-effectiveness) (18,86,99,124,134,160,188).

3.4.5 HTA and funding

The relationship between HTA recommendations and funding decisions is still not clear and very well understood. Evidence from middle-income European countries showed a lack of a legal framework for the implementation of HTA recommendations in funding decision-making (196), while another study highlighted that this phenomenon was also observed in high-income countries where HTA systems are well-developed and established (168). Another study highlighted that the lack of a framework that outlined the use of HTA recommendations in the decision-making process was the most important barrier to patient access, while the availability of such a framework was among "*the most important facilitators*" (197).

As the majority of HTA bodies publish recommendations for funding which are not legally binding, it is still unclear whether HTA recommendations are followed during decision-making processes (163,168). For instance, in Canada, uptake of HTA recommendations across provinces is not mandatory and it is in the competence of each province to make its own funding decisions (191). Moderate agreement between provincial funding and HTA recommendations by the Canadian Agency for Drugs and Technologies in Health (CADTH) has been observed in Canada, except for British Columbia where a substantial agreement was documented (198). Variations between provincial funding and HTA recommendations were explained due to price negotiations taking place in each province (198). Another study in Canada found that positive HTA recommendations by CADTH were a strong predictor of funding but the vice versa did not apply to negative ones (199). Similarly, a study in Poland, where HTA recommendations are not legally binding, showed only a fair agreement between national HTA recommendations and ministerial funding decisions between 2013 and 2015 (200). A more recent study in Central and Eastern Europe showed a low level of agreement between HTA recommendations and funding of cancer medicines in Poland, contrary to Latvia where HTA recommendations were binding (169). Therefore, in systems where HTA recommendations are binding, their implementation in funding decisions was more straightforward. For instance, the English NHS must reimburse and make

available within a timeframe of three months a medicine that have received a positive HTA recommendation by the English HTA body (18).

3.5 Rare diseases, orphan medicine regulations and specialised processes for their assessment and implications for access

A disease is considered rare when it affects a small fraction of the population. Rare diseases are predominately genetic and mainly occur in childhood (201), however, many types of cancer are now qualified as rare (71). Rare diseases are severe, sometimes life-threatening, or chronically debilitating (201,202).

3.5.1 Definition of rare diseases

Definitions of what diseases are considered 'rare' vary across settings (22,63,71,203,204). A lack of a universal definition is partly because of the heterogeneity of rare diseases, the geographic disparity due to differences in epidemiology, but also due to occasional considerations of other criteria beyond disease prevalence, such as disease severity or lack of alternative therapies (22,203,204). In Europe, a rare disease is defined as a condition that affects less than one in 2,000 people while in the US, it affects less than 200,000 citizens (202–204). A global average prevalence threshold of a rare disease is estimated to be around 40 cases in 100,000 people (203).

Even though rare diseases affect a small part of the population, there are about 5,000 to 8,000 documented rare diseases currently, affecting almost 3.5 to 5.9% of the worldwide population (203). A paradox is, thus, observed: despite the low number of patients suffering from a rare disease, the overall affected population remains high due to the high number of less common conditions detected over time. Nevertheless, the scientific and medical knowledge of rare diseases remains limited due to the rising number of identified rare diseases annually and their low prevalence (201,202).

3.5.2 Specialised regulations, processes and assessment frameworks for orphan medicines and their implications for access

Because of the low prevalence of rare diseases, sample sizes of relevant clinical trials can be very small with no comparators while the clinical benefit of orphan medicines might be limited to surrogate endpoints[5] (63,141,206). Usually, robust clinical evidence is rarely available, especially, when manufacturers are seeking MA and are subject to HTA assessment at national and regional levels (23,63,80,206,207). In addition, manufacturers might be reluctant to develop these medicines

[5] According to FDA, in some clinical trials, surrogate endpoints are used instead of clinical outcomes. This occurs when a clinical outcome might take a considerable time to study or when the clinical benefit of improving a surrogate endpoint is widely accepted and has been validated (205).

as expected sales would not be able to recoup their development costs (5,204,208). Over the last decade, many healthcare systems have introduced various incentives for manufacturers of medicines treating rare diseases by implementing specially designed regulations, processes, and assessment frameworks to improve access and make the market of rare diseases attractive for R&D investments (4–6,22,64,70,71,80,203,209,210). In addition, implementation of these processes aims to mitigate issues around high clinical uncertainty and steep prices of orphan medicines as well as ensure that other societal values around equity are captured during assessment processes, which would have otherwise deemed these medicines as cost-ineffective (i.e. the incremental benefits will be low due to high uncertainty and the incremental costs will be high due to high prices resulting in very high ICER in relation to the WTP threshold) (4,5,23,79,80,193,208,211).

3.5.2.1 Regulatory level

In the European Union, the UK and Australia, manufacturers of medicines treating rare diseases are granted an orphan designation and can benefit from various incentives. These incentives vary across countries but usually include early scientific advice at a lower cost, market exclusivity with no competition of medicines with similar indications for some years[6] reduced MA administrative fees and granting of research grants (5,6,22,70,71,80,126,201,209,212). Unlike other systems, Canada has no orphan designation nor a specific national strategy for orphan medicines. And medicines treating rare diseases are treated in the same way as any other medicine (22,80,201,213). Over the years, many efforts have taken place to implement a national plan for these medicines but so far these efforts have been unsuccessful (213–216). However, in 2022-2023, the Canadian government committed to introducing a national strategy for medicines treating rare diseases to eliminate access variations to these therapies across the Canadian provinces, create a common definition of 'rare diseases' and ensure that the regulatory environment supports and incentivises manufacturers to invest in R&D and launch their products in the Canadian market (206,207,213,217,217).

Beyond the implementation of regulations for orphan medicines, these medicines are more likely to undergo MA through specialised pathways (discussed in sub-section 3.3.1.1) as they address areas of high unmet need and usually have limited or incomplete clinical data at the time of MA assessment (5,22,80,213).

[6] In Australia, there is no formal provision for market exclusivity and no grants for the R&D of orphan medicines are provided (Lexchin and Moroz 2019)

3.5.2.2 HTA level

Challenges in the assessment of orphan medicines were further seen at HTA level. During value assessment processes, HTA bodies assess limited or incomplete evidence of high uncertainty, while cost-effectiveness analyses often find these medicines to have very high incremental costs in relation to the additional health benefits they provide (4,80,218). To mitigate such issues, some countries have specialised processes for the value assessment of orphan medicines to capture the needs of vulnerable and small populations, and account for their unique nature, while involving relevant stakeholders such as clinicians, patients and their families during the assessment process or decision-making (79,206,212,218–220). For instance, in England, the highly specialised technologies program (HSTP) assesses the benefits and costs of medicines that treat very rare conditions and meet certain pre-defined criteria. During this process, a specialised review committee appraises the available evidence considering equity criteria and recognising the high uncertainty of the clinical evidence. The committee further accounts for challenges manufacturers face when they invest in the development of these medicines (23,206). In other countries such as France, Germany and the Netherlands, orphan medicines approved by the EMA do not have to undergo HTA assessment at national level, if the annual budget impact remains under an agreed-upon threshold (e.g.: EU 50 million in Germany) (23,193,206).

However, designated frameworks for the assessment of orphan medicines are not seen across all healthcare systems (79,126,206,212,219,220). For instance, in Canada, CADTH does not apply different assessment criteria for medicines treating rare diseases. The same practice has been observed in the Polish HTA body (200).

3.5.2.3 Funding level

MEAs or specialised funds to make orphan medicines available to patients are seen in most settings as an effort to mitigate risks and ensure the sustainability and affordability of the healthcare system (23,24,80,206,218). In Italy, for example, a fund for 'innovative medicines' is available to optimise access to products with an indication that addresses a high unmet need and has an added therapeutic value (23,206). In Australia, orphan medicines that have received an unfavourable HTA recommendation may be listed under the Life Saving Drugs Program which provides funding for clinically effective, very expensive medicines, with no alternative treatment, and that do not meet cost-effectiveness requirements (206). While in Latvia[7] and Bulgaria, orphan

[7] Latvia has a separate government budget for medicines treating rare diseases for children (23).

medicines are exempted from HTA assessment and are reimbursed through separate funds dedicated to medicines for rare diseases (23).

3.5.3 Implications for access

Access variations to orphan medicines have captured the attention of many researchers while evidence of such variations across settings has been well reported in the literature (63,69,79,200,207,218,220–222). However, many of the studies have focused on small samples of orphan medicines or limited timeframes and either have focused on MA approvals or HTA recommendations rather than the national or regional funding status of these medicines. Furthermore, studies have not examined access to orphan medicines across all the stages of the access pathway (4,131,200,207,210,213,220,222).

At the MA level, studies have shown that since the implementation of the EU orphan medicines regulation the number of approved medicines treating rare diseases increased substantially in Europe, while it helped in encouraging the R&D of these medicines (79,126,203,210,223). Similarly, other studies found that orphan regulations at MA across various settings have ensured more approvals, achieving better availability of orphan medicines in these settings (22,80,207,224,225). For instance, a recent study looking at therapies with an orphan designation in the EU and the US showed that fewer orphan medicines were submitted for MA approval in Canada, where no orphan medicine regulation exists, compared to Europe or the US (207). Nevertheless, another study which compared Australia, where orphan designation exists and Canada where it does not, showed no differences in MA approvals, the time of the regulatory process, and launching delays for orphan medicines between the two countries (213).

Access implications might further arise due to exploitation of available incentives by manufacturers. For instance, market exclusivity offered in some settings has allowed manufacturers to act as monopolists and, in some instances, request the maximum price the healthcare system could potentially afford. Often, healthcare payers are forced to accept the requested price due to limited negotiating power and exerting pressure from patient organisations (5,80). On the other hand, strict pricing controls on orphan medicines might cause adverse effects, leading to low availability and shortages of orphan medicines within markets while disincentivising manufacturers to invest in R&D (69,221).

Differences in the national regulations and policies for pricing and reimbursement of medicines also emphasised issues around access inequalities and variations in price, and use of orphan medicines across countries (5,64,80,221). A recent survey in 12 Eurasian countries stated that inequality in patient access to new orphan medicines was still observed due to differences in local

healthcare budgets and reimbursement systems (208). Therefore, high prices of orphan medicines combined with incentives to manufacturers have placed a substantial financial burden on healthcare systems, making them unaffordable for some healthcare payers and inaccessible to some patients (64,70).

At HTA level, studies have shown a positive correlation between specialised HTA processes for orphan medicines and positive HTA recommendations for funding (4,80,211,212,219,220).

Overall, there is much controversy in the literature on whether specialised processes for orphan medicines should be implemented or whether they have been successful in improving access. Some researchers have argued that having these processes in place does not necessarily mean that the value of these medicines is sufficiently captured, or high uncertainty is managed. In addition, the sustainability of the healthcare system might be at risk due to the increasing number of MA approvals of orphan medicines even though evidence of their clinical benefit is highly uncertain, due to the very high prices manufacturers are requesting and finite local healthcare budgets which would have potentially been dedicated to medicines treating a very small fraction of the population, reducing financial resources for more common diseases (4,5,14,22,23,71,80,207,215,218,226–228). Other researchers and stakeholders have highlighted that in the absence of these processes, the opinions of patients and clinicians would not be explicitly considered during HTA assessment, especially because the power of patient organisations is smaller due to the low number of people affected by a certain rare disease. Or the societal and equality aspects would not be accounted for during HTA assessments which would have resulted in unfavourable recommendations for funding due to clinical- and cost-ineffectiveness. Or manufacturers might be disincentivised to develop orphan medicines due to uncertainty about potential funding across settings (22,23,69,71,206,229–232).

3.6 Summary

Looking at the findings of the scoping review, we can conclude that even though the peer-reviewed literature has used access definitions closely aligned with the ones used by international organisations, there were only very few instances where access was explored in a holistic way (i.e.: focusing on various access dimensions together, such as availability of clinically- and cost- effective medicines within markets, reimbursement of medicines and timely market access to medicines). In addition, evidence on whether access to medicines within markets was successful has not focused on all stages of the access pathway, failing to recognise that access hurdles and delays arising in one stage can have had a knock-on effect in subsequent stages. Even though there is much evidence on what features of HTA could facilitate or impede access, the views of relevant

stakeholders remain unknown and there is a lack of prioritisation on what areas of HTA should be improved to optimise access to medicines. Finally, despite the ongoing debate on whether specialised assessment processes for orphan medicines should be implemented or not, there has been no study comparing two systems with differences in the presence of these processes for orphan medicines. Similarly, there is very limited evidence on whether efforts to improve and expedite access to orphan medicines at the regulatory level have an impact on subsequent stages of the access pathway, such as HTA outcomes and funding decisions.

4 Literature gaps and research questions

Looking at the evidence summarised in the first chapters, numerous issues have been detected: Despite pharmaceutical spending having stabilised for a few years, a steep rise was observed recently. This rise was mainly explained by the COVID-19 pandemic but has been further intensified with the entry of novel therapies into markets and a shift in the interest of manufacturers in developing medicines for smaller patient populations. The performance of novel treatments in terms of efficacy and effectiveness and their contribution to better health outcomes have been criticised in the literature. Thus, a need was identified to implement value assessment practices that determined the added value of innovative medicines without discouraging manufacturers from investing in R&D. In addition, finite pharmaceutical budgets across settings have further escalated tensions in decision-making on allocating finite resources wisely across different disease areas.

To find the right balance between rewarding innovation, allocating local resources efficiently and ensuring access to highly effective therapies without compromising the sustainability of healthcare systems, HTA has been widely implemented as a value assessment, cost-optimisation, and reimbursement tool. Whilst HTA has captured the attention of many researchers, many unanswered questions remain on the relationship between HTA and access to medicines. Misalignment in the efforts to optimise access made by different institutions responsible at each stage of a medicine's access pathway have been further seen, given differences in their remits and objectives. For instance, having been granted a MA through specialised pathways does not necessarily mean that the medicine would be available through the public purse if deemed cost-ineffective by the HTA body or if the health insurance and manufacturers fail to reach an agreement on reimbursement prices.

This chapter summarises underlying issues seen in access to innovative medicines and HTA processes and outlines literature gaps that led to this thesis's research objectives. An analytical framework showcases how the main chapters of this thesis have addressed the research objectives, while a brief description of each paper is provided.

4.1 Gaps in the literature

The identified gaps in the literature stemming from the scoping review can be grouped into three thematic areas: (i) access to medicines within markets; (ii) HTA; (iii) access to medicines for rare diseases.

4.1.1 Evidence on the access of medicines within markets

A clear definition of access has been provided by international organisations and the peer-reviewed literature, while many researchers have studied access to medicines across markets by looking at individual regulatory policies, specifically HTA. However, three main overarching issues were observed.

First, access to medicines in the peer-reviewed literature have been explored by looking at the availability of medicines within markets after MA and access to medicines that are publicly reimbursed. HTA recommendations have been used as a proxy for reimbursement status. However, HTA recommendations do not always translate to public funding of innovative medicines, especially in systems where HTA recommendations are not legally binding and the role of HTA is advisory. Therefore, not all positive HTA recommendations can equate with funding and vice versa. Second, even if time-related metrics have been investigated in the literature, in most of the cases, they have not been studied conjointly with other access dimensions such as availability of clinically- and cost- effective medicines within markets and reimbursement status, which would have allowed to explore access to medicines in a holistic way. And time metrics have usually focused on the time from MA to the publication of HTA recommendations. Even though this is a validated metric and could potentially apply in a few HTA systems with a regulatory role (i.e.: having legally binding decisions), it cannot determine timely access to all settings without accounting for the characteristics of the healthcare system and the relationship of HTA and funding within these systems. Finally, current research has focused mostly on individual stages of a medicine's access pathway without studying them collectively. For instance, evidence has shown that medicines might have achieved faster access to national markets through MA from specialised pathways. Yet access might have been delayed or halted at HTA level where recommendations for funding may still have been unfavourable due to high uncertainty and financial risks to the healthcare system. As discussed above, evidence was also scarce on how HTA recommendations were translated into funding across systems, especially when the role of the HTA body was advisory, or when alternative risk-sharing options beyond general funds were available, such as specialised funds for certain medicines.

4.1.2 Evidence on HTA

HTA-related implications for access have been extensively studied in the literature. However, the evidence has come predominantly from studies that looked at variations in HTA recommendations for the same medicine across different bodies. Even though researchers have touched upon possible reasons why these discrepancies were observed, they have mainly focused on the evidence used during assessments and appraisals, differences in the evidentiary requirements and in the way

HTA bodies dealt with uncertainty. Nevertheless, HTA is multifaceted with different salient features implemented across settings that can impact access to medicines directly or indirectly. The way the healthcare system is organised and the way HTA is operationalised can both have implications for the implementation of HTA recommendations in funding decisions. Studies looking at the features of HTA, rather than HTA evaluation processes, were limited and focused only on very few well-developed and established HTA systems. Currently, a conceptual framework is lacking from the peer-review literature that would enable cross-country comparisons of HTA systems across jurisdictions and would showcase the dynamics of HTA and funding within settings. In addition, there is no mapping of HTA systems across a wide geographic range.

Another important gap in the literature has been identified: Even though there has been evidence on what features of HTA may impede or enable access to innovative medicines, this evidence has focused only on differences in HTA evaluation processes and not on HTA in a holistic way (i.e.: looking both at the system per se, HTA procedures, evaluation processes, and the relationship between HTA and funding decision-making). Despite many efforts being made at supranational and national levels to harmonise, simplify, and expedite processes, evidence was scarce on the success of HTA-related interventions in improving access to medicines in terms of availability of clinically- and cost- effective medicines within markets, timely access, and affordability of the healthcare system. In addition, current evidence rarely discusses the views of different stakeholders from different geographical settings and different stakeholders' groups, resulting in a limited understanding of what efforts targeting HTA are successful or not. Having a clear idea of which HTA features are considered the most essential in improving access, among stakeholders, could help in identifying and prioritising areas of improvement within HTA.

4.1.3 Evidence on access to medicines for rare diseases

Access to orphan medicines and rare diseases has been widely explored in the literature looking at different HTA recommendations for funding across settings, while many researchers have tried to identify possible factors that contribute to or explain the very high price tags of orphan medicines (5,60,65,69,71,218). However, available studies have focused mostly on small sample sizes and limited timeframes (79,131,207,220).

Studies have also mapped different frameworks and approaches employed in different countries for orphan medicines (22,23,79). However, there has not been a study that compares access to orphan medicines within markets where these medicines are treated differently. Therefore, whether dedicated frameworks for orphan medicines have been successful in terms of positive funding recommendations for orphan medicines and timely HTA recommendations after MA

remain unclear. Furthermore, no study has examined whether specialised MA pathways targeting medicines of high unmet need, such as orphan medicines, are related to positive funding recommendations and timely publication of HTA recommendations.

Furthermore, no study has explored whether there is alignment between HTA recommendations, outcomes of pricing negotiations and funding decisions in the context of orphan medicines, where alternative risk-sharing options are usually available. In addition, it is unclear whether there has been a positive relationship between favourable HTA recommendations and funding of orphan medicines in settings where HTA bodies act as advisors to healthcare insurance. And our understanding on what other factors that are important to decision-makers might influence funding decisions for orphan medicines.

The main issues identified across the three thematic areas are summarised in the box below.

Access:

- Access to medicines has not been studied holistically, looking at all access dimensions including availability of clinically- and cost- effective medicines within markets, their reimbursement status and timely access.
- HTA recommendations were used as a proxy for reimbursement status and access to medicines, without accounting for whether HTA recommendations were legally binding or not.
- Not all stages of medicine's access pathway have been explored in conjunction to test successful access to medicines.

HTA:

- Variations in access due to HTA have mainly been explored through comparisons of HTA recommendations for the same medicine across settings.
- Limited evidence on how salient features of HTA may impact HTA uptake on funding decisions.
- Lack of a conceptual framework that allows systematic comparisons of HTA systems across a wide geographic range.
- Stakeholders' views on what features of HTA enable or impede access to medicines were unclear.

Orphan medicines:

- Evidence on access to orphan medicines came from studies of small subsets of orphan medicines and short timelines.

- No evidence of whether dedicated assessment frameworks for orphan medicines translate to favourable HTA recommendations and timelier publication of HTA outcomes.
- No evidence on whether HTA recommendations for orphan medicines are aligned with funding decisions and outcomes of pricing negotiations.
- Limited evidence on what other factors, beyond HTA recommendations, that are important to decision-makers might influence funding decisions in a system where HTA outcomes are not legally binding.

4.2 Research questions and objectives

Having identified the above literature gaps and looking at the overarching questions of this thesis, a number of more explicit research objectives were shaped and addressed in four papers. The box below outlines the research questions and objectives of this thesis.

Broad research questions addressed in this thesis:

i. How does the implementation of HTA differ across settings and how these variations may contribute to differences in funding decisions and access to medicines?
ii. Considering finite budgets, should very expensive treatments, whose costs run in the millions of dollars and have potentially significant clinical benefits, be funded at public expense?
iii. Should decision- and policymakers treat orphan medicines differently than non-orphan medicines to optimise their access within markets?

Research objectives:

- Examine access to medicines within markets by measuring various metrics of access including the availability of clinically- and cost- effective medicines, timely patient access and affordability of the healthcare system. *(Papers 2, 3 and 4)*
- Understand the extent to which different countries are using HTA, how HTA bodies differ in terms of their salient features and what implications these differences have in the uptake of HTA recommendations during funding decisions. *(Papers 1 and 2)*
- Create a conceptual framework that allows cross-country comparisons of HTA systems regardless of how well-developed and established they are. *(Paper 1)*
- Explore whether current efforts and direction for the improvement of HTA systems are considered successful in optimising access across stakeholders from different geographic jurisdictions and/or different stakeholder groups. *(Paper 2)*

- Identify what dimension of access are improved by optimising HTA looking at HTA holistically. *(Paper 2)*
- Study differences in HTA recommendations for funding for medicines classed as "orphan" in one setting and "non-orphan" in another. *(Paper 3)*
- Explore whether the presence of orphan designation at MA and specialised HTA processes means more favourable HTA recommendations for and timelier access to orphan medicines. *(Paper 3)*
- Observe whether efforts to optimise access at regulatory level in terms of MA through specialised pathways are successful and translate into better access in the case of orphan medicines. *(Papers 3 and 4)*
- Test the alignment between national HTA recommendations, outcomes of pricing negotiations, and regional funding decisions for orphan medicines in a decentralised healthcare system where HTA outcomes are not legally binding and where a national strategy for orphan medicines is not present. *(Paper 4)*

4.2.1 Paper 1

Research question: *How do HTA systems differ in the way they operationalise within healthcare settings and what implications, if any, do these differences have on the uptake of HTA recommendations in funding decisions?*

The first paper of the thesis (Chapter 6) outlines and proposes a conceptual framework that captures the principal pillars and salient features of HTA systems, and further allows cross-country comparisons. Using this framework, a mapping exercise was conducted which outlined the similarities and differences of HTA systems in 32 countries including all EU Member states, the UK, Canada, and Australia. The different facets of HTA in terms of its focus, governance, role, scope and remit, the assessment model employed, and the extent of stakeholder involvement were explored.

The objectives of this paper were fourfold:

1. To build a conceptual framework that allows cross-country comparisons of HTA systems;
2. To collect information on the different procedures and operational features of different HTA bodies across a wide range of countries which are using HTA either extensively or to some degree;
3. To explore how HTA systems are set up within countries given differences in their organisation of various healthcare systems;

4. To understand the role of HTA in funding decisions across settings that use HTA in a different capacity.

To note, the latter objective did not aim to establish a causal relationship between HTA recommendations and funding decisions. The objective was rather to observe whether through current legislation, HTA outcomes are explicitly used during reimbursement decision-making.

The conceptual framework was designed through a review, update and extension of existing frameworks in the literature and through consultation with key HTA experts. To populate the HTA mapping exercise secondary data collection was conducted and was complemented by primary data collection.

In the 32 study countries, sixty-three HTA bodies were identified. Seventy-three percent of these bodies were independent of the local government. In terms of the type of organisations performing HTA, various types were identified highlighting that the organisation responsible for HTA depended on the structure of the healthcare system and the scope of HTA activities. Only 28% of organisations responsible for HTA within settings had HTA as their primary activity. Half of the HTA bodies had an advisory role to the local governments while almost 27% had a regulatory role meaning that they were directly accountable to the county's ministry of health or the authority which made pricing and reimbursement decisions. In 13 countries, more than one body undertook HTA activities at national level and eight countries had regional HTA bodies beyond national activities. A wide variation was observed in the technologies undergoing HTA with 76% of HTA bodies evaluating pharmaceuticals predominately or exclusively. The clinical and cost-effectiveness model was the most frequently employed model (73%), and 56% of HTA bodies performed appraisals instead of assessments meaning that the assessed evidence was contextualised according to local standards and needs. Stakeholder involvement in the HTA process was present across almost all HTA bodies, with few exceptions seen in some HTA bodies of England, Denmark, and Finland. Finally, HTA recommendations across the 32 countries were mostly (81%) not legally binding meaning that their implementation on the funding decision was not mandatory.

The results of this paper suggested that HTA systems were largely operationalised in a similar manner across countries. However, variations remained in the way HTA recommendations were used during funding decisions. Explicit use of HTA recommendations during decision-making was observed mainly in countries with more developed HTA systems. Transparency concerns about funding decision-making processes still remained.

The findings of this paper were used in the value dimensions included in the web-Delphi panel conducted amongst European stakeholders in the second paper of this thesis while they helped

me understand and contextualise the findings of papers 3 and 4 and their potential implications for access to medicines.

4.2.2 Paper 2

Research question: *What features of HTA could facilitate access to medicines and what HTA features need improvement?*

The second paper (chapter 7) validated findings from the current literature on what features of HTA can facilitate or impede access to clinically- and cost- effective medicines and assessed the success of recent efforts made at the EU and national levels to harmonise and simplify HTA processes. This paper used the Delphi technique to engage relevant European stakeholders and elicit their views on the performance of a list of value dimensions, extracted by the current literature related to HTA, against access dimensions (including the availability of clinically- and cost- effective medicines within markets, timely access, and the affordability of the healthcare system).

The objectives of this paper were the following:

1. To explore what features of HTA are more likely to have the most positive impact on all or some of the access dimensions, and;
2. To assess whether stakeholders from different geographic jurisdictions and/or different stakeholder groups agree with each other on the success of recent efforts targeting HTA systems and processes across European countries.

Based on the results of the scoping review on HTA and its implications for access (sub-section 3.4) and findings from the first paper, a set of HTA features relevant for optimising access to medicines were identified. A total of 39 value statements were included in the panel comprising 13 HTA features across three access dimensions (availability, time, affordability). The European stakeholders across Western and Eastern European countries who agreed to participate in the web-based Delphi panel were asked to rank the value statements, using a five-point Likert scale, regarding their favourable impact on individual access dimensions. Stakeholders were selected following a purposive and snowball sampling strategy and included experts from academic or health policy research institutions, the pharmaceutical industry, and representatives of patient organisations.

The Delphi technique was pursued to enable group communications amongst different stakeholders from various geographic jurisdictions and create an iterative process of controlled feedback. Participants had the opportunity to change their initial rankings in a second round when they were presented with the aggregate responses of other panellists.

Quantitative methods were used to test for agreement between stakeholders about the rank of different HTA features across access dimensions; explore whether stakeholders generally agree with each other; and, finally, test whether participants' responses were stable across rounds to draw safe conclusions.

From a list of 13 HTA features which showed to have an impact on access according to the results of the scoping review, 11 had a positive impact on at least one dimension of access according to stakeholders. Looking at the different access dimensions, HTA features had a mostly positive impact on timely access to medicines. According to stakeholders, 'reliance on RWE in HTA in case of limited, incomplete, immature, or early phase clinical evidence' had a positive impact on the availability of medicines within markets, while 'scientific advice provided to manufacturers ahead of the commencement of formal HTA process by HTA bodies can favourably affect the availability of medicines and safeguard the affordability of healthcare systems. Stakeholders concluded that timely patient access to medicines can be achieved through 'clarity of evidentiary requirements for value assessment in HTA'. Finally, the most positive impact on all three access dimensions was seen on HTA features related to more clear, consistent, and harmonised evaluation processes within and across countries. Overall, participants' views were broadly aligned with current initiatives and discussions on how HTA systems could be improved at regional, national, and supranational levels to optimise access.

4.2.3 Paper 3

Paper 3 and 4 explored access to orphan medicines due to their unique nature, high clinical uncertainty and price tags. Both papers looked at all the stages of the access pathway (i.e.: from MA to funding).

Research question: *How HTA recommendations and time to issue of HTA outcomes differ in two setting where medicines for rare diseases are treated differently both at MA and HTA levels?*

Recognising that some healthcare systems implement specialised pathways and/or processes for MA and/or HTA assessments for orphan medicines, paper 3 (chapter 8) explored whether the presence of these processes result in more favourable HTA recommendations in two settings which treat medicines for rare diseases differently. Comparisons in the availability, HTA recommendations for funding and time to market access for orphan medicines were made between Scotland and Canada. Scotland was chosen due to the implementation of clear and well-established evaluation processes for orphan medicines both at MA and HTA levels, while Canada has no orphan designation at MA and no designated HTA process for these medicines. A sample of 116

medicines-indications targeting rare diseases with MA approval from 2001 to 2019 in Europe and Canada was studied.

The objectives of this paper were the following:

1. To observe whether the presence of orphan designation at MA and specialised HTA processes is associated with more favourable funding recommendations and faster timelines from MA to HTA recommendations (i.e.: market access), and;
2. To compare HTA recommendations and time to market access between orphan medicines with a MA through a specialised pathway and orphan medicines approved through the standard pathway at regulatory level.

Data were collected through publicly available sources and descriptive statistics were used to study key trends across access to orphan medicines in the two countries. Kappa score analysis was performed to test the agreement of HTA recommendations and the main reasons for the recommendation for the matched sample in Scotland and Canada. Kaplan-Meier curves were used to estimate time to market access in both countries both for the entire sample and for subsamples of orphan medicines with MA through a specialised pathway and those with standard MA approvals.

Results of this study showed that in Canada, more MA approvals through specialised pathways were seen for the sampled medicines treating rare diseases, regardless absence of an orphan designation at regulatory level. Favourable funding recommendations were slightly higher in Scotland than in Canada. However, in both settings proportion of positive HTA recommendations with no suggested restrictions for their use was very low, highlighting that a managed access approach (i.e.: medicines being restricted to certain populations and/or financial arrangements are in place) was adopted in both countries. A small number of the sampled orphan medicines approved through specialised pathways at MA receive an unfavourable funding recommendation compared to medicines with standard MA in both settings. In the time to market access analysis, Scotland showed considerable slower timelines for market access (i.e.: from MA to HTA recommendations) than Canada. While in both countries, orphan medicines with MA through specialised pathways showed longer timelines for market access compared to medicines undergoing standard approval.

From the findings of this study which looked at all the stages of the access pathway, it was not possible to conclude whether the implementation of specialised frameworks for orphan medicines alone could lead to better access to these medicines, without factoring in other country-specific and healthcare system elements that may potentially influence access to orphan medicines.

4.2.4 Paper 4

Research question: *Do reimbursement recommendations by the Canadian Agency for Drugs and Technology in Health translate into coverage decisions for orphan drugs in the Canadian province of Ontario and what other factors might influence provincial funding decisions for orphan medicines?*

The final paper (chapter 9) focused on the Canadian healthcare system and the dynamics between HTA and provincial decision-making for funding in the case of orphan medicines. As described above, unlike other healthcare systems, Canada has no national orphan medicine policy and there are no dedicated assessment frameworks for orphan medicines neither at regulatory nor at HTA levels. However, specialised pathways for MA targeting medicines of high unmet need exist while specialised funds for highly innovative and expensive medicines are available across provinces. This study focused on Ontario, the largest and most populous province in Canada. A sample of 155 medicine-indication pairs for the treatment of rare diseases which were approved and marketed in Canada between 2002 and 2022 was studied.

The aim of this paper was the following:

1. To test alignment between HTA recommendations, outcomes of pan-Canadian pricing negotiations and provincial funding decisions in Ontario;
2. To explore the extent to which HTA recommendations inform funding in Ontario while accounting for other factors that could potentially influence funding decisions.

Publicly available data were extracted from the Canadian regulatory agency for MA, CADTH and the ministry of health in Ontario. Cohen's kappa was used to test agreement between HTA recommendations and funding decisions, and a logistic regression model was designed to explore the relationship between HTA recommendations, outcomes of pricing negotiations and funding while controlling for eight other factors that might have had potentially an impact on funding, such as MA through specialised pathways, a cancer indication, the year of MA and HTA.

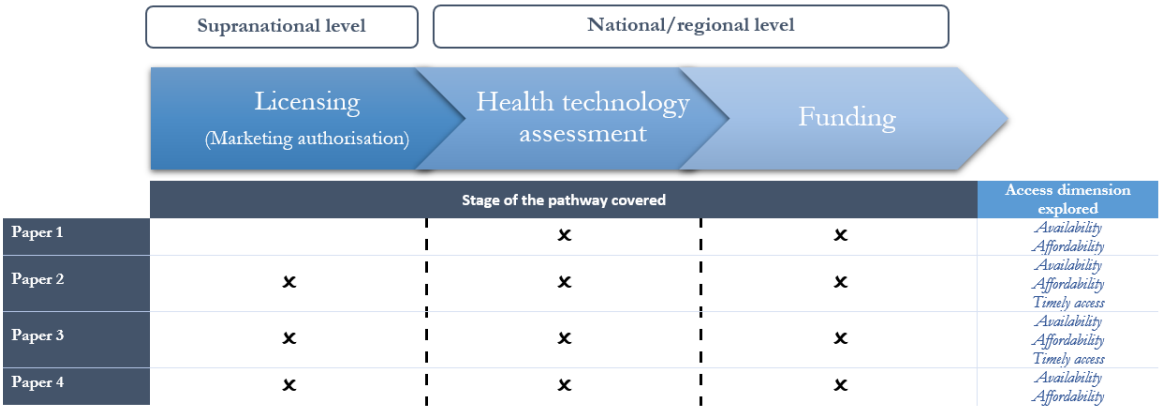
The results of this study showed that positive HTA recommendations were a good predictor of funding in Ontario for orphan medicines. However, there was only a fair agreement between HTA recommendations and funding decisions in Ontario, despite efforts made in Ontario to increase cooperation with CADTH and better align HTA and funding processes. According to the logistic regression analysis, there was a positive and statistically significant association between positive HTA recommendations and funding in Ontario. However, successful pan-Canadian pricing negotiations were the strongest predictor of funding. Interestingly, a negative HTA recommendation did not necessarily result in no pan-Canadian pricing negotiations and no funding in Ontario.

More than half of the sampled orphan medicine-indication pairs had a favourable recommendation for funding by CADTH (78%), and more than half of orphan medicines were funded in Ontario (73%), predominately through specialised funds. Interestingly, 52% of medicines with a negative HTA recommendation received funding in Ontario. Seventy-eight percent of the medicines in our sample with a positive HTA recommendation resulted in successful pricing negotiations while only 3% resulted in unsuccessful negotiations. From 102 medicine-indication pairs with successful pan-Canadian pricing negotiations, 88% received funding in Ontario while 12% did not.

Funding in Ontario was also likely (but not statistically significant) when a medicine-indication pair had received conditional MA, underwent priority review, and had a cancer indication. Contrary, first-in-class and ultra-orphan medicine-indication pairs were less likely to receive funding in Ontario.

Looking at the findings of this study, the translation of HTA recommendations into funding decisions in Ontario was not linear and clear, especially when the HTA outcome was unfavourable. Variations in access to medicines for treating rare diseases could have been seen possibly across provinces due to differences in regional budgets as well as differentiation in provincial policies related to medicines treating rare diseases. Therefore, implementation of a common, national strategy could help alleviate access variations to orphan medicines across Canada. Figure 6 shows the stages of a medicine's access pathway each paper has covered as well as what dimensions of access were explored.

Figure 6: Analytical framework of the thesis



Source: *The author.*

5 Thesis methods

This chapter aims to provide a more detailed overview of the data sources used and the methodological approach for data analysis in each chapter of this thesis. As this is a paper-based thesis, chapters 6-9 (papers 1-4) have a different geographic scope and use different datasets and analytical methods which were all carefully chosen to serve the research objectives and questions of each paper. The methodology followed in each paper is presented below.

5.1 Paper 1

Chapter 6 (paper 1) sets the scene of the thesis showcasing that even though HTA is being widely used across many developed countries, HTA systems are operationalised in different ways across settings. Variations in the way HTA systems are set-up within the healthcare system may explain, among many other factors, differences in the uptake of HTA recommendations during funding decisions. This chapter serves as a guide for choosing the geographic scope for chapters 8-9 (papers 3 and 4), as it helped in identifying countries with similar HTA systems that are comparable to each other.

5.1.1 Geographic scope

A broad geographic scope was chosen for this chapter to allow for systematic comparisons across various settings and include as many countries as possible to serve the basis of this thesis. All 27 EU member states, the UK, Australia and Canada were studied. Since, all EU member states were included in the study, the European network of health technology assessment (EUnetHTA) was included as a European organisation which performs joint HTA assessments at the EU level in order to study how an HTA body is set up in the supranational rather than national or regional level.

All sampled countries are developed countries, and their healthcare system is funded through general taxation or national health insurance contributions. In addition, they all provide universal health coverage to their citizens. Furthermore, they are all using HTA explicitly to inform funding decisions. Even though some regional HTA activities (which are captured in this paper) are seen in these countries, they all conduct HTA at national level and they all have explicit HTA processes which are performed on a routine basis. Their HTA functions are clearly outlined in the current legislation of each country and information about the HTA set-up and processes are publicly available and easy to access.

5.1.2 Conceptual framework and methodology

A conceptual framework to allow for comparisons of different HTA systems was designed. To build the conceptual framework, a literature review was conducted to identify salient features of

HTA. The aim of the literature review was to retrieve studies that were using validated frameworks to compare the HTA systems they were focusing on or explained the function of an HTA body or the relationship between HTA and reimbursement within a setting. The search was conducted using MEDLINE via PubMed and Scopus databases. The following key terms were used: (i) ('health technology assessment'; 'HTA'; 'value assessment'; 'comparative assessment',) and (ii) 'framework'. The search was restricted to keywords presented within the titles only to limit irrelevant hits. The search was limited to the English language, and the timeline was set between 2005 to 2017 which was the year when this study commenced. 2005 was chosen as the start date since by this year different independent HTA bodies with clear responsibilities had already been established in some of the study countries. Thus, evidence of their function would have been reported in the literature. For instance, the French HTA body and one of the German HTA bodies were established in 2004, the Polish HTA body was established in 2005 and the common drug review of Canada became permanent in 2004. The search did not apply any geographic restrictions to not limit results as the initial database search was limited to titles only. Search results were downloaded using EndNote, a commercial reference management software, and duplicates were removed. The remaining papers were screened through their titles and abstracts based on their relevance to the broader scope (i.e.: studying HTA systems). Papers which were focusing on other geographic settings than our study countries were excluded. The initial title and abstract screening was conducted by myself, and the second screening was done by one of my co-authors (EV). The relevant papers were downloaded for full-text review.

Papers were included only when a conceptual or analytical framework was designed originally by the authors to (i) compare HTA systems across settings and/or (ii) explain the way an HTA system is set up and operationalised within a country, and/or (iii) describe the relationship between HTA and reimbursement within the study country(ies). Exclusion criteria applied were the following: (i) studies that used previously published frameworks or (ii) studies comparing HTA outcomes for the same medicines across settings which focused only on the evaluation process such as discrepancies in the clinical and economic evidence submitted or evidentiary requirements of HTA bodies. These studies were outside the scope of this review which aimed to identify how HTA systems are set up within healthcare systems and observe how HTA recommendations inform reimbursement decision-making within a setting.

An additional targeted search was conducted on the websites of EUnetHTA and the European Commission to identify studies that summarise and map European HTA systems. The websites were navigated using the search tool and the same keywords as the ones used in the literature search. The same inclusion and exclusion criteria were applied. Only recent studies, from 2015-

onwards, were considered in the targeted search to avoid dated evidence. The targeted search allowed us to identify recent evidence on how HTA bodies are currently set up within European healthcare systems and provide us with information on the way HTA outcomes inform funding decisions within European countries in order to update and expand conceptual frameworks found in the peer-reviewed literature.

Using an excel spreadsheet, relevant information was extracted after reading the content of all the papers and reports extracted from both searches and met the inclusion criteria. The titles of the papers were presented in rows while the identified key thematic areas on the salient features of HTA systems were recorded across the columns.

The included salient features of HTA, hence the endpoints of this study were based on existing frameworks of the literature. However, they were further adjusted, updated, extended, and categorised into sub-groups following an iterative approach. This was because existing frameworks mainly focus on HTA assessments and the criteria used to make recommendations for funding in combination with a few structural features or key components such as transparency and scientific rigour (14,17,233–239).

The conceptual framework created in this paper differs from existing ones as it provides a holistic overview of HTA systems and enables key stakeholders to understand how and why HTA systems differ across settings and whether HTA recommendations inform funding decisions and to what extent. The design of the framework and the classification of the feature's options were further validated by a round of expert consultation with European key stakeholders (more information about the expert consultation is provided in sub-section 5.1.4.2).

5.1.3 Study endpoints

The salient features of HTA systems stemming from the conceptual framework along with the relevant categories seen across settings are presented in Table 3. These features served as the main study endpoints which allowed us to explore the similarities and differences of HTA systems across the study countries. Two additional endpoints, beyond the ones of the conceptual framework, were included to allow capturing additional HTA activities within healthcare systems. These additional dimensions explore the dynamics within settings when more than one organisation undertakes HTA activities and outlines the mechanisms of reimbursement decision-making process when more than one responsible agency is present within a setting. Information about these endpoints was collected through a round of expert consultation (more information is provided in sub-section 5.1.4.2).

Table 3: Study endpoints derived by the conceptual framework

Endpoint	HTA governance	Type of organisation performing HTA	HTA role	HTA scope and geographical coverage	HTA remit	HTA model	Assessment Vs. appraisal	Stakeholder involvement	HTA and funding
Categories	1.Arms' length 2.Integrated	1. Research Institution 2. HTA-Research Institution 3. National insurance organisation 4. National/Regional healthcare system organisations 5. National/Regional HTA Body 6. Governmental organisation 7. Medicines Regulator	1. Advisory 2. Regulatory 3. Coordination	1. National 2. Regional	1. Medicines 2. Medical devices 3. Other technologies including public health interventions	1. Clinical and cost-effectiveness 2. Clinical benefit 3. Value-based	1. Assessment 2. Appraisal	1. In the HTA committee 2. As external consultation	1. Binding 2. Non-binding
Description	Whether the HTA body operates independently from the government or is integrated within governmental structures.	Different types of institutions can perform HTA or HTA activities within settings.	The role of the HTA body in the decision-making process for funding depending on the intent and type of assessment required, the general mission and overall objectives of the review body.	The scope of and where the HTA body operates depending on the structure of the healthcare system and the balance between local	What type of health technologies are subject to HTA.	The way healthcare technologies are assessed depending on the evaluation criteria used during HTA which reflect the objectives and priorities of the healthcare system.	Assessment refers to the process of collecting, reviewing and synthesising clinical and economic evidence. Appraisal uses the same clinical and economic evidence but	At what point of the HTA assessment relevant stakeholders are involved and the type of stakeholders.	Whether decision-makers are legally obliged to follow HTA recommendations or not.

				autonomy and centralised control.			interprets it in the context of the healthcare system considering other factors that may be of relevance for decision-making.		

Source: *The authors.*

5.1.4 Data sources

Both primary and secondary data collection was conducted for this study. Even though information against the study endpoints was available through public sources, my co-authors and I deemed that validation, through expert consultation, of our conceptual framework and findings from our mapping exercise was further needed. In addition, primary sources allowed us to capture how and to what extent HTA informs funding decisions as well as better understand how multiple HTA bodies within settings, if applicable, collaborate with each other.

5.1.4.1 Secondary data collection

To identify whether the study countries have an organisation (or more) which performs HTA activities, thorough desk research was first conducted (by myself) by visiting and navigating through the websites of the country's ministry of health and the social health insurance and of international organisations such as the WHO, EUnetHTA, INAHTA, the European Commission, and the ISPOR Global Health Care Systems Road Map. Further searches were conducted on Google Scholar using 'health technology assessment' and the country's name as key terms to cross-reference whether the information found from the initial search was up to date.

Using an excel spreadsheet, I created a list of all the organisations performing HTA across the study countries along with a link to their websites. Countries were included in the study only if they had an organisation that performs HTA routinely and HTA activities are stipulated under local legislation. Northern Ireland was the only country excluded from this study as there is no HTA body or any other institution that performs HTA activities. The Northern Irish Department of Health predominately relies on the English HTA body, and no assessments are taking place at a local level. Multiple institutions which conduct HTA within a country were recorded, if existed. When more than one national HTA body was identified in any given country were all included in the sample. In the same excel spreadsheet, the scope of the identified institutions was recorded by specifying whether they conduct HTA at national or regional level. Organisations that perform HTA only on an ad-hoc basis or hospitals and local providers which perform HTA at a small scale, such as mini-HTA on ambulatory care medicines or hospital technologies, were excluded. Similarly, only key regional bodies were included in the sample due to data availability. For instance, Spain, beyond regional HTA bodies which are evaluation units of the general state administration and the autonomous communities, has numerous smaller regional bodies which mainly assess ambulatory care medicines. These bodies were not included in the sample as they conduct HTA in a small scale.

In the final sample, 63 institutions performing HTA activities explicitly were identified in 32 countries. Institutions were classified into seven categories based on their nature and structure, where these institutions lie within the healthcare system and the way they are funded. For example, research and HTA-research institutions are independent of the government and do not necessarily receive their entire funding from the government. The seven categories included were: 1) Research Institution; 2) HTA-Research Institution when there is a dedicated department for HTA activities; 3) National insurance organisation; 4) National/regional healthcare organisation which might be independent or under the supervision of the Ministry of Health focusing on public health matters; 5) National/regional HTA body when HTA is the main activity of this body; 6) Governmental organisation when it is part of the Ministry of Health, and 7) Medicines Regulator which is a regulatory body for approval of medicines and/or medical devices with a clear separate HTA function. All the information was recorded in the same excel spreadsheet, where countries and organisations performing HTA were in rows and the study endpoints were in columns. At this point, the classification of the type of institutions performing HTA was cross-checked by my co-authors (EV and PK).

To identify information against the remaining study endpoints for the identified organisations performing HTA across the study countries, I searched through the websites of the competent authorities including the bodies performing HTA, the national and/or regional ministries of health and the national/regional health insurance(s). I searched through the relevant sections of the websites in their original language using the Google translate extension of the Google Chrome browser to translate the website's content into English. I decided against using the English version offered in countries where English is not the official language, as often less information is documented in this version of the website compared to the original one. Relevant reports and legislations which outlined the methodology used in HTA, HTA procedures, HTA organisation and stipulations on stakeholders' involvement were downloaded for review. These documents were translated, when needed, using the Google Translate website. I conducted additional searches on the websites of INAHTA, WHO and the ISPOR Global Health Care Systems Road Map to cross-reference the information retrieved. Finally, when further clarifications or additional information were needed, a literature search was conducted on MEDLINE via PubMed and Scopus databases, through the tiles of papers and using the search terms "Health technology assessment" or "HTA" and the name of the country. The literature search was limited to English and on a short timeframe between 2015 and 2018 (when the data collection was performed). In cases where I was unsure about the recorded information or when I could not locate relevant

information, I consulted with my co-authors (EV and PK). All the information retrieved by the secondary data collection was recorded in the same excel spreadsheet. The secondary data collection took place initially between December 2016 to July 2018. Data were updated, when applicable, in March 2020.

5.1.4.2 Primary data collection

To validate and complement the conceptual framework, the categorisation of the HTA salient features and the evidence from the secondary data collection, primary data collection was conducted through a consultation round with key HTA experts. Information on two additional study endpoints for which evidence was not available through publicly available sources was collected at this stage (i.e.: information about any formal or informal HTA activity taking place which was not captured in our desk search and details on how multiple organisations performing HTA within countries collaborate in relation to assessments and final decision-making).

Key experts were identified through the members of the European Commission's DG SANTE Unit B4—Medical products: quality, safety, innovation as a part of a European research project named improved methods and actionable tools for enhancing HTA (IMPACT-HTA). A purposive sample was used for the inclusion of experts aiming to include leading European HTA and pharmaceutical policy experts affiliated with universities and national competent institutions, such as regulatory agencies, departments responsible for pricing or reimbursement decisions and HTA agencies. Due to the nature of our study which was to capture how HTA systems are set up within the healthcare system, we deemed that representation of different stakeholder groups (i.e.: pharmaceutical industry, patient groups, clinicians) was not necessary. And representation of one expert from each country will suffice to validate our findings. Experts from countries with less well-established HTA systems and countries where more than one institution performing HTA exists were prioritised as little available information was identified from secondary sources in English, and because additional information was needed to understand how multiple HTA bodies collaborate and interact with each other.

Twenty-nine HTA experts across the European Union and the UK were initially contacted via email in June 2019. We identified one expert for each EU member state, with the exception of Poland, where three suitable experts were identified and Hungary and Austria, where two relevant experts were included. In these three countries, more than one expert were included due to differences in their affiliations (i.e.: academia, HTA body, regulatory agency). Even though including more than one expert in these countries (in contrast to the rest of the countries in our

sample) may have introduced sample imbalances, we were able to cross-reference the information provided from the different individuals and test whether there is a mismatch in their opinions. We were unable to identify relevant experts from Australia, Canada, Lithuania, Latvia and Luxembourg. One expert was identified for the UK.

Of the 29 contacted experts, 18 experts from 14 European Union member states, including Estonia, Ireland, Poland (n=3), Portugal, Romania, Slovakia, Slovenia, Spain, Sweden (n=2), Malta, Bulgaria, Austria (n=2), Belgium and Czech Republic, responded to our call within the set timeframe and shared their comments and feedback on the questions asked. The remaining 11 experts did not respond to our request.

Sample bias was introduced due to (i) the lack of representation of experts from some of the study countries and (ii) inclusion of only one expert across the study countries. However, given that the primary aim of this study was to build a conceptual framework that allows cross-country comparisons based on existing frameworks and the iterative process described earlier, lack of experts from some of the countries did not necessarily have an impact on the study's objective. This is because, the designed framework would have been already reviewed by experts from other countries with a broadly similar system to that of the countries we could not identify relevant experts from. In addition, bias due to inclusion of one expert from each country did not reduce the validity of our results, given that the main objective of the expert consultation was to validate and complement the findings of the secondary data collection, rather than contribute to evidence generation.

In the email to experts, two Word documents were attached: One document outlining the research objectives and clear instructions on the process and a second document which included the conceptual framework and the classification of HTA salient features as well as country-specific information extracted through secondary data collection and presented in a concise and narrative way (an example of the second document is presented Appendix 1). The second document was individualised for each participant with relevant information about the country they represented. Specifically, we asked the experts to: i) Comment on the design of the conceptual framework; ii) Confirm whether we had classified appropriately the key features of HTA systems according to our findings from secondary sources; iii) Provide additional information about any formal or informal HTA activity taking place in their countries which we had not been captured in our search (if applicable); and iv) To provide details about how multiple organisations which undertake HTA activities within countries collaborate in relation to assessments and final decision-making (if the

respondent was based in a country with more than one HTA agency). All stakeholders were asked to return the second document via email with their comments and feedback by the end of July 2019. A follow-up email was sent after two weeks of the initial email to the participants who had not responded to our request.

5.1.5 Data analysis

Evidence collected from both primary and secondary data collection was summarised and presented in a narrative way. Descriptive statistics in terms of percentages were used to summarise data against each endpoint of the conceptual framework. Percentages were calculated in Excel. Information was arranged by the study endpoints: (i) governance of HTA; (ii) type of organisation performing HTA; (iii) role of HTA; (iv) scope and geographical coverage of HTA; (v) remit of HTA; (vi) model of HTA; (vii) assessment vs. appraisal; (viii) HTA recommendations and funding decisions; (ix) involvement of stakeholders, and; (x) relationship of multiple HTA bodies within countries and how coverage decisions are informed.

5.2 Paper 2

Extensive research has been conducted to understand why access to medicines varies across settings due to differences in HTA evaluation processes. Current research focuses on HTA recommendations for the same medicines, however, access variations might be intensified by other features of HTA, such as HTA timelines or stakeholder involvement during evaluation and/or decision-making. Through a scoping review of the literature, in chapter 7 (paper 2), I identified areas of HTA that are considered to be the drivers of access variations or hurdles to innovative medicines in Europe. In addition, I gathered evidence on current efforts at national or supernational level, in Europe, to optimise access to innovative medicines at HTA level. Using a comprehensive definition of access and aiming to validate the findings of the scoping review, this paper elicits the views and opinions of relevant stakeholders, using the Delphi technique, on what features of HTA facilitate access to new medicines and what features needs improvement. Through this exercise, performance of HTA processes is explored in a holistic way, from its set-up, the evaluation processes employed and its role in funding decision-making, against different access metrics.

5.2.1 Selection of value dimensions

A two-step approach was employed to create a list of value dimensions for the Delphi panel: The list of value dimensions included (i) HTA features that are considered to have a positive impact

on access to innovative medicines, according to the findings of the scoping review, and (ii) included a comprehensive definition of access using different access metrics.

5.2.1.1 HTA features

Firstly, a scoping review was conducted to identify general features of HTA that showed to have an impact on access or features that can be improved in order to optimise access to new and innovative medicines. I decided to conduct a scoping review over a systematic literature review, as the scope of this search and the inclusion criteria were broader than the ones usually used in a systematic literature review. According to Munn et al. 2018, scoping reviews can help to identify and map available evidence that is still unclear and cannot yet be addressed through a more precise systematic review (240). In addition, a scoping review can be conducted when key characteristics or factors related to a concept are identified (240). Therefore, in alignment with the objectives of this chapter, a scoping review was performed.

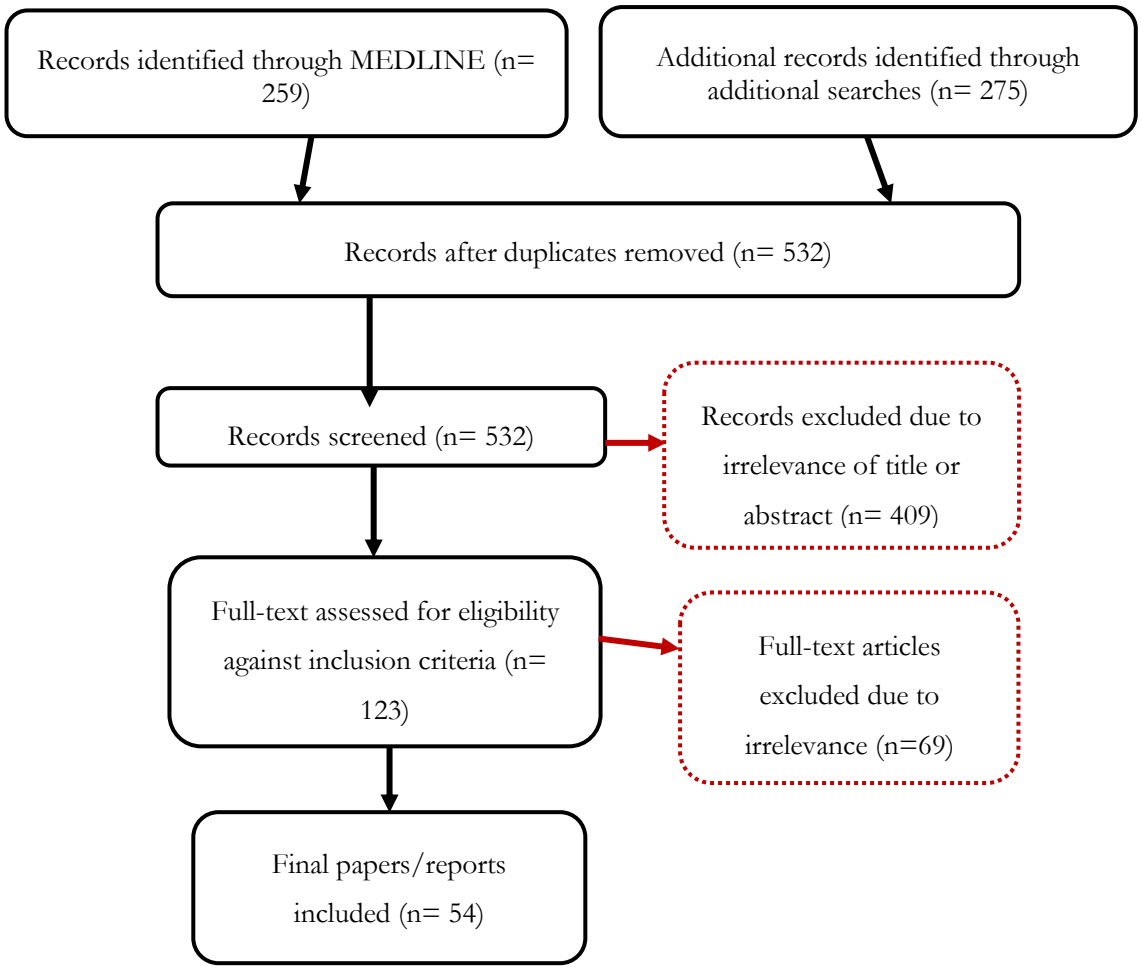
An advanced search was conducted in the MEDLINE via PubMed database to identify peer-reviewed papers from January 2011 to December 2021. The following keywords were used: ('health technology assessment' OR 'HTA' OR 'value assessment') AND 'Europe'. The relevant terms were searched through the titles and abstracts of the papers and the search was limited to the English language. Initially, 'access' was used as an additional key term, however, it had to be removed from the search terms as it was limiting our results substantially.

Search results were downloaded using EndNote and duplicates were removed, when identified. An initial screening through the titles and abstracts was conducted to identify relevant papers that focuses on HTA of in-patent medicines and study access variations due to HTA. An additional screening in the titles and abstracts was conducted by one of my co-authors (BK). Papers were excluded from the initial screening, when they were focusing on medical devices or other technologies (i.e.: vaccines, diagnostics, biomarkers or surgical procedures) or off-patent and generic medicines or hospital-based HTA; when they were clinical and cost-effectiveness assessments conducted by the authors instead of relevant national or regional authorities which officially conduct HTA; when alternative value assessment processes than HTA were explored, such as multiple-criteria decision analysis (MCDA), and; when other stages of a medicine's access pathway such as regulatory and MA processes, the development phase of medicines or innovative pricing mechanisms and MEAs or clinical guidelines, were studied. The full texts of the remaining papers were screened, by me, to identify features of HTA that facilitate or impede access or are responsible for observed variations in HTA recommendations for the same medicines across

settings. Any information on current efforts to improve HTA processes at national or supranational level in Europe was also extracted. An additional search was conducted on the website of the European Commission and EUnetHTA to identify relevant grey literature on HTA in Europe. 'Health technology assessment' OR 'HTA' were used as key terms for the search and the same inclusion and exclusion criteria as the ones used in the scoping review were used for the screening of the relevant hits. Reports published from 2017 and onwards were only included to capture recent developments and the current landscape of HTA in Europe.

The different steps and the search results of each step are presented in Figure 7 below.

Figure 7: Flow diagram of the scoping review process



Relevant information from both searches was recorded in an excel spreadsheet. To organise the extracted information, I follow an iterative process and I classified the extracted evidence into the following four main categories: (1) HTA system, which included features related to how HTA is set up within the healthcare system ; (2) HTA procedures, which were related to administrative stipulations; (3) HTA evaluation process, which were related to the assessment of the submitted evidence and (4) HTA and funding decisions, which reflected how and to what extent HTA is being used during funding decision-making. Initially, information was recorded as a full text extracted from the initial source but was subsequently re-worded as statements after three reiterations with my co-authors (BK and PK).

5.2.1.1.1 Scoping review results on HTA features and areas for improvement to optimise access to medicines

HTA system: The way healthcare and HTA systems are organised and set up can contribute to access delays (15,18,20,86,156–158,235). This can manifest itself within the HTA system, such as in Greece, where HTA is integrated within the government and the national payer and unclear or non-transparent connections and interactions between the multiple institutions involved result in unnecessary delays in funding negotiations (15,157), or in Italy, where the multi-level structure of HTA results in increased inequality of access to new medical technologies (158). Characteristics of the wider healthcare system may also create variation in patient access, such as the decentralised healthcare systems of Italy or Spain which can result in variation across regions because of divergent HTA recommendations or funding decisions due to differences in the methodologies used to assess technologies and the selection of technologies undergoing assessment (18,20,86,159,235).

HTA procedures: Extensive evidence variations in the HTA procedures employed by different HTA bodies, (such as whether HTA commences before or after marketing authorisation, the actual timelines of HTA evaluations, and whether and/or to what extent external stakeholders are involved in the HTA process) might result in access delays or create unnecessary access hurdles (15–17,21,87,126,160,161,173,234,235). An example of how HTA processes can impact access negatively is seen in a few European countries: Bulgaria and Romania both rely on HTA decisions of other well-established HTA agencies, and as such, HTA processes in these countries might be delayed until HTA recommendations are published in the countries they use as a reference (169). Or, how timelines for HTA recommendations to be published after marketing authorisation vary significantly across countries in practice: Spain had the longest timelines (mean time of 713 days),

followed by Italy and Poland (504 and 462 days respectively), while France and Germany were the fastest, publishing HTA recommendations in 227 days and 199 days on average after marketing authorisation (86). Similar results were seen in another study where France had the fastest timelines (155 days) and Italy had the slowest ones (375 days) (160). When looking at the median timelines between MA and HTA submission, timelines also differed with seven days seen on average in England, 23 days in Italy, 29 days in France, 42 days in Germany and 49 days in Spain (160). These variations in time are due to different stipulations of HTA procedures. For instance, in Germany, the HTA assessment must be initiated within three months from MA approval according to German law (160). However, in other settings, HTA processes can only be initiated by manufacturers upon dossier submission (163). Stop-the-clock mechanisms, allowed by the English HTA for some medicines, can further lead to longer evaluation processes (160,164).

Better cooperation between regulatory and HTA bodies seems to be crucial for optimal and timely market access, with some collaborative processes being implemented in some settings to support this (172,183–186). The presence of early scientific advice from the HTA body to manufacturers before dossier submissions or during the medicine development process is a way to expedite HTA assessments (85,160,172,183–186,192). The provision of early scientific advice has aided manufacturers to generate evidence that meets the standards of both regulatory agencies and HTA bodies, however, according to key stakeholders this initiative had not yet succeeded to align regulatory and HTA requirements (85). Despite efforts to expedite assessment processes at regulatory level and harmonise assessment processes at both levels, still, a proportion of approved medicines do not result in positive HTA recommendations, and only in a few cases, HTA bodies seem to accept a lower quality of evidence which has already been approved by regulatory agencies (18,86,134,160,173,187–189).

Other elements which may have a positive impact is the stakeholder involvement in the HTA process (i.e.: for selecting which technologies should be assessed by the HTA body, during technology assessment or in the decision-making process for issuing HTA recommendation) (15,17,156,163,165–167). However, some researchers mentioned that divergent HTA recommendations for the same medicine across HTA bodies could be attributed to differences in the interpretation of the assessed evidence due to varying levels and types of stakeholders' involvement (87,129,131,163,168).

HTA evaluation processes: Differences in HTA recommendations across HTA bodies or observed access delays can also be attributed to variations in the assessment practices followed by

HTA bodies such as differences in evidentiary requirements, the potential inclusion of other value dimensions beyond clinical and cost-effectiveness, divergent ways to deal with uncertainty, and acceptance of real-world evidence (16–18,21,81,86,87,129,131,136,136,160,161,170–172,174–177,183,235). For example, HTA evaluation in Romania is mainly focused on costs rather than other additional value criteria creating challenges for patient access to innovative medicines (181), while in England a number of value and end-of-life criteria are considered explicitly in the assessment of some medicines, together with recognition of elements such as medicine innovation in deliberations on whether to accept higher willingness to pay thresholds (166,182). However, a study looking at 29 jurisdictions reported that more similarities than differences exist between major methodological aspects used in the HTA processes of the study countries, showing room for better cross-country co-operations (175). Another study reported, though, that manufacturers had to generate local contextualised evidence, including evidence on the local comparator, to meet specific evidentiary requirements of European HTA bodies. Almost 90% of submissions in England incorporated local information such as local standard of care and clinical practice, followed by 82% of the submission in Germany, 80% in Italy, 79% in Spain and 72% in France (160). Similarly, another study discussed that country-specific practice-related factors can explain differences in HTA recommendations across settings (126).

Heterogeneity in HTA recommendations across countries might also be attributed to differences in the acceptance of evidence from observational studies and indirect comparisons (81,129,136,175,178–180). However, evidence on whether acceptance of real-world data might improve access at HTA level is not widely positive: one study discussed that generation of real-world evidence might be one of the contributing factors for longer delays of access, as setting up registries can be time-consuming and bureaucratic (161), and another study highlighted that in Bulgaria, limited epidemiological data may pose an additional challenge to manufacturers for the preparation and submission of pharmacoeconomic and HTA dossiers beyond the lack of expertise for gathering data from real-world evidence (181).

HTA and funding: The relationship between HTA recommendations and funding decisions might play an important role for patient access. The most important challenge for patient access is a lack of an explicit framework on how to use HTA evidence in the decision-making process, while the availability of such a framework is among the most important facilitators (197). Evidence from middle-income European countries showed a lack of a legal framework for the implementation of HTA recommendations in funding decision-making (196), while another study

highlighted that this phenomenon is also observed in high-income countries where HTA systems are well-developed and established (168).

Across Europe, there are countries where HTA recommendations are not legally binding and, thus, not always followed during decision-making processes (15,163,168,235). A study looking at the agreement between HTA recommendations and funding decisions for oncology medicines in Central and Eastern Europe showed that there was a low level of agreement between HTA and funding in Poland where HTA recommendations are non-binding, contrary to Latvia where recommendations are binding (169). Similarly, a study in Poland, where HTA recommendations are not legally binding, showed only a fair agreement between national HTA recommendations and ministerial funding decisions between 2013 and 2015 (241). A more recent study focusing on oncology medicines in Central and Eastern Europe showed that there was a low level of agreement between HTA and funding in Poland, contrary to Latvia where recommendations are binding (169). Therefore, in systems where HTA recommendations are binding, their implementation in funding decisions is more straightforward. For instance, the English NHS should reimburse and make available within a timeframe of three months a medicine that received a positive HTA recommendation by the English HTA body (18).

Based on the above results, a list of HTA features that have or potentially could have a positive impact on access to innovative medicines in Europe was compiled and is presented in the box below.

HTA system	
1	Presence of an independent HTA body
HTA procedures	
2	Scientific advice provided to manufacturers ahead of commencement of formal HTA process by HTA bodies
3	Introduction of parallel review process to streamline MA and HTA
4	Stakeholder involvement during the HTA process
5	No reliance on "HTA referencing"
6	Agreed-upon timelines for the completion of HTA process
HTA evaluation processes	
7	Clarity of evidentiary requirements for value assessment in HTA
8	Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence
9	Harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level
10	Coordination of HTA rules, methods and processes across national and regional level, if both co-exist
11	Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies
12	Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe

HTA and funding decisions	
13	Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations

Source: *The authors based on the results of the scoping review.*

5.2.1.2 Access metrics

Secondly, as described earlier in sub-section 3.2, in the current literature, various metrics are used to test access to medicines within and across settings. Studies on how HTA can impact access focus predominately on HTA recommendations for funding, which are considered a proxy for the availability of innovative medicines within markets. However, evidence on how well HTA performs against other access metrics such as timely market access and affordability of the healthcare system is limited, while evidence across all access dimensions is lacking.

To provide a comprehensive definition of access to medicines, the different definitions or metrics of access used in the resulted papers of the scoping review were explored, when available. An additional search was conducted on the websites of international organisations such as the WHO, the United Nations and the European Commission to identify relevant metrics to HTA. Through this search, my co-authors (BK and PK) and I were able to define access using three relevant metrics which include:

- ***Availability of medicines***, whether clinically- and cost- effective medicines are available and marketed in a given market;
- ***Time to patient access (timeliness):*** the timely access of patients to publicly reimbursed medicines, and;
- ***Affordability:*** whether the prices of clinically- and cost- effective medicines are in line with the purchasing ability of healthcare systems and of patients.

Through the Delphi panel, stakeholders were asked to rank the HTA features according to whether they agree or disagree about their positive impact across the identified access metrics (e.g.: whether they agree that '*stakeholder involvement during HTA*' has a positive impact on '*the availability of medicines within markets*'; whether they agree that '*stakeholder involvement during HTA'* has a positive impact on '*the timely patient access'*; whether they agree that '*stakeholder involvement during HTA*' has a positive impact on '*affordability of the healthcare system and/or of patients'*).

5.2.2 The Delphi method

As discussed earlier the reasons why HTA can impact access to medicines and cause access variations across settings have been extensively studied in the literature by looking into HTA

recommendations of different HTA bodies for the same medicines. However, whether key stakeholders agree with the findings of the literature on how HTA systems and processes could be improved to positively impact access to new medicines has scarcely been explored, and evidence comes predominately from interviews with a few stakeholders. Even though interviews are a useful method to engage participants, they do so at an individual level, thus, group opinions and views cannot be elicited. A questionnaire can elicit the opinions of a group of participants; however, it does not allow for group communication (242).

The Delphi technique, unlike simple surveys, structures and organises group communications while allowing for controlled feedback to gain consensus of opinion of a group of participants, which are usually experts in the field (243–245). The Delphi method can be used for various research objectives such as reaching consensus of participants on a complex topic, prioritisation of policies or topics, generation of debate among participants who might not share a common vision or underlying set of values, and scenario development, among many others (246,247). The Delphi method is the appropriate methodology in case current knowledge is incomplete, uncertain or is lacking (248). Therefore, for the purpose of this paper, the Delphi method was employed to validate the findings of the current literature by soliciting controlled feedback from a group of experts on HTA from different geographic backgrounds and stakeholder groups. Given that stakeholders were from different countries in Europe, the Delphi technique was suitable as geographic proximity of the participants was not required.

The Delphi technique follows a series of consecutive questionnaires, known as rounds, to elicit the opinions of a group of individuals while respecting their anonymity. This way, participants can express their true opinion freely without introducing potential bias due to peer pressure or the presence of potentially dominant or more vocal experts, as observed in focus groups (243,247,249–255). During a series of rounds, panel participants can first respond to a set of questions and, in subsequent rounds, are given the opportunity to re-consider and re-assess their initial opinions after seeing the aggregate responses of other panel participants who might have different expertise and perspectives (243,247,249–255). Hence, the Delphi method is an iterative process that avoids intentional and unintentional noise, such as irrelevant and non-productive communication amongst the participants (245,247).

In the literature, there is extensive, and sometimes divergent, evidence on how a Delphi panel should be designed and conducted. There are still no strict guidelines on the correct number of rounds, the suitable number of participants and suitable methods of analysing results, which all

depend on the research objectives of each study (248,256–262). Delphi rounds can be either set prior or can continue until consensus amongst participants is reached. Research guidelines for the Delphi technique mentioned that usually a Delphi panel has four rounds (252,263), however, many studies have conducted three or two rounds according to their research objectives (256–258,264). Given that the aim of this study is to validate the findings of the scoping review, and not generate a list of value dimensions according to participants input, two rounds were deemed sufficient.

No set minimum or maximum participant number for Delphi panels exists, with Delphi panels being conducted from five up to thousands of participants with an appropriate number of participants dictated by the objectives and nature of the study (248,256–262). According to methodological advice, and Delphi panels in practice, participants often range between 10 to 20 participants (252,260–262,265).

As any other method, the Delphi technique comes with some limitations. High dropout and poor response rates have been documented in the literature (245). In addition, convergence towards the group opinion is hard to be avoided when many iterations are taking place. However, consideration of the opinions of others is a necessary part of the process of building consensus (266). In addition, the Delphi technique dictates considerable preparation time and needs very thorough planning (245). To tackle these limitations, in this study, we performed only two rounds to ensure desirable completion rates and reduce convergence towards group opinions due to fatigue as much as possible. In addition, an online software was used, Welphi®, to design the panel using an effective lay-out and supporting us throughout the process with the dissemination of the questionnaires across all participants and aggregation of group responses for the second round. Table 4 summarises the main strengths and weaknesses of the Delphi method.

Table 4: Strengths and weaknesses of the Delphi method

Strengths	Weaknesses
• Anonymity of participants • Iterative process • Controlled feedback • No geographical proximity required • Statistical group response • Building of consensus in areas of uncertainty	• High drop-out rates due to participants' fatigue. • Convergence towards group opinion • Considerable preparation time and planning. • Lack of clear guidance on how to design and conduct a Delphi panel and what analytical methods to use, which can all lead to inconclusive results.

Source: The author adapted by existing literature on the Delphi technique presented in this sub-section.

5.2.3 Geographic scope and selection of relevant stakeholders

The geographic scope for this chapter followed similar criteria as the ones used in paper 1 (chapter 6, as discussed in sub-section 5.1.1). A broad geographic scope was selected to explore whether stakeholders agree with each other despite differences in the HTA systems they represent. Similarly, to paper 1, in this paper, stakeholders from various countries are involved to avoid bias in our findings in case of over-representation of only well-developed HTA systems. However, in this study, recognising that harmonisation of HTA processes is easier to occur in countries which are geographically close and have broadly similar socioeconomic profiles and healthcare systems, Canada and Australia were excluded.

To select relevant stakeholders that could participate in this study a purposive sampling strategy was employed aiming to have a good representation of participants from different stakeholders' groups. My co-authors and I started to compile a list of relevant stakeholders across all EU member states countries, including Norway, Switzerland, and the UK. Invited experts (n=128) were either from academic or health policy research institutions, the pharmaceutical industry, decision-making/payer bodies, or patient organisations in order to capture the views of relevant stakeholders.

To ensure a representative sample of European stakeholders, we invited a minimum of four experts, one of each stakeholder group, across all study countries. We tried to ensure that invited experts had considerable knowledge of HTA and they had been somehow involved in HTA activities to some extent. For example, they conduct research on HTA, are responsible of HTA strategy within their countries or they are part of an HTA committee.

Recognising that some of the participants would have not been able to participate in this study due to busy schedules, we also followed a snowball sampling strategy. This entailed that in case contacted stakeholders would not have been able to participate in the study, they were asked to suggest other people from their network or their affiliated institution with expertise on HTA and who would be potentially willing to participate. Where an alternate expert was identified, the original invitee was asked to provide the name, email and job title of their suggested colleague. Subsequently, my co-authors and I assessed whether the suggested the expertise of the suggested participant was relevant to the research objectives of this study. This way, we tried to avoid a low participation rate or bias introduced in our study when a country was not represented by at least one relevant stakeholder.

However, a limitation of this study is that healthcare professionals were not included in the sample as my co-authors, and I were unable to identify clinicians that were familiar with and/or involved in HTA through either their network or the sampling strategies used.

5.2.4 Study design and administration

To test the web-Delphi tool before sending it to stakeholders and improve its structure or content to be more user friendly, we piloted the first round of the Delphi panel to five members of our research team at the London School of Economics and Political Science. Once our colleagues completed the online survey, a meeting was set up with them to discuss their comments and feedback. Their feedback was subsequently incorporated in the final version of the questionnaire which was sent to all the 128 potential participants. The online survey was taking approximately 10 minutes to complete.

Initially, an email was sent to all stakeholders, inviting them to participate in this study. In the email, we briefly outlined the objectives of the study, explained the Delphi process and clearly stated the deadlines for completion of the requested task. As explained above, we asked the contacted stakeholders to forward the email to their colleagues in case they would not have been able to participate. We kindly asked the stakeholders who opt for this option to respond to our email with the name, email and job title of their suggested colleagues. An additional Word document was sent as an attachment to the email explaining in detail how we derive to the final list of value dimensions, how a Delphi panel works and what we expect from their participation.

Subsequently, an automated email with a unique URL link was sent to each participant and their suggested colleague, if applicable, through Welphi® (the selected software for the web-Delphi survey). With this link, participants were able to commence the first round of the Delphi panel. At this point all participants were blinded by Welphi® and each participant had a unique identifier containing an alphanumeric string (e.g.: 079AB). In the online platform, participants were requested to complete an informed consent form in order to be able to continue with the Delphi process. This was in line with the ethics approval granted by the London School of Economics and Political Science with the reference number 86998. All participants were asked to respond to demographic questions including the country they live and work in, their organisation affiliation, and their perspective selected from a list of pre-defined categories: research and policy, patient/patient organisation, industry, or decision-maker/payer. Participants were given clear definitions of all three access domains (i.e.: availability, time to patient access, affordability) which were also appearing as pop-up boxes in the survey.

The list of HTA features appeared in rows and the access dimensions appeared in columns (as seen in Appendix 2). A total of 39 value statements was included in this Delphi panel (13 HTA features across three access dimensions). Participants were able to rank their agreement using a 5-point Likert scale ('strongly agree' (SA), agree' (A), 'neither agree nor disagree', 'disagree' (D), 'strongly disagree' (SD)) on the positive impact of the HTA features on the three access dimensions. To ensure reliability of the panel's outcomes, participants were given the option to select 'do not know' for instances where they did not feel confident about their response in a given value statement and a 'not applicable' option was also given to allow participants to indicate HTA features they felt might not be relevant to a metric of access. According to the literature, an optimal number of points in Likert-scale is between four to seven and Delphi panels should provide a 'do not know' option given that participants have different knowledge, expertise and backgrounds (248,267). However, it is important to note that by having a midpoint in the Likert scale (i.e.: 'neither agree nor disagree') gave the possibility to some participants to remain neutral (248). However, we deemed that a more neutral choice could help us identify areas of HTA that do not need to be prioritised and adapted imminently to optimise access to medicines. An open-ended question was available to the participants only in the first round to provide the opportunity to add any factor that, in their opinion, might have a positive impact on access and was not included in our pre-defined list.

The first round of the Delphi panel remained open for a month. Automated thank you emails were sent to participants who completed the first round, including details about the second round and relevant timelines. Automated reminders were sent every week to participants who had not started the survey and participants who have not yet completed their responses. In total, three reminders were sent in each round to encourage experts to participate or finalise their responses, when applicable.

Once the first round was completed on the upon agreed deadline, the list of the participants' unique ID who completed fully the first round was generated. These participants were the only ones who received an invitation to the second round of the web-Delphi panel. Similarly, to the first round, participants had a month to complete the round. In round 2, participants saw the same interface of the webpage as the one used for the first round. However, in this round, participants were able to see the aggregate responses of all the participants from the first round as percentages. Participants were asked to either keep their initial responses or revised the responses by ranking the value statements using the 5-point Likert scale and the 'do not know' and 'not applicable'

options, as described above. Unlike the first round, participants did not have the option to make any comments through an open-ended question.

As in the first round, participants who did not commence the second round or who did not complete their responses were sent automated reminders through the platform every week. And automated thank you emails were sent to the participants who completed the second round successfully.

Once the two rounds of the web-Delphi process were completed, an Excel document was sent to me by Welphi®. Six separate spreadsheets were included in the Excel document. The first two spreadsheets included the general characteristics of the participants in the first and second rounds, respectively. In the rows, the unique identifier for each participant was recorded and, in the columns, the country each participant was represented, and their affiliation were recorded. The four remaining spreadsheets included one spreadsheet with the responses of the participants presented in an aggregate way as percentages and one spreadsheet included raw data for each round, respectively. In the aggregate data, HTA features were presented in the rows and the three access dimensions in the columns, while in the respective cells the percentage agreement of the participants across all the points of the Likert scale were presented including the 'do not know' and 'not applicable' options. In the spreadsheets containing the raw data, in the rows the unique identifier of participants was recorded while in the columns each HTA feature was presented three times for each access dimension (e.g.: Stakeholder involvement-availability, Stakeholder involvement - timely access and Stakeholder involvement - affordability). In the cells, the response of each participant was recorded in text (e.g.: 'agree'). The text was, then, coded numerically to allow for statistical analysis, where 'strongly agree=1'; 'agree'=2; 'neither agree nor disagree'=3; 'disagree'=4; 'strongly disagree'=5; 'do not know'=6, and; 'not applicable'=7.

5.2.5 Data analysis

To analyse the data generated by the Delphi panel, we had to take into consideration the objectives of this study. Unlike other studies which have received a lot of criticism (247,248,268), consensus was not used as a stopping criterion for the dissemination of additional rounds (i.e.: the Delphi panel is sent to participants for additional iterations until group agreement is reached), rather, it was used as one of our objectives. However, it is important to note, that consensus is a term poorly and ambiguously defined in the literature (247) while its measurement greatly varies across studies (247,248,269). Different definitions have been used for consensus. According to Mitchell (1991) these include*: "group opinion, general agreement, or group solidarity in sentiment and belief*" (270). However,

a generally agreed term is lacking. To tackle such issues, in this study, we tried to differentiate between agreement and consensus using different criteria to test whether these have been achieved. For consensus, stricter criteria were applied compared to group agreement in order to be able to avoid inconclusive results. However, given that consensus is based on subjective criteria, it was only used for the discussion of the paper rather than actual findings.

As focusing only on the agreement or consensus reached amongst participants could introduce bias, group stability, defined as "*the consistency of responses between successive rounds of a study*" was tested following suggestions of relevant literature (243,247,268). Therefore, in this study, group stability was further calculated. Group stability is, generally, preferred over individual stability since the Delphi method is focusing on group opinions rather than that of individuals (268,271). Finally, bearing in mind that convergence towards group agreement can occur due to the nature of Delphi technique, as discussed earlier in sub-section 5.2.2, we further explored whether stakeholders converged their judgments towards group agreement/consensus.

All the analytical methods were chosen after the dissemination of the Delphi questionnaire, taking into consideration the ordinal nature of the Likert scale and our study objectives. All the analysis focused on the individual HTA features and their impact on access metrics rather than focusing on stakeholder groups or rankings across the board, given that our aim was to identify which of these features can positively impact access. Therefore, all analysis was conducted for 39 statements, covering each of the 13 HTA dimensions across the three access domains. In the analysis, 'do not know' and 'not applicable' responses were not included to limit analysis to participants who were confident with their responses. Strongly agree (SA) and agree (A) and strongly disagree (SD) and disagree(D) responses were grouped, respectively, for the percentage agreement analysis. Responses on the open-ended question available in round 1 were used only as contextual information to avoid mismatch on how many times value statements were included, and therefore, ranked in subsequent rounds. All analyses were conducted in Stata SE 16.1 and SPSS Version 27.

To decide what type of analytical methods should be used for our analysis, I conducted a thorough search of the literature on Delphi panel methodologies (247,255,258,259,272–274) and other studies using the Delphi technique (251,260,275–284). Quantitative methods were used, including both descriptive and inferential statistics. In some applicable cases, to validate the robustness of the Delphi panel results and recognising that there is limited to no evidence on which exact method is the most suitable to use in specific circumstances, or how results can change when using different methodologies, additional analysis was conducted using other commonly used methods. To test

for the agreement of participants and whether consensus was achieved results of the second round of the Delphi panel were used. While to test for stability, responses from both rounds were used.

5.2.5.1 Agreement

The agreement was tested for two different endpoints. First, to identify ***what features of HTA had the most positive impact on the access metrics***, percentage agreement and central tendency with level of dispersion were used to analyse the responses of participants in the second round. Both these analytical methods have been used extensively and interchangeably in the literature. Therefore, we decided to analyse our results with both techniques to explore whether different conclusions are drawn.

For percentage agreement, a statement was approved by absolute majority when aggregate responses of 'strongly agree' were higher than 50% and 'strongly disagree' and 'disagree' was lower than 33.3%. A statement was approved by qualified majority when 'strongly agree' and 'agree' responses were higher than 75%. And a statement was rejected by absolute majority when 'strongly disagree' and 'disagree responses' were higher than 50% (247,251).

The central tendency and dispersion were calculated using the median and the interquartile range. The median showed what respondents think on average or in other words, what is the likeliest response. Value dimensions with a median of 1 or 2, which relate to 'strongly agree' and 'agree' where the ones that showed the features of HTA that had the most positive impact on access metrics. While statements with a median of 4 and 5 ('disagree' and 'strongly disagree') showed the HTA features that participants thought had the least positive impact on access. To test whether participants generally agreed with each other, the interquartile range (IQR) was calculated. Agreement amongst participants was considered when the IQR equal or less than 1, meaning that more than 50% of all opinions fall within one point of the Likert scale. An IQR of more than one showed lack of agreement (high level of dissent) amongst participants. According to the literature, when a Likert scale has 4 to 5 units, an IQR of 1 or less is suitable to test for agreement (247,269,285). The median and the IQR were chosen as measures of central tendency and dispersion over mean and standard deviation given that they are more robust as they do not tend to change with extreme responses that might be outliers (247).

Second, to explore ***whether participants agree with each other on the ranking they gave to each value statement in each round, regardless of the ranking they gave,*** inter-rater reliability (IRR) was calculated using Gwet's kappa coefficient applying weights for ordinal data (due to the Likert-scale ranking) to account for different levels of disagreement between categories or in other

words to test for the closeness of agreement between categories. This analysis did not show what features of HTA had the most and the least positive impact on access, according to participants' opinions, rather than showed whether participants generally agreed with each other while accounting for agreement occurring simply by chance (unlike percentage agreement). The following formula was used to measure the Gwet's kappa coefficient:

$$\kappa_g = \frac{P_{og} - P_{eg}}{1 - P_{eg}}$$

Where P_{og} is the observed percent agreement and P_{eg} is the expected percent agreement. The benchmark scale by Landis and Koch (1977) was used to interpret the results.

Gwet's kappa coefficient was used over Cohen's kappa as more than two raters participated in the Delphi panel (64). In addition, Fleiss' kappa or Scott's pi which allow for more raters are measures of nominal scale agreement (similarly to Cohen's Kappa) assuming that the ratings have no natural ordering (247). Unlike the other kappa coefficients, Gwet's allow for missing values, which was the case in this Delphi panel, when participants were responding with a 'do not know' or 'not applicable' responses, which were removed from our analysis (286–289).

5.2.5.2 Stability and consistency

To test whether the group responses of participants were stable and consistent between rounds, the ***likelihood of participants changing their opinion as a group from round 1 to round 2*** was calculated. For this analysis, responses of participants who participated in both rounds were only analysed to avoid a mismatch of the responses in both rounds which could have led to over- or under-estimation of the change of the responses between the two rounds.

In the literature, both stability and consistency of responses have been calculated interchangeably to deem whether the results of the Delphi panel are robust (247,280,290). To test for the stability of group responses, the non-parametric Wilcoxon matched-pairs signed rank test was used. Stability was considered when the group responses for each value statement had no statistically significant change from round one to two (p value >0.05). Instability was seen when there was a statistically significant change (p-value ≤ 0.05) from round one to two, showing that the magnitude of change in the stakeholders' opinions was much larger. The Wilcoxon matched-pairs singed rank test was used as it allows for analysis of paired data of the same group of individuals. Unlike McNemar chi-square test which has been used in other studies, the Wilcoxon matched-pairs singed rank test is suitable for ordinal, rather than nominal-scaled data (247,291,292).

To test the level of correlation of stakeholders' opinions between round 1 and 2, the Spearman's rank correlation coefficient was calculated using the following formula:

$$\rho = 1 - \frac{6\Sigma d_i^2}{n(n^2 - 1)}$$

Where ρ is Spearman's rank correlation coefficient; d_i is the difference between the two rounds for each observation, and; n is the number of total observations.

Spearman's rank correlation coefficient falls between -1 and +1. High degree of concordance was deemed when there was a positive correlation coefficient ($\varrho \geq 0.75$) with p value ≤ 0.05 showing that is statistically significant. While, low degree of concordance was deemed when there was a negative correlation coefficient ($\varrho < 0.75$)with p value >0.05 showing that is non-statistically significant (247,279,290).

Spearman's rank correlation coefficient was chosen over Kendall T rank correlation coefficient as it is able to detect unusual sensitivities due to discrepancies between the rankings from round 1 or 2. In addition, Kendall's T has an intuitive interpretation compared to the Spearman's rank correlation coefficient (247). In addition, the one-way analysis of variance (ANOVA) was not used for this exercise as it tests variability between two or more unrelated and independent groups. However, this was not the case in our study.

5.2.5.3 Consensus

As discussed earlier, consensus is a term defined arbitrarily in the literature and there is a lack of consensus on how to define consensus. Given that it a subjective measure, consensus was used only for the discussion part of this exercise rather as a part of our findings. However, to draw robust conclusions we tried to set stringent criteria to define consensus. We considered that a value statement reached consensus across participants when it was approved by qualified majority, had a median of 1 and 2 and IQR$\leq$1 in round 2, had high degree of concordance and showcased stability (non-statistically significant change) between rounds.

5.3 Paper 3

Chapters 8-9 (papers 3 and 4) focus on the unique case of orphan medicines. The reasons why access to orphan medicines is of great interest amongst policy- and decision-makers are discussed in detail in sub-sections 2.3.1 and 3.5. In short, orphan medicines are challenging to develop due to a low number of patients suffering from the disease and lack of scientific knowledge. Evidence of their clinical benefit is often limited or incomplete while R&D costs are difficult to recoup. In

some settings, orphan medicines are subject to flexible value assessment and pricing and reimbursement regulations and alternative sources of funding might be available to ensure access to patients. As a result, prices of orphan medicines have skyrocketed applying high pressure on already strained healthcare budgets. Evidence has shown that access to medicines treating rare diseases varies across healthcare systems. This paper's objective is to observe whether timely market access and more favourable funding recommendations are seen in Scotland, where orphan medicines are treated differently (i.e.: with more flexibility) than non-orphan medicines, compared to Canada, where these medicines are treated as any other medicine.

5.3.1 Analytical framework

To systematically compare and assess whether access to orphan medicines is successful or differs across two settings which treat medicines for rare diseases differently, I designed an analytical framework stemming from the results of the scoping review (please refer to section 3 for more information): The analytical framework follows the main stages of a medicine's access pathway from MA to their funding. And it uses different access metrics such as availability of medicines within countries (i.e.: commercial availability of the medicine after MA), access to publicly funded medicines (i.e.: positive/restricted HTA recommendations) and time to access (i.e.: from MA to positive/restricted HTA recommendation). The access pathway and the access dimensions reflected the way these two HTA systems are set up within the two countries, and the way HTA recommendations inform funding decisions (please refer to sub-section 5.3.2 for more information on the comparability of these two settings). It is important to note that using this framework, I was able to determine access to orphan medicines within markets, rather than patient access to medicines, since the latter depends on various factors such as local prescribing patterns, distribution and the local supply chain, and other system-specific dynamics which cannot be easily controlled for and/or quantified. In addition, the way funding deliberations are taking place when a medicine has received a negative HTA recommendation is unclear, and observations cannot be made due to lack of publicly available data on negotiations and discussions between manufacturers and the local payers.

5.3.1.1 Stages of the access pathway

For each stage, I captured whether specialised processes or pathways for medicines treating rare diseases are present, as per the scoping review results presented in sub-section 3.5.2.

At ***MA (regulatory)*** level, some settings offer an orphan designation to manufacturers which is usually accompanied by various incentives aiming to facilitate and encourage the R&D of orphan

medicines. However, orphan designation is not present in all settings. Having an orphan designation does not mean that other assessment criteria compared to non-orphan medicines, are used during MA decision-making. However, orphan medicines are more likely to be approved through specialised MA pathways such as conditional MA or undergo accelerated assessment due to their nature (i.e.: treat serious and life-threatening conditions and address high unmet need), even in systems where specific policies for orphan medicines are not present (213).

During ***HTA*** processes, the value assessment of orphan medicines is often challenging due to high clinical uncertainty and high incremental costs in relation to their proven additional health benefits (4). To mitigate such issues, some HTA bodies have specialised frameworks to assess orphan medicines which allow capturing in an explicit way the needs of vulnerable and small populations and allow for greater flexibility in the available evidence (i.e.: acceptance of more uncertainty in the clinical evidence and economic case) to account for the unique nature of these medicines. However, specialised processes for the assessment of orphan medicines are not present across all settings (23,79,212,219,220,226).

As an effort to better align MA and HTA processes, some new initiatives have been implemented in some countries to facilitate and accelerate access to medicines of high unmet need. Firstly, parallel review processes between MA and HTA have been introduced in some countries to allow for the value assessment to commence prior to MA approval and enable the exchange of information between the responsible institutions. Secondly, interim acceptance at HTA level has been introduced in some settings which allows HTA bodies to provisionally recommend a medicine for reimbursement, which has been granted MA through specialised pathways (both conditional MA and accelerated assessment), subject to ongoing evaluation and future reassessment.

Once HTA has been completed, ***funding*** negotiations are taking place between payers and manufacturers. Depending on the HTA system, HTA recommendations might not always determine funding decisions. However, in most settings with well-developed and well-established HTA processes, positive HTA recommendations will result in funding. Nevertheless, negative HTA recommendations do not always translate into no funding. In this case, further negotiations and alternative funding options, such as funding through specialised funds or risk-sharing mechanisms, are explored by manufacturers and healthcare payers. However, the latter is outside the scope of chapter 8 (paper 3) due to the unavailability of public data in one of the settings

(Scotland) which would not allow for cross-border comparisons. However, this endpoint is explored in chapter 9 (paper 4).

5.3.1.2 Access metrics-study endpoints

For each access metric, different stages of the access pathway were relevant and different data were used. I measured the ***availability*** of orphan medicines within markets by exploring whether orphan medicines with a MA were commercially launched within countries (102). Successful ***market access*** to orphan medicines was defined by positive HTA recommendations for funding, including positive recommendations with or without restrictions for use. Positive HTA recommendations were considered given that they are more likely to translate into funding compared to negative HTA recommendations, especially in these two settings, as discussed earlier. The market access metric covers partially the healthcare system's ***affordability*** since positive HTA recommendations mean that medicines were deemed both clinically and cost-effective by the HTA body or that the HTA body has taken into consideration MEAs between payers and manufacturers which can protect the sustainability and affordability of the healthcare system (as discussed in sub-section 3.3.3.1). Finally, ***timely access*** was determined by the time between MA approval to the issue of a positive/restricted HTA recommendation (as positive recommendations are more likely to be funded) by the respective HTA body, given that in both study settings, it is on manufacturer's discretion to submit their dossier for HTA evaluation after having granted MA. Additional time to access analyses were performed looking at the time of MA to market launch to explore whether market launch occurs before or after the issue of HTA recommendations, and at the time of MA submission to HTA positive/restricted HTA recommendations to explore how quickly MA occurs within settings given that these medicines are likely to undergo MA through specialised pathways such as accelerated assessments/priority review. Finally, a sub-group analysis of timely access (time from MA to positive/restricted HTA recommendation) was conducted in Canada only to explore differences in timelines of HTA submissions which were initiated before MA approval versus standard HTA submissions (i.e.: the HTA process was initiated after MA was granted to the manufacturer). A graphic representation of the analytical framework is presented in chapter 8.

In order to observe whether the presence of specialised processes for orphan medicines at MA and HTA levels may be associated with better market access, as defined and explored in this study, two settings with very similar HTA systems but with the differences on the way they treat orphan medicines were chosen. In the next sub-section 5.3.2, I discussed extensively why such associations can be observed by looking at these two settings. In a nutshell, medicines in both countries are

granted MA after evaluation of a medicine's clinical efficacy and safety. In addition, both settings follow the same HTA model (assessing both the comparative clinical benefit and cost-effectiveness of the medicine, using their own WTP threshold), assess all newly approved medicines and similarly use HTA recommendations to inform funding decisions. Therefore, focusing only on MA and HTA outcomes, associations between presence of specialised processes for orphan medicines and favourable HTA recommendations and faster market access can be explored.

5.3.2 Geographic scope

To explore whether the presence of specialised processes for orphan medicines may have an impact on access, I had to carefully select two settings which have highly similar HTA systems but differ in the way they treat orphan medicines. Therefore, I considered the results of chapter 6 (paper 1), which maps different HTA systems across 32 countries, and I selected two countries which have similarities in terms of the HTA model they follow, the medicines subject to HTA, the role of the HTA body and the way HTA informs funding decisions. To identify two settings that treat orphan medicines differently across all the stages of the access pathway, I relied on the scoping review results (please refer to sub-section 3.5.2). ***Canada and Scotland*** were selected for the purpose of this chapter. Australia could be considered a good alternative option to Scotland, however, there is no specialised assessment framework at HTA level, and orphan medicines undergo the same evaluation process as non-orphan medicines. Only if they receive a negative HTA recommendation by the Australian HTA body due to poor cost-effectiveness they could be funded by the Life Saving Drugs Program (137).

Canada has no national strategy for medicines treating rare diseases and orphan medicines are broadly treated in the same way as all other medicines (22,23,213,220). At regulatory level, there is no orphan designation. However, these medicines can still undergo MA through specialised pathways (see Table 2 for more information).

HTA is performed predominantly at national level and HTA recommendations act as advice for funding across provinces. At HTA level, there is no special framework for the assessment of orphan medicines. Participation of relevant stakeholders is seen on an ad-hoc basis and neither different nor additional criteria are applied explicitly during evaluations of medicines treating rare diseases to account for other value dimensions beyond clinical- and cost-effectiveness. Nevertheless, it has been noted by CADTH that rarity is a key consideration to issue a favourable recommendation despite uncertainty in the evidence submitted (293).

Across provinces, where funding decisions are made based on local healthcare budgets, specific frameworks for the assessment of orphan medicines might exist, MEAs might be implemented, and specialised funds might be available at provincial level to ensure access to these medicines. Therefore, variation in access to orphan medicines across Canadian provinces might be observed. However, for the purpose of this chapter, we focus on access to medicines treating rare diseases at national level (excluding Quebec), rather than the provincial level. And successful access to orphan medicines within markets is determined by looking at positive HTA recommendations which are good determinants for funding in Canada (198,199).

Scotland has well-established processes aimed at facilitating access to orphan medicines. These medicines are granted an orphan designation at the regulatory level, and similarly to Canada, they can undergo MA assessment through specialised pathways. The Scottish HTA body has adopted multiple explicit criteria and processes for the value assessment of orphan medicines: First, ultra-orphan medicines, which treat 1 in 50,000 or fewer people of the general population, can undergo assessment through the ultra-orphan pathway which may grant conditional positive recommendations for three years while further clinical data are collected (23,206). Second, SMC modifiers, applied in the case of orphan medicines, allow for a high level of flexibility for higher uncertainty in the economic analysis by the Scottish HTA body which subsequently results in accepting higher cost per QALY when specific modifiers are applied to account for additional value dimensions such as whether the medicine treats a life-threatening disease, substantially improves the quality of life or bridges a gap to "definitive" treatment (206,294). Finally, with the introduction of the Patient and Clinician Engagement (PACE) process, the opinions of clinicians, patients and patient organisations are accounted for during decision-making, in case an initial negative recommendation has been issued for the orphan medicine under evaluation (295).

Once the HTA process is complete and a medicine has received a favourable HTA recommendation, the Scottish National Health Service (NHS) should make the medicine available to patients within three months. Similar to Canada, medicines with negative HTA recommendations might still receive funding from the Scottish NHS through specialised funds or MEAs.

However, it is important to note that Canada and Scotland differ considerably in country size, population, and gross domestic product. In addition, they have a different willingness-to-pay thresholds per QALY. And they also differ on where funding decisions are made (i.e.: in Canada, funding of medicines is the competence of provincial jurisdictions), among many other factors

which may have an impact on market and patient access to orphan medicines. Even so, comparisons between the two countries can be considered appropriate for the purposes of this study, i.e.: comparisons of MA decisions and HTA recommendations for funding and time from MA to HTA decisions.

First, marketing authorisation decisions for both Canada and Europe, are based on whether a medicine is clinically effective and safe to use. These two questions rely solely on the clinical evidence submitted by the manufacturer, and it is not dependent on the wealth and the purchasing power of the country. Second, in both settings, specialised processes for medicines targeting areas of unmet need and serious, life-threatening conditions are available. Even though the latter is an objective criterion, the former (i.e.: unmet need) is dependent to the country's disease epidemiology and prevalence. To tackle this limitation, I focused on treatments that had granted an orphan designation by both the FDA and the EMA. Even though an orphan designation is not available in Canada, the orphan designation by the FDA was used to capture whether a disease is likely to be rare in Canada (as has been done in previous studies). Third, in both Canada and Scotland all new medicines approved at regulatory level are subject to HTA after submission of the dossier by the manufacturer. And HTA assessments take place immediately after the manufacturer has been granted MA for their medicines. Fourth, in both settings, HTA are based on assessment of the comparative clinical effectiveness and the cost-effectiveness of the medicine. Even though assessments of comparative clinical effectiveness do not depend on the country's GDP and negotiating power, WTP thresholds may related to the wealth of a nation. To overcome this limitation, comparisons between the two countries were not made using the same WTP threshold. Observations were rather made using two options: (i) the medicines were considered cost-effective for the setting considering the HTA body-specific WTP threshold; (ii) the medicines were not considered cost-effective for the setting considering the HTA body-specific WTP threshold. Therefore, observations were not made using a single WTP threshold for both countries. In addition, unlike Canada, Scotland does not have a pre-specified and rigid WTP threshold, even though Scotland is a smaller, less wealthy country than Canada. Fifth, while in both settings HTA recommendations are non-binding, there is an association between positive HTA recommendations and positive funding decisions. Finally, given that the two countries differ considerably in terms of population size, one would expect that the burden of funding an orphan medicine would have been much higher in Canada as a proportion of the population. However, unlike the FDA definition which considers a proportion of the general population, both Health Canada and the Canadian Organization for Rare Disorders (296,297) unofficially use the EMA's

definition of rare disease (i.e.: a disease that affects <5 in 10,000 people(298)). Therefore, the burden of funding these medicines should be similar in both Scotland and Canada as a proportion of the population in need of these medicines.

Despite that these countries can be considered comparable only for the purposes of this study, conclusions made should be interpreted with caution to reflect the limitations arising from comparisons of two countries that differ in many respects.

5.3.3 Sample selection

A detailed description, step-by-step, of the sample selection is provided in chapter 8. In summary, I started the sample selection process by downloading a list of approved medicines with an orphan designation by the Food and Drug Administration (FDA) in the US from January 2000 till December 2018 using the Orphan Medicine Product designation database. The FDA was used as the starting point since more MA approvals are seen in the US compared to Europe[8] (101). In addition, as an orphan designation does not exist in Canada, the FDA was used as a surrogate for Health Canada, given that there is an established collaboration and exchange of information between the FDA and Health Canada based on the Memorandum of Understanding, established in 2003 (299). The identified orphan medicine-indication pairs of the FDA were matched with approved medicine-indication pairs by the EMA. Indication pairs which never had an orphan designation by the EMA were excluded from the sample. Medicine-indication pairs with a later withdrawn orphan designation by the EMA or medicines which were subsequently withdrawn from the EU market but had undergone HTA at national level were included to not limit the sample size since it would not affect the results of my analysis. The matched orphan medicine-indication pairs by the FDA and the EMA were searched through the website of the Health Canada to see whether they have been authorised for human use in Canada. Indication pairs which were not approved by the Health Canada or orphan medicines with a different approved indication in Canada than that of the FDA and the EMA were excluded from the sample. Orphan medicine-indication pairs with a MA from the FDA, the EMA, and the Health Canada, were searched through the websites of the Canadian and Scottish HTA bodies: CADTH and SMC, respectively. Orphan medicine-indication pairs which were not assessed or had no HTA dossier submission by the manufacturer in both HTA bodies (SMC and CADTH) were excluded. Orphan medicines with

[8] At the time of the study, Scotland was still part of the European Union. Therefore, data at the regulatory level were collected through the EMA.

an abbreviated submission[9] in Scotland were included in the sample. Orphan medicine-indication pairs which were assessed at least by one of the two bodies until December 2019 (when the data collection was completed) were included in the final sample.

Table 5 provides a summary of all the study variables and the sources used to extract relevant data from Canada and Scotland. All the data sources were publicly available. Relevant information was collected for each medicine-indication pair separately and not at molecule level. This is because, the sample included molecules with multiple indications for rare diseases, when available and when meeting the sample selection criteria. Orphan medicines indicated for some rare types of cancer were included in the sample. Therefore, data on HTA-related study variables from Canada were recorded from both the Canadian Drug Expert committee (CDEC), which evaluates medicines that are non-oncology medicines and follow the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review Expert committee (pERC) which evaluates oncology medicines though the pan-Canadian Oncology Drug Review (pCODR). Even though, these two committees follow two different and independent review processes, their recommendations are similar and are published by CADTH (293).

Categorisation of the variables of 'specialised pathways at MA',' HTA recommendations', 'HTA restrictions', 'Clinical restrictions', 'Economic restrictions', and 'Main reasons for HTA recommendation' followed existing categories found in the literature(14,131,141,193,194,220,301).

However, the respective groups were further updated through an iterative process during data collection in order to be adapted to the two study countries, if needed.

Table 5: List of study variables and data sources used for Canada and Scotland

Variable	Description	Sources	
		Canada	**Scotland[1]**
MA			
Date of MA	*Date of MA for the first indication and, when applicable, the extension of indication.*	Notice of compliance (NOC)[2] database of the Health Canada	The human medicine European public assessment report (EPAR) and reports of the procedural steps taken and scientific information after the authorisation published on the EMA

[9] Abbreviate submission for some new molecules can be made by manufacturers if they deem that a full submission is not required due to low net budget impact of the medicine (300).

Variable	Description	Sources	
		Canada	**Scotland[1]**
Date of MA submission	*Date of MA submission for the first indication and, when applicable, the extension of indication.*	Drug and health product register database of the Health Canada and information shared by the Information Dissemination Unit of the Pharmaceutical Drugs Directorate of the Health Canada	EPAR published on the EMA
Specialised pathways at MA	*Specialised regulatory pathways were recorded at the time of MA of the first indication and, when applicable, for the extension of indication.* *Conditional MA and accelerated assessment/priority review were recorded and grouped into one category called "MA through specialised pathways".* *The remaining medicines which underwent MA through the standard process were recorded as "standard MA".*	NOC database and the list of notice of compliance with conditions (NOC/c) of the Health Canada	EPAR and reports of the procedural steps taken and scientific information after the authorisation published on the EMA
Market launch	*Information on whether the medicine-indication pair has been commercially marketed within a setting.*	The status of the medicine as per the results of the Drug product database of the Health Canada	Product availability information found in the detailed advice of the evaluated medicine published by SMC and additional searches through the British National Formulary (BNF)
Date of market launch	*The date the medicine-indication pair was commercially launched in the market.*	The original market date found in the product information of the drug product database of the Health Canada	Product availability date found in the detailed advice of the evaluated medicine published by SMC
HTA			
Date of HTA recommendation	*In case, of more than one HTA submission(s), the date of the latest HTA recommendation was recorded for the medicine-indication pair.* *For the time to access analysis, medicine-indication pairs with a previous assessment which resulted in a favourable recommendation, the date of the first positive/restricted recommendation was recorded, when available.*	Date of final recommendation found in the reimbursement review reports of CADTH	Published date of detailed advice of SMC
Re-submission	*Presence of previous submissions/assessments for the same*	Submission type under details found in the	Submission type under medicine details

Variable	Description	Sources	
		Canada	**Scotland[1]**
	medicine-indication pair were recorded along with the previous HTA recommendation(s), when available.	reimbursement review reports published by CADTH	published in the medicine advice of SMC
HTA recommendations	*HTA outcomes were collected for the most recent assessment (including re-submissions) for each medicine-indication pair* *HTA outcomes were grouped into four main categories:* *(i) Positive* *(ii) Positive with restrictions* *(iii) Negative* *(iv) Not assessed* *In case of non-submission by the manufacturer, HTA recommendation was categorised as negative.* *For the market access and timely access endpoints, positive and positive with restrictions recommendations were grouped together under one group 'favourable HTA recommendations' versus 'unfavourable HTA recommendations'.*	Reimbursement review reports published by CADTH	Detailed advice published by SMC
HTA restrictions	*Listed with restrictions outcomes for each medicine-indication pair, when applicable, were recorded and categorised into:* *(i) Clinical restrictions* *(ii) Economic restrictions.*	Reimbursement review reports published by CADTH	Detailed advice published by SMC
Clinical restrictions	*Clinical restrictions included:* *(i) Limited access to specific populations;* *(ii) Monitoring or prescription only by specialists;* *(iii) Restrict medicine administration (i.e.: in hospital setting or special health clinic);* *(iv) Suggestions on when treatment should be initiated, continued and/or discontinued;* *(v) Multiple clinical restrictions, when more than one clinical restriction was suggested by the HTA body.*	Reimbursement review reports published by CADTH	Detailed advice published by SMC
Economic restrictions	*Economic restrictions included:* *(i) Funding mechanisms such as patient access schemes (PAS)[3] (applicable only in Scotland);* *(ii) Reductions in price of the medicine;* *(iii) Similar funding with therapeutic equivalents* *(iv) Reimbursement in some jurisdictions only (applicable to a few cases in Canada).*	Reimbursement review reports published by CADTH	Detailed advice published by SMC

Variable	Description	Sources	
		Canada	**Scotland[1]**
Main reasons for HTA recommendation	*The main reasons for HTA recommendation for each medicine-indication pair were categorised in four categories:* *(i) Clinical achievement (significant improvement in the clinical benefit);* *(ii) Optimal cost-effectiveness;* *(iii) Achievement of both clinical- and cost-effectiveness;* *(iv) Failure to achieve both clinical and cost-effectiveness.* *Medicine-indication pairs with no HTA dossier submission and those not assessed by the HTA body were excluded from analysis on this study variable.*	Reimbursement review reports published by CADTH	Detailed advice published by SMC
Parallel review	*This variable was only applicable to Canada: Medicines where HTA started prior to MA were recorded.*	NOC status at filing found under details published in the reimbursement review reports of CADTH	N/A

Notes: *[1] At the time of the study, Scotland was still part of the European Union. Therefore, data at the regulatory level were collected through the EMA.*
[2]Notice of compliance (NOC) is the MA in Canada.
[3] Patient access schemes (PAS) are innovative pricing agreements proposed by pharmaceutical companies to improve the cost-effectiveness of their medicines and facilitate patient access (302)
Source*: The author.*

All the extracted information was recorded initially in full text in an Excel spreadsheet, where the countries were included in the rows and the study variables were presented in the columns. Each medicine-indication pair was recorded twice: one row containing information from Scotland and one row containing information from Canada for the respective medicine-indication pair. Subsequently, all the data were numerically coded in binary or categorical variables as described in Table 5 above and stored in a separate Excel spreadsheet to allow for statistical analysis.

5.3.4 Data analysis

Descriptive statistics were used to compare the following endpoints in Canada and Scotland: (i) how many orphan medicine-indication pairs had undergone MA through a specialised pathway, including conditional MA and accelerated assessment/priority review; (ii) how many orphan medicine-indication pairs had undergone MA through the standard pathway; (iii) how many orphan medicine-indication pairs were commercially launched; (iv) how many orphan medicine-indication pairs had an HTA re-submission; (v) HTA recommendations across the orphan medicine-indication pairs including restrictions and the types of restrictions, when applicable; (vi) how many orphan-medicine indication pairs received a positive/restricted HTA recommendation;

(vii) main reasons for HTA recommendation across the orphan medicine-indication pairs, and; (viii) for how many orphan medicine-indication pairs the HTA assessment started prior to MA approval in Canada. Endpoint (iii) determined the ***availability*** of medicines within markets and endpoint (vi) determined successful ***market access*** within markets.

A sub-group analysis in both Canada and Scotland on all aforementioned study variables (except (i) and (ii)) was conducted for medicines that had undergone MA through a specialised pathway versus those who had MA through the standard pathway to test whether orphan medicines with a specialised pathway showed more favourable access patterns compared to medicines with standard MA. This way, I was able to observe whether efforts made at the regulatory level to facilitate access to medicines are successful also in the subsequent stages of a medicine's access pathway. It is important to note that at the time of the data collection and analysis, no interim acceptance was recorded for my sampled medicines in Scotland. Therefore, comparisons with Canada were possible since all the included orphan medicines underwent the standard HTA process in both countries.

To determine that there are no random associations seen from the descriptive statistics, and thus test for statistical significance, both Pearson's chi-square and Fisher's exact test were used. The Fisher's exact test was used as the sample size of some of the study variables was very small (less than 10 observations), and the Pearson's chi-square test would have not been accurate. A p-value ≤ 0.05 was considered to show statistically significant results.

To test for agreement between the two HTA bodies in their HTA recommendations and the main reasons for the recommendation, I conducted Cohen's kappa score analysis. This analysis tests for inter-rater agreement, among two raters, while controlling for any agreement that might occur simply by chance. Therefore, it is more robust than a simple percentage agreement (250).However, observations should be reported for both raters (i.e.: HTA bodies) to avoid underestimating the observed agreement (303). For this reason, matched medicine-indication pairs assessed by both agencies were only included in the analysis to avoid an unbalanced sample.

To calculate the Cohen's kappa score the following formula was used:

$$\kappa = \left(\frac{\varrho_0 - \rho_e}{1 - \rho_e}\right)$$

Where ϱ_0= relative observed agreement between the HTA bodies; and ρ_e= hypothetical probability of chance agreement.

Kappa score can range from -1 to +1. A score of zero shows inter-rater agreement simply occurring by random chance, while a score of one shows perfect agreement between raters (304). Results of the kappa score analyses were interpreted using the benchmark scale suggested By Landis and Koch (1977) (305), where a kappa value of ≤0.2 indicates a poor level of agreement while values ranging from 0.21–0.40 to 0.81–1.0 define levels of fair to very good agreement, respectively. The level of concordance of identical HTA recommendations and main reasons for recommendation between the two HTA bodies was also calculated. Pearson's chi-square was used to test the statistical significance of the results, where a p-value ≤0.05 was statistically significant.

To test for timely access to medicines within markets and make comparisons between Canada and Scotland, Kaplan-Meier curves were used for all the time analyses. Kaplan-Meier curves allowed to estimate the time in months from MA to market launch and the time from MA to market access (i.e.: a positive/restricted HTA which would more likely translate into funding) in both countries. Through the time to market access analysis, I was able to observe how fast access to orphan medicine-indication pairs might occur in Scotland and Canada, respectively, by comparing the median time in months from MA to a positive/restricted HTA recommendation in both countries but also calculating the minimum and maximum time to market access. An additional time analysis estimated the time in months from MA submission by a manufacturer to a positive/restricted HTA recommendation. All the three-time analyses were performed across the entire sample and for subsamples of orphan medicine-indications pairs which were granted MA through a specialised pathway and those who underwent standard MA. A subgroup analysis was performed for Canada only, for medicines with an HTA pre-MA approval (parallel review) and medicines which underwent standard HTA to test how successful the parallel review process is in terms of how faster access to orphan medicines occurs.

The Kaplan-Meir curve estimates the likelihood of survival (in this case positive/restricted HTA recommendation, thus reimbursement) over time while considering time in small intervals. Kaplan-Meir curve can estimate survival over time even when missing values (known as censored data) might appear in a dataset (306–308). In my sample, missing values were found in orphan medicine-indication pairs with no assessment, while "failure to survive" was recorded for orphan medicine-indication pairs with a negative HTA recommendation for which funding at the local level was uncertain. Survival was defined as positive HTA recommendations including both positive and positive with restrictions recommendations, which were more likely to result in fundings. The Kaplan-Meir curves showed graphically access to orphan medicine-indication pairs

against time in months and the reimbursement probability at any particular year was calculated by the formula given below:

$$\hat{\hat{S}}_t = \prod_{t_i \leq t} \left[1 - \frac{d_i}{n_i}\right]$$

Where t = the time (year);
t_i =the time when at least one event occured;
d_i =the number of negative HTA recommendations that happened at t_i;
n_i =the number of medicine-indication pairs with a positive HTA recommendation up to time t_i.

It is important to mention that one key limitation of the Kaplan-Meir method is that it provides only unadjusted survival or failure probabilities without adjusting for other potential confounders, such as other potential factors that might have influenced access to orphan medicines within the two markets.

Since missing values appeared in my dataset and my data were not following a normal distribution, thus, they were unmatched, the Mann-Whitney U test was performed, instead of a simple t-test, to test whether the two independent samples included orphan medicine-indication pairs with the same distribution. This way, I was able to test for statistical significance in the results from the Kaplan-Meir curves (309). As I also calculated the mean time from MA to a positive/restricted HTA recommendation, Welch's *t*-test was used to determine whether the results of the mean times were statistically significant by testing the hypothesis that Canada and Scotland had equal mean times to access. A p-value ≤0.05 was considered to show statistical significance.

All data analysis was performed using the statistical software STATA SE.17 (StataCorp).

5.4 Paper 4

Chapter 8 (paper 4) explores access to orphan medicines within a decentralised healthcare setting where recommendations for funding and pricing negotiations are made at a national level and funding decisions are made at a regional level according to available regional healthcare budgets. Unlike most of the studies in the literature which focus only on HTA recommendations, in this paper, I explored whether recommendations for funding are translated into the outcome of pricing negotiations and funding decisions for orphan medicines.

As discussed extensively in this thesis, orphan medicines are an interesting case study to dive into, as one would assume that healthcare payers would rely heavily on HTA recommendations that

recommend funding of medicines which are both clinically- and cost-effective, as a measure to protect the sustainability of healthcare systems.

5.4.1 Geographic scope

Similar to paper 3, to select the geographic scope of this chapter, I relied on the findings of paper 1 which mapped HTA systems across 32 countries. Given that this study aims to explore the dynamics between national and regional decision-making, Canada was deemed to be the most suitable setting to focus on. Unlike other countries with decentralised healthcare systems such as Italy, Spain, Denmark or Sweden, in Canada, the relationship between the national HTA body and regional decision-making is clearer and more transparent, the same rules apply to all medicines regardless of the setting where they are administered (i.e.: all medicines are subjected to HTA which subsequently acts as advice to provinces for funding decisions) and data on the funding status of medicines are publicly available through provincial medicines formularies. For instance, in Sweden, outcomes of the national HTA assessments of out-patient pharmaceuticals are directly translated into funding decisions. However, national HTA recommendations for in-patient medicines are used only as advice to the Swedish regions which are responsible for their funding.

The province of Ontario was selected over other provinces as Ontario is the largest and most populous province in Canada. Since April 2016, the Ontario Ministry of Health stopped the routine assessment of medicines which have undergone review by CADTH as an effort to better align HTA recommendations and provincial funding decisions. Therefore, one would expect that there will be a good alignment between HTA recommendations and funding decisions in Ontario, at least after 2016. Finally, even though a national strategy to facilitate access to medicines treating rare diseases is absent in Canada, the Ontario Ministry of Health in collaboration with the Ontario Citizen's council developed a value framework in 2010, which is being updated routinely, to evaluate medicines for rare diseases. This value framework aims to identify groups of patients or individuals that are likely to benefit the most from a treatment, so use of orphan medicines will be more limited and more efficient (310–312). Nevertheless, in the suggested framework, it is highlighted that medicines for rare diseases should be treated, as much as possible, similarly to all other medicines and that the rarity of a disease should not be a special consideration that might benefit patients suffering from rare diseases over patients suffering from more common diseases (310–312). Therefore, according to the Ontario Ministry of Health, if a medicine is considered too expensive by the national HTA body, it should not be funded through the public purse. However, in Ontario, there are many available specialised funds which offer reimbursement to very expensive medicines, even if they have been deemed cost-ineffective by CADTH.

5.4.2 Sample selection

The sample selection process of this study follows similar steps used in the sample selection of paper 3, described in the previous sub-section 5.3.3. However, the sample of this study included orphan medicine-indication pairs which were not approved by the EMA, but had been granted an orphan designation, as evidence has shown that more orphan medicines were granted MA by the FDA than the EMA(101). In addition, the sample was extended to include more orphan medicines with recent assessments by CADTH until June 2022 (when the data collection was completed).

The detailed process of sample selection is described in chapter 9. However, the main differences between the sample selection process of this paper versus paper 3 are outlined below:

1) The FDA Orphan Drug Product designation database was searched between January 2000 and December 2021 to extend the sample and include orphan medicines which have an MA by the FDA after December 2018;
2) Orphan medicine-indication pairs which were not approved by the EMA, but had been granted an orphan designation and were approved and granted an orphan status by the FDA were included in the sample;
3) Medicine-indication pairs which were not commercially marketed in Canada or were subsequently withdrawn from the Canadian market after approval of MA were excluded from our sample since these medicine-indication pairs would not be available in Canada and would not appear in the provincial formulary;
4) Medicine-indication pairs which did not have a reimbursement review by CADTH or for which there was no dossier submission by the manufacturer until June 2022 were excluded from our sample, as a comparison between HTA recommendations and funding decisions in Ontario would not be possible.

5.4.3 Study variables and data sources

Some of the study variables and the data sources used in this paper are similar to the ones used in paper 3. These include: 'date of MA', 'date of HTA recommendation', 're-submission', 'HTA restrictions', 'clinical restrictions', and 'main reasons for HTA recommendation'. A detailed description of these variables and the data sources used to extract relevant information are presented in Table 5 under the 'Canada' column.

In this paper, medicines with 'specialised pathways at MA' were separated into four groups: medicines with 'conditional MA' and medicines undergoing a 'priority review', and were compared with medicines with 'standard MA' and medicines with 'non-priority review', respectively.

'HTA recommendations' were classified into three groups: 'listed', 'listed with restrictions' and 'do not list'. Medicine-indication pairs which were not assessed by CADTH were excluded from the sample. For the logistic regression and the kappa analyses, HTA recommendations were categorised into binary variables: (i) positive HTA recommendations, which included listed and listed with restrictions recommendations, and (ii) negative HTA recommendations which included do not list recommendations by CADTH. By grouping HTA recommendations into two groups, comparisons between funding decisions could be conducted. The categories under 'economic restrictions' were categorised into three groups instead of four, as the category 'Funding mechanisms' is not an option in Canada. Other funding mechanisms or MEAs are considered after the publication of CADTH's recommendations at the provincial level.

The outcomes of pricing negotiations were extracted by the Brand Name Drug Negotiations Status database of the pCPA. Pricing negotiations were categorised in: (i) "successful negotiations" (i.e.: resulting in a letter of intent), (ii) "unsuccessful negotiations" (i.e.: when an agreement was not reached or when a negotiation was not pursued), and (iii) no information available (i.e.: when a medicine-indication pair was not found in the database or when negotiations were active or under consideration at the time of data collection). The negotiation status was recorded for the most recent negotiation (in cases of re-negotiations). For the logistic regression and the kappa analyses, negotiations with no information were recorded as "unsuccessful" as their outcomes were unknown.

Similar to paper 3, extracted information from the publicly available sources was first collected in full text and recorded in an Excel spreadsheet. The data were subsequently numerically coded in binary or categorical variables according to the nature of each variable and the statistical method used for data analysis following an iterative process. An extensive list of all the study variables, their respective grouping and the sources used to extract relevant information are presented in Table 6.

Table 6: List of study variables, their description and sources used for data collection

Variable	Description	Sources
General		
Anatomical Therapeutic Chemical code (ATC)	*The ATC code was extracted to identify orphan medicines indicated for cancer and non-cancer treatments*	ATC/DDD Index 2020 of the World Health Organisation Collaborating Centre for Medicine Statistics Methodology
First-in-class	*Whether the medicines was the first approved within a therapeutic class or a medicine using new mechanisms of action*(313,314)	FDA's Novel Approvals reports and a previous study(314)

Variable	Description	Sources
Safety recall and alerts	*Whether a recall or safely alert has been issued.*	Recalls and Safety Alerts database of Health Canada
Ultra-rare indication	*Whether the medicines were designed to treat ultra-orphan diseases (prevalence of 1 in 50,000 or 2 in 100,000*(315–317)*)*	Prevalence and Incidence of Rare Diseases data from Orphanet
MA		
Date of MA	*Date of MA for the first indication and, when applicable, the extension of indication.*	Notice of compliance (NOC) database of the Health Canada
Specialised pathways at MA	*Specialised regulatory pathways were recorded at the time of MA of the first indication and, when applicable, for the extension of indication. Medicine-indication pairs were grouped into medicines with:* *(i) Conditional MA* *(ii) Priority review* *(iii) Standard MA* *(iv) Non-priority review* *For the subgroup analysis of medicines with a specialised pathway and the logistic regression model, medicine-indication pairs were grouped into:* *(i) MA through specialised pathways* *(ii) Standard MA*	NOC database and the list of notice of compliance with conditions (NOC/c) of the Health Canada
Cancer indication	*The MA indication was extracted to identify the disease area and target population.*	Notice of compliance (NOC) database of the Health Canada
Paediatric indication	*The MA indication was extracted to identify the disease area and target population.*	Notice of compliance (NOC) database of the Health Canada
Pan-Canadian pricing negotiations		
Pricing negotiation outcomes	*Pricing negotiations were categorised in:* *(i) Successful negotiations* *(ii) Unsuccessful negotiations* *(iii) No information available*	Brand Name Drug Negotiations Status database of the pCPA
HTA		
Date of HTA recommendation	*In case, of more than one HTA submission(s), the date of the latest HTA recommendation was recorded for the medicine-indication pair.*	Date of final recommendation found in the reimbursement review reports of CADTH
Re-submission	*Presence of previous submissions/assessments for the same medicine-indication pair were recorded, when available, and were grouped into medicines with:* *(i) Re-submission* *(ii) No re-submission*	Submission type under details found in the reimbursement review reports published by CADTH
HTA recommendations	*HTA outcomes were collected for the most recent assessment (including re-submissions) for each medicine-indication pair. HTA outcomes were grouped into three main categories:* *(i) Listed* *(ii) Listed with restrictions* *(iii) Do not list* *For the logistic regression model, positive and positive with restrictions recommendations were grouped together under one group 'favourable HTA recommendations' versus 'unfavourable HTA recommendations'*	Reimbursement review reports published by CADTH
HTA restrictions	*Listed with restrictions outcomes for each medicine-indication pair, when applicable, were recorded and categorised into:* *(i) Clinical restrictions*	Reimbursement review reports published by CADTH

Variable	Description	Sources
	(ii) Economic restrictions	
Clinical restrictions	*Clinical restrictions included:* *(i) Limited access to specific populations;* *(ii) Monitoring or prescription only by specialists;* *(iii) Restrict medicine administration (i.e.: in hospital setting or special health clinic);* *(iv) Suggestions on when treatment should be initiated, continued and/or discontinued;* *(v) Multiple clinical restrictions, when more than one clinical restriction was suggested by the HTA body.*	Reimbursement review reports published by CADTH
Economic restrictions	*Economic restrictions included:* *(i) Reductions in price of the medicine;* *(ii) Similar funding with therapeutic equivalents* *(iii) Reimbursement in some jurisdictions only*	Reimbursement review reports published by CADTH
Main reasons for HTA recommendation	*The main reasons for HTA recommendation for each medicine-indication pair were categorised in four categories:* *(i) Clinical achievement (significant improvement in the clinical benefit);* *(ii) Optimal cost-effectiveness;* *(iii) Achievement of both clinical- and cost-effectiveness;* *(iv) Failure to achieve both clinical and cost-effectiveness.*	Reimbursement review reports published by CADTH
Reported ICERs	*The reported ICERs following the categorisation used in another study*(318)*:* *(i) < CAD50,000/QALY* *(ii) CAD50,000 to CAD175,000/QALY* *(iii) CAD175,000 to CAD500,000/QALY* *(iv) ≥ CAD500,000/QALY* *(v) Not reported*	Reimbursement review reports published by CADTH
Funding in Ontario		
Funding status	*The funding status for each medicine-indication pair in Ontario was recorded and grouped into two categories:* *(i) Funded* *(ii) Not funded*	General formulary database of the Ontario Drug Benefit Formulary/Comparative Drug Index, the drug formulary of the Cancer Care Ontario, and the search tool of the Ontario Drug Benefit program. The exact indication for which medicines are funded in Ontario was extracted through the Exceptional Access Program Reimbursement: Criteria for Frequently Requested Drugs Reports available through the Ontario Ministry of Health and the drug formulary of the Cancer Care Ontario.
Specialised fund	*In case a medicine-indication pair was funded in Ontario through a specialised fund and not through the general drug formulary, the name of the fund was recorded.* *The funds identified through the data collection were the following:* *(i) Exceptional Access Program*	General formulary database of the Ontario Drug Benefit Formulary/Comparative Drug Index, the drug formulary of the Cancer Care Ontario, and the search tool of the Ontario Drug Benefit program.

Variable	Description	Sources
	(ii) The High-Cost Therapy Funding Program *(iii) The New Drug Funding Program*	
Reasons for funding decision (when available)	*The main reasons for funding recommendation by the Ontario independent expert advisory committee to evaluate drugs (CED) and coverage decisions by the executive officer (EO) of the Ontario Ministry of Health for medicine-indication pairs which underwent evaluation before April 2016 were recorded, when available.*	Reports found on EO Decisions and CED Recommendations published on the website of the Ontario Ministry of Health.

Source: *The author.*

5.4.4 Data analysis

Descriptive statistics were used to study general trends in the sample of orphan medicine-indication pairs for the following study endpoints: (i) General sample characteristics including how many orphan medicine-indication pairs have an oncology indication, how many had an HTA re-submission, how many were approved through a specialised pathway and how many of them had a favourable HTA recommendation for funding (including listed and listed with restrictions outcomes); (ii) HTA recommendations across the orphan medicine-indication pairs including restrictions and the types of restrictions, when applicable; (iii) Main reasons for HTA recommendation across the orphan medicine-indication pairs and across the three different HTA outcomes; (iv) Pricing negotiation outcomes at pan-Canadian level; (v) Funding decisions across the orphan medicine-indication pairs and across the three different HTA outcomes; and (vi) If a medicine-indication pair was funded, the name of the specialised fund orphan medicine-indication pairs were available through.

When applicable, to test the distribution of categorical variables in one sub-sample compared to their distribution to another sub-sample (e.g.: HTA recommendations for medicine-indication pairs approved through specialised pathways versus HTA recommendations for medicine-indication pairs approved through standard MA), Pearson's chi-square and Fisher's exact tests were used and a p-value of ≤ 0.05 indicated statistical significance. Similarly, to paper 3, Fisher's exact test was used since some of the study variables had observations of less than 10.

To test for the level of agreement between HTA recommendations by CADTH, pricing negotiation outcomes by the pCPA and funding decisions in Ontario, while accounting for agreement expected by chance, Cohen's kappa score analysis was used. Results of the kappa score analysis were interpreted using the benchmark scale suggested by Landis and Koch (1977) (305). Kappa score analysis was conducted for the full sample of orphan medicine-indication pairs and a sub-sample of medicine-indication pairs that had undergone assessment after April 2016, which was the date when provincial value assessment was no longer required for medicines that had

undergone assessment through CADTH. Pearson's chi-square was used to test the statistical significance of the results, where a p-value ≤0.05 was statistically significant.

To be able to understand what drives funding in Ontario and test whether there is an association between funding and favourable HTA recommendations by CADTH, a binary logistic regression model was designed. Logistic regression was used over simple linear regression as the dependent variable **(funding status in Ontario: funded vs. not funded)** was dichotomous. Similarly, most of the independent (explanatory) variables were binary rather than continuous numerical variables. The year of the HTA decision and MA approval were the only variables that were continuous and numerical in nature. The remaining ones were binary variables using nominal data, meaning that there was no intrinsic ordering across the categories and there were no associated quantitative values.

The independent variables, and the justification for their inclusion in the model are described below.

(i) HTA recommendation **(positive vs. negative):** *HTA recommendations by CADTH are used as an advice for funding decision-making across provinces.*

(ii) **The year of MA approval:** *Due to updates and alterations in the MA processes or administrative changes that can occur over time;*

(iii) **The year of the HTA decision:** *Due to updates and alterations in the HTA assessment processes or administrative changes that occur over time;*

(iv) **Whether the medicine-indication pair has a conditional MA or has undergone standard MA (conditional MA vs. standard MA):** *Medicines with an MA through specialised pathways are usually medicines of high unmet need and are more likely to be prioritised for funding over other therapies;*

(v) **Whether the medicine-indication pair has undergone priority review or has undergone review through the standard MA timelines (priority review MA vs. standard MA):** *Medicines with an MA through specialised pathways are usually medicines of high unmet need and are more likely to be prioritised for funding over other therapies;*

(vi) **Whether the medicine-indication pair has a cancer indication or not (cancer vs non-cancer):** *In Canada, cancer medicines are being assessed by a different committee than non-oncology medicines and other societal dimensions might be accounted for, or different stakeholders might have been involved during assessment and decision-making;*

(vii) **Whether the medicine-indication pair has a paediatric indication or not (paediatric indication vs non-paediatric indication):** *As decision-makers seem to be more flexible when the medicines under review target children and adolescents;*

(viii) **Whether the medicine-indication pairs were first-in-class,** *as a proxy for market competition;*

(ix) **Whether there has been a recall or safety alert given that this might trigger de-listing.** *However, evidence from 2015 showed that serious safety alerts did not have an impact on funding status in Ontario* (319);

(x) **Whether they are considered ultra-orphan,** *as decision-makers might show greater flexibility*;

(xi) **Whether there has been an HTA re-submission or not (re-submission vs. first assessment):** *HTA Dossier re-submission is usually triggered by manufacturers when additional evidence has been generated to revert a previously negative decision.*

(xii) **Whether pricing negotiations by the pCPA were successful or not,** and;

(xiii) **The ICER reported by CADTH** *as funding of orphan medicines can be sensitive to the medicine's cost-effectiveness* (318).

Odds ratios (OR) were calculated for each independent variable to measure their association with the dependent variable (i.e.: funding in Ontario). An OR equal to one showed that the independent variable does not affect the odds of the dependent variable occurring, an OR less than one showed that the independent variable is associated with lower odds of the dependent variable occurring, while an OR of more than one showed that the independent variable is associated with higher odds of the dependent variable occurring (320). The 95% confidence interval (CI) was calculated to estimate the precision of the OR values: a high CI shows low levels of OR precision and a low CI shows high levels of precision of the OR (320). Pearson's chi-square was used to test the statistical significance of the results, where a p-value ≤ 0.05 was statistically significant.

Through this logistic regression model, the probability to receive funding status in Ontario with the presence of each independent variable was explored through the following steps:

$$P_f = \Pr(Y = 1 | X = x_i) \quad \textbf{(1)}$$

Where P_f is the probability of funding in Ontario;

Y is the dependent variable (1=funding in Ontario or 0= no funding in Ontario);

X is the independent variable (e.g.: HTA recommendation);

x_i is the category of the independent variable tested (e.g.: positive HTA recommendation).

Therefore, the model to calculate the probability of receiving funding in Ontario is:

$$P_f = \frac{\exp(\beta_0+\beta_1 x_i)}{1+\exp(\beta_0+\beta_1 x_i)} \quad \textbf{(2)}$$

Where the parameter β_0 gives the log odds of one category of the independent variable (e.g. negative HTA recommendation to receive funding in Ontario, when $x_i = 0$) and β_1 shows how these odds differ for the other category of the independent variable (e.g. positive HTA recommendation, when $x_i = 1$). Exp stands for exponential function where $f(x) = \exp(x) or\ e^x$ and x is the exponent and e is the base of the natural logarithm which equals 2.718281828.

A main limitation of following a logistic regression model was that it assumes that there is linearity between the dependent variable and the independent variables. However, dynamics between funding and the explanatory variables are expected to be more complex in real life. In addition, other cofounding factors that might have not been easily quantified or detected or might have been confidential, might have influenced funding in Ontario, which could potentially change the resulted values of the model.

To test the robustness of the results, a sensitivity analysis was conducted to explore the impact of therapeutic alternatives within the sample, and the annual medicine costs per patient on funding in Ontario.

All data analysis was performed using the statistical software STATA SE.17 (StataCorp).

6 Similarities and Differences in Health Technology Assessment Systems and Implications for Coverage Decisions: Evidence from 32 Countries

This study has been published in *PharmacoEconomics – Open. "Fontrier, A.M., Visintin, E. and Kanavos, P., 2021. Similarities and differences in health technology assessment systems and implications for coverage decisions: evidence from 32 countries. PharmacoEconomics-open, pp.1-14".*

The text in this chapter has been slightly edited[10] to follow the flow of the thesis.

Key messages

- HTA is an evidence-based tool used to inform funding coverage decisions by national/regional healthcare systems. Key features of HTA set up and operationalisation within settings can have an impact on whether, and to what extent, HTA recommendations influence funding decisions.
- While there are well-developed HTA processes for the assessment of pharmaceuticals, there is an urgent need for the development of established HTA processes for medical devices and other technologies such as public health interventions.
- Even though HTA is now present across many settings, a lack of transparency in reimbursement and negotiation processes results in a limited understanding of whether or not HTA recommendations are considered in coverage decisions in practice. Because of this, there is a need to make these processes more transparent.

[10] The numerical ordering of tables and figures have been updated to follow the flow of the thesis, and the spell out of acronyms have been removed if acronyms have been explained previously.

Abstract

HTA systems across countries vary in the way they are set up, according to their role and based on how funding decisions are reached. Our objective was to study the characteristics of these systems and their likely impact on the funding of technologies undergoing HTA. Based on a literature review, we created a conceptual framework that captures key operating features of HTA systems. We used this framework to map current HTA activities across 32 countries in the European Union, the UK, Canada and Australia. Evidence was collected through a systematic search of competent body websites and grey literature sources. Primary data collection through expert consultation validated our findings and further complemented the analysis. Sixty-three HTA bodies were identified. Most have a national scope (76%), are independent (73%), have an advisory role (52%), evaluate pharmaceuticals predominantly or exclusively (76%), assess health technologies based on their clinical and cost-effectiveness (73%) and involve various stakeholders as members of the HTA committee (94%) and/or through external consultation (76%). The majority of HTA outcomes are not legally binding (81%). Although all study countries implement HTA, the way it fits into decision-making, negotiation processes, and coverage and funding decisions differ significantly across countries. HTA is a dynamic and transformative process and there is a need for transparency to investigate whether evidence-based information influences coverage decisions.

6.1 Background

HTA is "the systematic evaluation of properties, effects and/or impacts of health technology"(321). It aims to improve both quality and value for money (322,323) and facilitate coverage decisions based on evidence-based information and other socioeconomic factors beyond the clinical and cost-effectiveness of a technology. HTA comprises multiple operational features and practices the application of which may differ substantially by setting, resulting in different use and application (324,325). The context and structure of HTA systems reflect health system priorities and underpin a country's history, culture, values and preferences. Therefore, HTA is a concept with many facets and may differ in its focus and method, its governance and role, scope and remit, the assessment method employed and its impact on coverage decisions (18,86,125,168,326–328). Taking into consideration these variations, it is important to study the different HTA parameters which can influence the way HTA systems are set up, operate, and are integrated within national policies. These variations make HTA processes unique resulting in different levels of use, implementation and impact on the decision-making process and final coverage decision (329). Whilst some countries directly translate HTA recommendations into coverage decisions, this may not be the case in others where HTA only provides an assessment to be used by healthcare systems when deciding whether health technologies should be included in the reimbursement list or not.

Our main objectives are threefold: first, to understand the multiplicity of approaches employed by different HTA bodies across a wide range of countries; second, to study the role of HTA within the healthcare system and the extent to which is integrated into or is independent of the healthcare system and what this implies for HTA recommendations; and, third, to identify the link between HTA recommendations and funding decisions.

In this paper we develop and extend a conceptual framework capturing the main operational pillars of HTA. We consider HTA within the broader healthcare system with a view to understanding the links between assessment of new technologies, their appraisal and the implications for coverage and funding. Using this framework, we map HTA activities and analyse HTA systems from an international and comparative perspective, drawing on the operational features of HTA systems from a wide range of countries. To this end, the paper provides a holistic approach to the process of value assessment and its implications for coverage, analyses how different applications of HTA can result in practice variations across settings and discusses how these variations impact HTA recommendations and, possibly, coverage decisions.

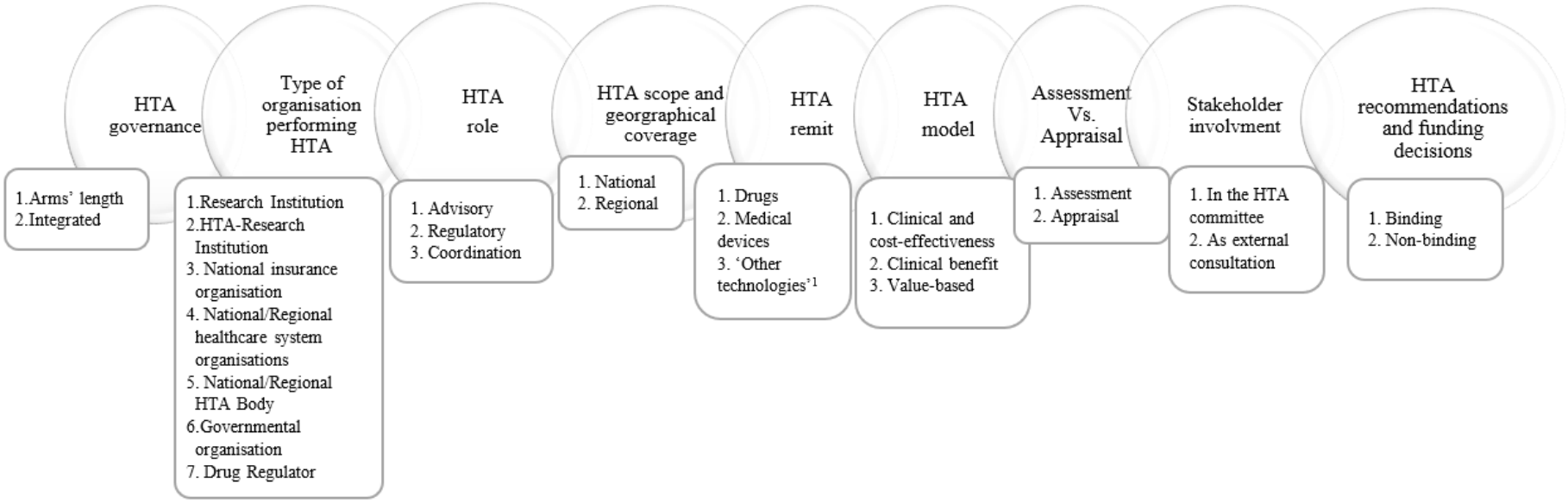
6.2 Conceptual framework

Earlier research (86,126,129,141) has focused predominantly on studying HTA outcomes of the same technologies among different HTA bodies, while examining the clinical and/or economic evidence submitted. Whilst the submitted evidence can differ due to national and/or regional evidentiary requirements and preferences, there are other important parameters which might shape or influence the way HTA functions (86,126,129,141). In order to understand better why reimbursement decisions differ amongst jurisdictions using HTA and to systematically showcase similarities and differences among HTA systems, we propose a conceptual framework that captures the salient features of HTA systems (Figure 8). We reviewed and analysed existing frameworks focusing on how HTA is organised and how it operates within healthcare systems (14,17,233–239). To identify relevant literature, we conducted a search through Medline and Scopus and a targeted search on the websites of EUnetHTA and the European Commission. We searched Medline and Scopus using the following keywords: "health technology assessment", "value assessment", "comparative assessment", and "framework". We limited the search to English and set up the study period for inclusion from 2005 to 2017. The start date of the search timeframe was selected based on the period when independent HTA bodies with refined responsibilities started to be established (330–332). We screened studies through titles and abstracts and selected studies for inclusion only when the authors had designed a conceptual or analytical framework looking at HTA systems, their operation within countries and their potential role in reimbursement. We excluded studies using existing frameworks created by other authors and studies focusing only on the HTA process and the evaluation of the clinical and economic evidence as they were out of scope for our study. For the targeted search, we navigated the websites of EUnetHTA and the European Commission to identify recent studies focusing on European HTA systems as these studies often draw comparisons across the systems of EU member states. We navigated the websites by using the search tool of both websites and the same keywords used in literature search.

Based on our findings, existing frameworks (14,17,233–239) (a) focus on the HTA process itself in combination with few structural features such as the role of HTA, topic selection, or stakeholder involvement; (b) examine HTA as a reimbursement policy which determines technologies' availability within markets, specifically focusing on manufacturers' perspectives; (c) explore decision-making criteria at HTA level; or (d) analyse key components such as level of transparency and scientific rigour, which could influence HTA recommendations. Our framework, in contrast to existing ones, provides a holistic overview capturing the main operational components of HTA

together with salient features of HTA systems and their interactions, to help us understand how HTA processes differ across settings and why, how HTA systems function, and whether HTA recommendations are likely to be directly linked to coverage decisions or not.

Figure 8: Conceptual Framework outlining type, scope and nature of HTA activities



Notes: *[1] "Other technologies" refer to public health interventions such as screening programmes, vaccination campaigns, evaluation of surgical and non-surgical interventional procedures, stem cell therapies, innovative cancer vaccines, cell & gene therapies, other forms of personalized treatments and screening programmes. Assessments that consider the introduction of treatments for diseases as a part of a holistic health and social intervention are included in this category.*

Source: *The authors.*

6.2.1 Governance of HTA

HTA bodies may either be independent review bodies operating at arms' length of governmental structures or may be bodies integrated within governmental structures with decision-making and priority-setting responsibilities (17,333). The key differences that distinguish arms' length from integrated systems lie in (i), the degree of independence in the way HTA bodies operate within the healthcare system and, (ii) the transparency of the process. Independent bodies are considered to be more transparent than integrated ones as the former tend to take a broader and more society focused perspective into consideration (17,333).

6.2.2 Type of organisation performing HTA

Different types of institutions can perform HTA or HTA activities (234): (i) research institutions include academic bodies with broader research initiatives which could encompass some HTA activities; (ii) HTA-research institutions have a special department dedicated to HTA activities; (iii) national insurance organisations; (iv) national/regional health organisations, which could be under the supervision of the Ministry of Health focusing on public health and pharmaceutical policy either at national or regional level but usually functioning at arms' length of the government; (v) national/regional HTA bodies, which perform HTA as their main activity; (vi) governmental organisations which are integrated within the Ministry of Health, and; (vii) medicine regulators, which authorise medicines and/or medical devices with a clear separate HTA function.

6.2.3 Role of HTA

HTA bodies can either have an advisory, a regulatory or a coordinating role in the decision-making process, depending on the intent and type of assessment required, the general mission and overall objectives of the review body (17,233). Advisory HTA bodies produce coverage recommendations for decision-makers (233), but the latter are not obliged to follow this advice or take it into consideration when negotiating with manufacturers. By contrast, regulatory bodies are directly accountable to the Ministry of Health and are responsible for the listing and pricing of new technologies (233). Hence, regulatory systems have an impact on pricing and coverage decisions compared to advisory systems. Coordination bodies usually conduct independent research on HTA and might be responsible for coordinating HTA activities at national, regional and provider level (234). HTA recommendations from coordination bodies are rarely considered or accounted for in coverage decisions. This is due to the nature of these bodies and the way they carry the assessment which usually simply evaluates clinical and economic evidence without contextualising healthcare system's needs. However, healthcare systems can appoint a coordination body as an advisor and further produce recommendations that are used in decision-making.

6.2.4 Scope and geographical coverage of HTA

The structure of a healthcare system and the balance between local autonomy and centralised control influence how HTA systems are organised (333,334). Healthcare systems, which make pricing and reimbursement decisions centrally, also tend to conduct HTA centrally. Healthcare systems with decentralised structures and resource allocation at regional level can justify HTA activities performed regionally. However, given the unique nature of healthcare systems, there are cases where HTA activities are taking place at both levels.

6.2.5 Remit of HTA

In principle, all types of medical technologies can undergo HTA, including pharmaceuticals, medical devices and 'other technologies' (164,234,235,335). The precise remit of HTA showcases which technologies are subject to assessment for listing.

6.2.6 Model of HTA

There are three distinct HTA models, which reflect the objectives and priorities of healthcare systems (17). First, the clinical and cost-effectiveness model uses both economic evidence and comparative clinical benefit to assess health technologies. Second, the comparative clinical benefit assessment model relies on ranking new interventions based on comparative benefit assessment. Under this model, the pricing decision is subject to negotiation between purchasers and manufacturers. The value-based assessment model is directly related to the aforementioned models and further takes into consideration explicitly additional dimensions of value beyond effects and/or costs that are considered important, such as disease severity, burden of disease, treatment innovativeness and equity considerations. It is possible that HTA bodies may adopt more than one HTA model based on certain criteria. For instance, in France, HAS is assessing technologies based on the comparative clinical benefit model. However, since 2013, the submission of cost-effectiveness analysis is mandatory for technologies with a moderate to major improvement in clinical benefit (ASMR I-III)(330).

6.2.7 Assessment Vs. Appraisal

Assessment and appraisal are the two different facets of HTA (14,17,234). Assessment refers to a process of collecting, reviewing and synthesising clinical and economic evidence to support funding decisions (125,126). Appraisal uses the same clinical and economic evidence but interprets it in the context of the healthcare system in question and takes into account factors that may be of relevance in that context (125,336). These contextual factors are known as social value judgements and can be both explicitly recognised such as the end-of-life criteria in England and severity in

France, or implicit, for example, the possible burden on patients' activities of daily living or the impact on family (127). The contextualisation of the evidence thus leads to recommendations that reflect the national/regional needs and values.

6.2.8 Stakeholder involvement in HTA

Consultation of various stakeholders, including healthcare professionals, patients/patient organisations, citizens, health insurers, ethicists and the industry has become an essential part of HTA procedures, contributing to increased transparency, reduced appeals and inclusiveness. To ensure that HTA recommendations are considering preferences, values, judgments, opinions and individual insights, stakeholder participation can occur via two main routes: (i) stakeholders participate as members of an HTA committee, and (ii) stakeholders are engaged through public calls (external engagement). The way stakeholders are engaged and involved in the process varies across HTA systems and the type of stakeholders involved can reflect the inclusiveness of the HTA process and its ability to incorporate values and preferences that matter to different segments of society.

6.2.9 HTA recommendations and funding decisions

HTA recommendations can either be binding or non-binding to the final funding decision (234). In the non-binding case, a negative recommendation is not necessarily associated with a negative coverage decision. In the binding case, purchasers/commissioners of care are legally obliged to consider the HTA outcome when deciding on coverage.

6.3 Methods

6.3.1 Scope and Data sources

The scope of our analysis captured the 27 EU member states, the UK (England, Scotland, Wales and Northern Ireland), Australia and Canada and further includes the EUnetHTA to account for joint assessments conducted by more than one EU member states. We focused on Europe, the UK, Canada and Australia as they have, for a large majority, well-established HTA systems that are used to inform national and regional funding decisions. The refinement of processes that often accompanies well-established HTA systems, allowed us to easily categorise our findings using the conceptual framework and to make comparisons across countries. Therefore, we included countries with explicit HTA systems defined as systems performing HTA routinely and whose existence is enshrined into legislation. We included multiple HTA bodies operating at national and regional level from the same country if they existed. We categorised the types of bodies/institutions performing HTA based on their nature and structure, where these institutions

lie within the healthcare system and the way they are funded (e.g.: research and HTA-research institutions are independent of the government and do not necessarily receive their entire funding from the government). We excluded from our sample informal HTA processes, HTA-like activities (e.g.: consideration of pharmacoeconomic studies on an ad hoc basis only), and mini-HTA activities (mainly assessing ambulatory care medicines or hospital technologies and, therefore, being small scale and not explicit).

6.3.2 Secondary data collection

We used both primary and secondary sources to collect relevant data. We collected evidence on the differences and similarities of HTA processes across the study countries through a search of the websites of all relevant competent institutions (including the Ministry of Health, national health insurance organisations and the HTA bodies), EUnetHTA, INAHTA and the ISPOR Global Health Care Systems Road Map. When we needed further clarification or additional information, we identified evidence through a literature search of Medline and Scopus, using the search terms: "Health technology assessment (HTA)" and the name of the country. We limited the literature search to English. We conducted the secondary data collection in December 2016 to July 2018, and we updated the information, when applicable, in March 2020. We created a list of all identified institutions undertaking HTA along with their websites.

6.3.3 Primary data collection through expert consultation

We contacted 29 stakeholders via email in June 2019 to validate and complement findings from secondary sources and provide further clarification on the nature of HTA activities and operational features in their respective countries. We purposively sampled these stakeholders to ensure the inclusion of leading European health, HTA and pharmaceutical policy experts affiliated with universities and national competent institutions, such as regulatory agencies, departments responsible for pricing or reimbursement decisions and HTA agencies. In particular, we endeavoured to include experts from countries with less well-established HTA systems, since there was little available information from secondary sources in English. We asked the experts to: (a) comment on the design of the conceptual framework; (b) confirm whether we had classified appropriately the key features of HTA systems according to our findings from secondary sources; (c) provide additional information about any formal or informal HTA activity taking place in their countries which we had not captured in our search (if applicable); and (d) to provide details about how multiple organisations which undertake HTA activities within countries collaborate in relation to assessments and final decision-making (if the respondent was based in a country with more than one HTA agency).

6.4 Results

6.4.1 Final sample of HTA activities

We identified 63 HTA bodies/ institutions undertaking HTA activities across 32 settings. We excluded Northern Ireland as HTA activities are very limited and rely on reviews of the English national institute for health and care excellence (NICE) decisions (337). We included EUnetHTA as a supranational organisation that has been created to coordinate joint HTA activities at EU level. We further acknowledged the proposed regulation of the EU commission regarding HTA cooperation, but we did not consider it in this study as it was still under deliberation and consultation at that time.

Out of the 29 contacted experts, 18 experts from 14 countries (Estonia, Ireland, Poland (n=3), Portugal, Romania, Slovakia, Slovenia, Spain, Sweden (n=2), Malta, Bulgaria, Austria (n=2), Belgium and Czech Republic) responded to our call and participated in the consultation round. The results of the primary and secondary data collection are presented according to the attributes of the conceptual framework. Table 7 summarises the key findings on the bodies or institutions undertaking HTA activities across the study countries (see Appendix 1 for complete results by country).

Table 7: Summary of HTA systems across EU Member States, the United Kingdom, Canada and Australia

Variable	Summary of evidence	Country examples
Governance of HTA	**Arms' length:** 46	Austria, Croatia, Finland, the Netherlands, Canada, England, France, Germany, Australia, Poland
	Integrated: 16	Cyprus, Greece, Malta, Slovakia, Slovenia, Italy, Spain (regional), Canada (regional)
	N/A[1]: 1	EU level
Type of organisation performing HTA	**Research institution:** 6	Austria, Belgium, Denmark, Estonia, Slovakia, England
	HTA-Research institution: 6	Austria, Finland, Ireland, Lithuania, Spain (national and regional)
	Drug Regulator: 6	Czech Republic, Finland, Hungary, Italy, Portugal, Romania
	Governmental institution: 8	Cyprus, Greece, Lithuania, Luxembourg, Malta, Slovakia, Slovenia, Spain
	HTA Body: 18	France, Germany, Poland, Scotland, England, Wales, EU level, Canada, Australia
	National/Regional healthcare organisation: 14	Bulgaria, Croatia, Finland, Germany, Italy, Latvia, Lithuania, the Netherlands, Spain, Sweden
	National insurance organisation: 5	Austria, Belgium, Croatia, Estonia, Slovenia
Role of HTA	**Advisory:** 33	Luxembourg, the Netherlands, Portugal, England, Canada, Australia
	Coordination: 2	Finland, UK
	Regulatory: 17	Bulgaria, Croatia, Cyprus, Czech Republic, Italy, Estonia, Germany, Sweden
	Advisory & Coordination: 10	Austria, Belgium, Denmark, Ireland, Spain (national and regional), Canada
	N/A[1]: 1	EU level
HTA scope	**National:** 48	Australia, Germany, France, Sweden, Slovakia, Austria, Lithuania, Malta, Luxembourg, the Netherlands
	Regional: 14	Spain (AQuAS-Catalonia, OSTEBA-Basque County, AETSA-Andalusia, SECS-Canary Islands, UETS-Madrid, Avalia-t -Galicia, IACS -Aragon), Italy (AGENAS, CRU-Veneto, ER Salute-Emilia Romagna, Canada (INESSS-Quebec, HQO-Ontario, CED-Ontrario, British Columbia)
	N/A[1]: 1	EU level
Remit of HTA[2]	**Pharmaceuticals:** 48	Austria, Belgium, Bulgaria, Croatia, Cyprus, Finland, France, Germany, Greece, Malta, Scotland, Australia, Canada
	Medical Devices: 43	Denmark, Germany, Hungary, Ireland, Latvia, Lithuania, Portugal, Spain, Sweden
	Other technologies: 35	Canada, EU level, England, Wales, Sweden, the Netherlands, Lithuania, Belgium, Croatia
	All: 20	Belgium, Estonia, France, Finland, the Netherlands, Poland, England, EU level

Variable	Summary of evidence	Country examples
Model of HTA	**Comparative clinical benefit assessment:** 7	Austria (GÖG and AIHTA), Germany (GBA and IQWiG), Greece[3], Slovenia (Health Council), EU level
	Clinical and cost-effectiveness: 46	Belgium, Croatia (both agencies) Cyprus, Spain (national and regional), Malta, Lithuania, Ireland, Finland, Hungary, Denmark, Wales
	Clinical and cost-effectiveness/ MCDA: 2	Bulgaria, Canada
	Value-based assessment: 8	France, Slovakia (both HTA bodies), Slovenia (ZZZS), Sweden, England, Scotland, Australia
Assessment Vs. Appraisal	**Assessment only:** 28	Austria, Belgium, Croatia, Cyprus, Estonia, Denmark, Greece, Ireland, Italy (regional), Spain (regional), EU level, Canada (regional)
	Assessment and Appraisal: 35	Austria, Belgium, France, Finland, Croatia, Canada, Australia, Romania, Luxembourg, Portugal, Poland, Slovenia, Sweden, Spain, England, Scotland, Wales
Stakeholder involvement in HTA	**Stakeholder participation as members of HTA committee:** 59	Croatia, Cyprus, Finland, Greece, the Netherlands, Portugal, Poland, Spain, Sweden, Canada, Australia
	Stakeholders through public calls: 48	Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Ireland, Latvia, Lithuania, Malta, Portugal, Slovakia, Slovenia, Spain, UK, EU level,
HTA recommendations and funding decisions	**Binding:** 12	Bulgaria, Cyprus, Finland, Germany, Italy, Lithuania, Portugal, Sweden
	Non-binding: 51	Austria, Belgium, Croatia, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland, Italy (regional), Poland, the Netherlands, Spain, Wales, Canada**,** EU level
Publicly available reports	**Yes:** 48	Australia, Canada, England, Scotland, Wales, Sweden, Spain, the Netherlands, Germany, Belgium
	No: 15	Croatia, Estonia, Greece, Hungary, Luxembourg, Slovakia, Slovenia

Notes: *[1]EUnetHTA has been categorised as a supranational organisation that has been created and now coordinates the HTA Core Model, which is a methodological framework for collaborative production and sharing of HTA information. Therefore, EUnetHTA does not fall into the classification we have placed national HTA bodies.*

[2] Under the remit of HTA different organisations in each country may perform HTA for different technologies. Examples of agencies which perform HTA for pharmaceuticals only are SUKL in the Czech Republic and DPA in Malta. Examples of agencies which perform HTA for medical devices only are AGENAS in Italy and UETS in Spain. Examples of agencies which perform HTA for other technologies are SBU in Sweden and the Institute of Hygiene in Lithuania.

Source: *The authors based on primary and secondary data collection.*

6.4.2 Governance of HTA

The majority (73%, n=46) of the identified institutions are at arms' length of government, including regulatory bodies, which are, by definition independent of government. Similarly, we categorised as independent organisations the national insurance organisations which all perform in-house HTA and use cost-effectiveness as one of the criteria for coverage decisions. This is because national insurance organisations are independent entities and do not function as governmental organisations, even though they are a part of national healthcare systems. Institutions or organisations, which do not operate within the national or regional Ministry of Health are categorised as independent bodies. Integrated agencies to a governmental structure were predominately regional bodies or newly established HTA committees which are responsible for performing HTA within the Ministry of Health (e.g.: Greece, Cyprus and Malta).

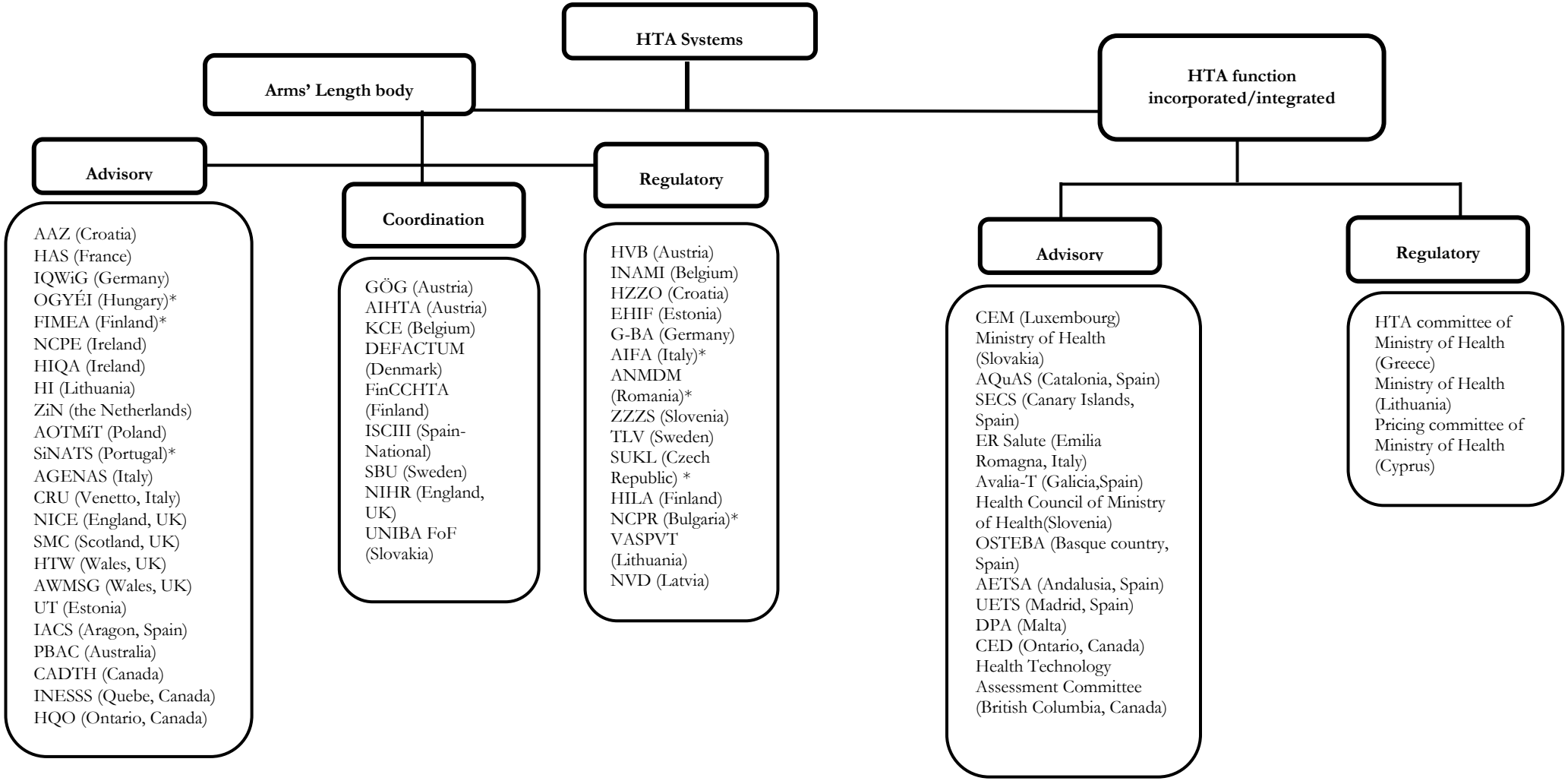
6.4.3 Type of organisation performing HTA

Twenty- eight percent (n=18) of the identified entities performing HTA had formal HTA agency status, i.e. HTA being their predominant activity. Twenty-two percent (n=14) were national or regional healthcare organisations and twelve percent (n=8) were governmental institutions (refer to table 1 for all the different types of organisations performing HTA). Under this category, there was variation across the sample as to which types of institutions perform HTA, showcasing that various institution types can undertake HTA activities predominantly depending on the structure of the healthcare system and the scope and objectives of HTA.

6.4.4 Role of HTA

According to our findings on the governance endpoint and that of the role of HTA bodies, we created a taxonomy (Figure 9) to differentiate the included bodies based on their level of integration within the government, as well as their function as advisory, coordination or regulatory entities.

Figure 9: Taxonomy of HTA bodies



Notes: **Regulatory body for approval of medicines and/or medical devices with a clear separate HTA function.* **Source:** *The authors based on primary and secondary data collection.*

6.4.5 Scope and geographical coverage of HTA

In 13 countries (Austria, Belgium, Croatia, Estonia, Finland, Germany, Ireland, Lithuania, Slovakia, Slovenia, Sweden, England, and Wales), we identified more than one institution with varying roles undertaking HTA activities at national level. Stakeholders who participated in the expert consultation, from Austria, Belgium, Estonia, Slovakia, Slovenia, Sweden and Ireland, provided additional information on the responsibilities of multiple national HTA bodies (see appendix 2 for a detailed description on how multiple national HTA bodies are set up in country's system, how these bodies interact with each other and their impact on funding decisions). HTA bodies with a regional and provider level scope were identified in eight countries (Austria, Canada, Germany, Italy, Spain, Denmark, Poland and Sweden). Due to limited access and data, we were able to include regional HTA bodies from Spain, Italy and Canada. In Spain and Italy, organisations performing HTA at regional level are mainly integrated within the regional government. In Sweden, there are about fifteen regional HTA bodies, which assess the clinical and cost-effectiveness of procedures and medical devices, they have an advisory role to the county councils and help informing reimbursement decisions at state level. However, their recommendations are not binding (338). Due to limited evidence, they were not included in our sample. In Austria, universities such as the University for Health Sciences Medical Informatics and Technology (UMIT), the IAMEV unit in the Medical University of Graz and the Danube University Krems (DUK), perform HTA activities independently by assessing various health technologies. DUK and the IAMEV unit conduct clinical assessments whereas UMIT follows the clinical and cost-effectiveness model (338). In Poland, hospital-based HTA is evolving and performed by some university hospitals and institutes to support investment decisions on hospitals. However, their scope and impact on funding decisions are still unknown (338).

6.4.6 Remit of HTA

In the sample, there is wide variation on the technologies, which undergo HTA. From our sample, we identified bodies, which assess a specific type of pharmaceuticals only. For instance, the Finnish medicines agency (FIMEA) in Finland perform HTA only for in-patient pharmaceuticals. SUKL in Czech Republic performs HTA only for out-patient pharmaceuticals, while TLV in Sweden assess mainly out-patient pharmaceuticals, whereas in-patient pharmaceuticals are assessed at county level (338) (see appendix 3 for a detailed list of which technologies undergo HTA assessment by the identified HTA bodies).

6.4.7 Model of HTA

All national insurance organisations in Austria, Belgium, Croatia, Estonia, and Slovenia use the clinical and cost-effectiveness model as an additional criterion during the decision-making process on what technologies to include in their positive lists. In Sweden, value-based assessments by TLV always take into consideration explicitly the human dignity and solidarity principles to derive funding decisions (338). In Slovakia, since the implementation of the new legislation in 2011, decisions on resource allocation are based on criteria beyond the clinical effectiveness, safety and the economic benefit of the technologies, notably, disease severity, impact on society and risk of abuse (338). In France, the award of total therapeutic benefit (SMR) and improvement in therapeutic benefit (ASMR) rests on criteria beyond efficacy; for example, ASMR I is awarded to significant innovations in terms of efficacy improvement in a severe disease setting, in other words, severity is taken explicitly into account; similar criteria inform the SMR rating. Therefore, additional dimensions of value are taken into account during the assessment and appraisal process.

6.4.8 Assessment Vs. Appraisal

Fifty-six percent (n=35) of HTA bodies perform appraisals and are not solely collecting and synthesising evidence on the clinical and/or economic effectiveness of technologies. HTA bodies conducting appraisals are mainly national institutions. Approximately 44% (n=28) of the HTA bodies limit their evaluations in the assessment phase. Regional HTA bodies in Spain, Italy and Canada, research institutions and integrated committees within the Ministry of Health responsible for HTA in Malta, Greece, Bulgaria and Cyprus are all performing assessments rather than appraisals.

6.4.9 Stakeholder involvement in the HTA process

Involvement of various stakeholders as members of HTA committees was present across almost all the HTA bodies except bodies with a coordination role in Denmark, Finland and England, where assessments are performed by external institutions. The type of stakeholders involved in decision-making varied considerably across the sample from representatives of healthcare insurance funds and public health organisations, healthcare experts, ethicists, health economists, healthcare professionals as well as patient and citizens advocates. External expert consultation was not present in 15 HTA bodies, which by majority were regulatory bodies. External consultation was heavily dependent on patients who were able to submit their opinion on the topic selection, the evaluation process, or the final recommendations.

6.4.10 HTA recommendations and funding decisions

HTA recommendations are not always translated into funding decisions regardless on how well HTA systems are developed, their role and where they are set up in the healthcare system. In 81% (n=51) of our sample, HTA outcomes are non-binding and their impact during reimbursement negotiations is unclear. Nevertheless, HTA outcomes, even if non-binding, weigh heavily on final reimbursement decision in some countries such as France, England, Scotland, Australia, Poland and Romania (338). In Poland, the HTA body (AOTMIT) plays a key role in the reimbursement process. Any health technology subject to coverage by the public healthcare system has to be assessed by AOTMiT. Both the president of the agency and the Transparency Council (TC), serving as an advisory body to the president, provide a formal position (338). Non-binding recommendations are sent to the Ministry of Health where negotiations are taking place between the Economic Commission of the Ministry of Health and the manufacturer. The Ministry of Health makes the final decision taking into consideration the opinions of both the TC and the president as this is one of the reimbursement criteria established by law (338). In Romania, legislation stipulates that the HTA body (ANMDM) makes a recommendation to the Ministry of Health based on a scorecard and a budget impact analysis. Scorecard points are given taking into account HTA recommendations in England, Scotland, France and Germany. Additional points are further attributed when the product under evaluation has been granted reimbursement status in EU countries. According to primary evidence, the Ministry of Health will always include in the reimbursement list products with a positive recommendation by ANMDM (338). Moreover, if ANMDM makes a conditional reimbursement recommendation, then the manufacturer must submit a request to the National Health Insurance House to attend price-volume negotiations. The request is analysed by a negotiation commission which decides if contract negotiations will be initiated (338). In England and Scotland, NICE and SMC have an advisory role and the local NHS must fund all positive HTA recommendations. Technologies receiving a negative recommendation may be subject to negotiations in order to improve their cost-effectiveness and if there is agreement then the NHS will fund the technology; alternatively, if clinical benefit is highly uncertain or is considered inadequate, alternative mechanisms or pathways exist (339,340). In Australia, the government or the cabinet should consider all HTA recommendations by PBAC if the medicine is expected to cost more than AUD 20 million per year (341).

6.5 Discussion

The results in this study point to a number of key features of HTA processes and their relationship to coverage decisions. First, HTA is not a single mechanism but consists of several salient features which can differ substantially across countries and further determine the way it is implemented to inform coverage decisions. HTA operates mainly at national level except in countries with decentralised systems (e.g.: Italy, Spain, UK, Sweden) or autonomous regions/provinces (e.g.: Canada). As such, HTA infrastructure and activities reflect the structure of the healthcare systems in which they operate. The scope of HTA systems can directly mirror the administrative division of a country (highly regional systems vs centralized ones). In countries where HTA activities are performed both at national and regional level, assessments of clinical benefit for the same technology could amount to duplication of effort. Similarly, when considering comparable HTA structures across Europe, assessment of clinical evidence performed by HTA agencies duplicates effort as manufacturers tend to submit very similar, if not the same, evidence. Therefore, EU HTA cooperation may be able to streamline HTA activities and homogenise methodologies and procedures in assessing health technologies within the European Union (334).

Second, institutions performing HTA at national level are mostly independent from the competent authorities they serve (e.g.: Ministries of Health, health insurance organisations, pricing committees), even though their activities may be sometimes supervised by these authorities. Considering that HTA activities can, in general, be grouped into (a) assessment; (b) appraisal; (c) coverage recommendations; and (d) funding negotiation, the remit of independent bodies covers (a), (b) and (c), while integrated bodies cover (a), (b) and (d). Given that HTA recommendations by integrated bodies can result in negotiations, they can play a key role in funding decisions. However, this depends on the role of the HTA and whether the recommendation is binding or not. Overall, HTA bodies operating at arm's length are present in more developed HTA systems and tend to be transparent and independent, avoid conflicts of interest and offer dispassionate advice on the costs and/or effects of assessed technologies adapted for contextual considerations. By contrast, newly founded and less well-developed HTA systems such as those found in Greece, Cyprus and Malta tend to be integrated within existing competent authorities. They may lack transparency as assessments are internalised, and recommendations are not reported in publicly available documents, rendering decision-making and negotiation processes unclear and non-transparent. Nevertheless, it could be argued that integrated HTA functions can be very useful as a starting point in the implementation of HTA activities particularly in circumstances where there is a lack of capacity for the development of an independent HTA body. Unsurprisingly, most

independent bodies make their HTA reports and outcomes publicly available (see Appendix), whereas integrated bodies tend to keep their reports confidential. Overall, more transparency improves the extent to which a decision can be controlled by the organisation that has commissioned it in the first place (237).

Third, irrespective of operating at arm's length or being integrated with competent authorities, the majority of HTA bodies have an advisory role where HTA outcomes act only as recommendations and can be used as supplementary tools or additional criteria during negotiations. HTA bodies with a coordination role may operate in an advisory capacity to competent authorities when asked to assess technologies, however, the extent of their contribution to the final coverage decision is unclear and the consideration of their recommendation is mostly made in a non-systematic manner. Coordination bodies are few, and in our opinion, entities with this role are urgently needed to assist with the coordination and interoperability of HTA activities as well as to generate evidence on how new technologies impact society, including cost benefit analyses. Coordination bodies can also assist in the transformation of HTA recommendations into clinical guidelines contributing to optimal resource allocation by positioning new technologies along treatment pathways, monitoring their use and assessing the impact they have.

Fourth, the type of HTA evaluation plays an essential role in the way HTA outcomes are translated into funding decisions. During the assessment phase comparative clinical and/or economic evidence is reviewed, whereas during the appraisal phase the evidence is assessed and interpreted based on its scientific rigour, the achievement of the endpoints of interest, the design of the included studies, the economic effectiveness, the budget and/or economic model submitted and a host of contextual considerations that may be relevant to the setting in question. Value dimensions are examined to investigate the extent to which a new technology is relevant for the healthcare system of interest (325). Under appraisal these dimensions are always taken into consideration regardless of the nature and the disease context. Therefore, when appraisals are performed, recommendations are context specific as they take into consideration how a technology can be adopted at national or regional level and what budget impact it will have. Appraisals can inform purchaser-manufacturer negotiations by providing steer, among others, on whether any risk mitigation strategies should be implemented.

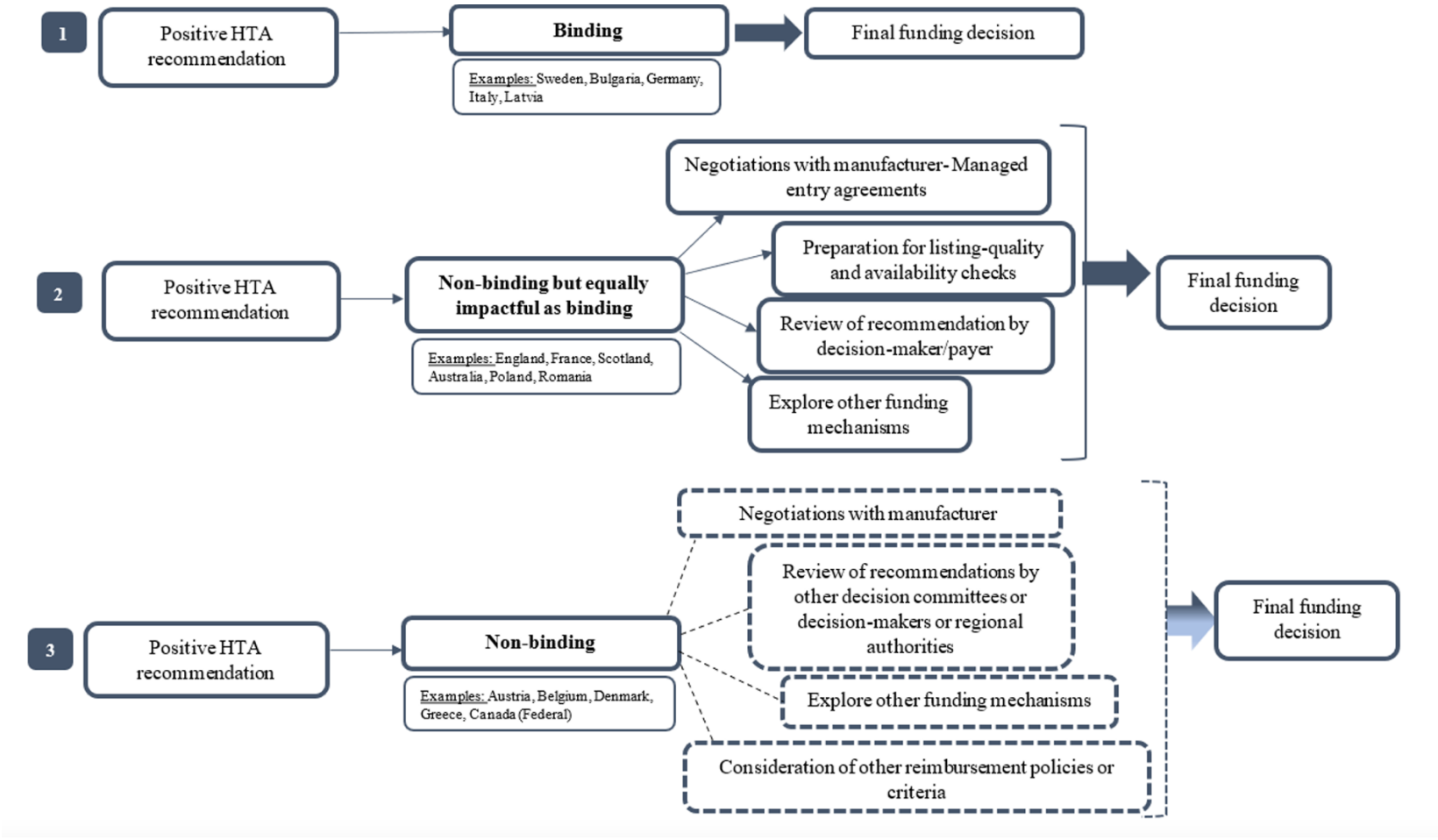
Fifth, the vast majority of HTA bodies or institutions performing HTA has some form of stakeholder involvement or engagement. Whether stakeholders were involved in the HTA process itself or whether they were part of the HTA committee varied, with more developed and well-

established systems giving patients, carers, citizens, and health experts the possibility to act as external stakeholders through public calls. However, engagement of external stakeholders does not always serve the same purpose and ranges across systems from opinions and insights on topic selection and scoping to consultations during HTA assessment or appeals on the final recommendations. In many systems where patient representatives or patient organisations are not involved in HTA, members who are ethicists are bringing the societal perspective into decision-making. However, even though in theory stakeholder participation or engagement can result in better uptake of HTA recommendations, there is no evidence establishing a direct link. Undoubtedly, participation of healthcare experts and professionals, experts on ethics, patients, their families and carers in either the HTA process itself or decision-making can ensure transparency, inclusiveness and the reflection of different perspectives in the final recommendations.

Sixth, to assess whether HTA recommendations are translated into funding decisions, we looked at whether HTA outcomes across our sample countries are legally binding. This means that decision-makers are legally bound to respect and follow the final HTA recommendation when making coverage decisions. Based on our findings, the majority of HTA systems issue non-binding recommendations, however, the importance and the weight these recommendations might have on the decision-making process vary across countries. In less-developed HTA systems, such as that of Greece, the role and the impact of HTA recommendations, which are non-binding, is still unknown due to lack of transparency in the decision-making process. Nevertheless, from our sample we identified countries such as Poland, France, England, Scotland, Australia and Romania where recommendations are non-binding but their role during pricing and reimbursement processes at national level is considered crucial.

In order to be able to capture all types of recommendations, we created three alternative scenarios on how HTA outcomes feed into final funding decisions and what their contribution to the final coverage decision of technologies is. Figure 10 shows three categories of recommendations: (i) binding; (ii) non-binding but as impactful as binding and (iii) non-binding. We created the second category to be able to include the HTA systems of England, Scotland, Australia, France, Poland and Romania, which have an advisory role according to legal statutes, however, (positive) recommendations are considered binding for coverage purposes. For instance, the NHS in England is legally obliged to fund technologies recommended by NICE and ensure they are available within three months from the date of the NICE recommendation being published (339).

Figure 10: Positive HTA recommendations and links to final funding decisions



Notes: *The dotted lines show the use of alternative pathways.*
Source: *The authors.*

HTA recommendations which do not fall into the first two categories might jeopardize transparency by creating uncertainty on how evidence-based information is used meaningfully during negotiations or is translated into either price discounts or any other type of Managed Entry Agreements. Importantly, however, non-binding HTAs might inform decision processes further upstream. For instance, in the Greek context, the HTA committee's recommendations inform the negotiation committee which has decision-making power over what is reimbursed. In Poland, HTA recommendations play an important role and are extensively used by the Ministry of Health which decides on reimbursement based on negotiations between the Economic Commission of the Ministry of Health and the manufacturer (338).

Seventh, while HTA systems across the study countries seem to have well-developed processes for the assessment of pharmaceuticals, these do not appear to be in place for medical devices and other technologies, including public health interventions; there is significant need for refinement in the assessment of both medical devices and other technologies (234). Among other reasons, this is due to the highly fragmented market structure of medical devices, the lack of clear guidance on evidence requirements, and the inconsistency in the methods employed in their assessment (234). Overall, the range of relevant technologies undergoing HTA is determined by budget holders wishing to optimise the available resources. The identification of more than one HTA agency at national level often coincided with the identified HTA bodies having different remits and assessing different health technologies. For instance, in Wales the All Wales Medicines Strategy Group (AWMSG) assesses pharmaceuticals only, while the Health Technology Wales (HTW) assesses medical devices and other technologies. This was further validated by experts who participated in the consultation round: according to primary evidence, the majority of countries, reporting more than one body/institution performing HTA at national level, except Belgium and Estonia have different national bodies for the assessment of different technologies.

Finally, there are different avenues of how HTA recommendations can be used which depends on the way HTA systems operate, their role, and the technologies undergoing assessment, such as (i) reimbursement and coverage, (ii) price setting, (iii) strategic purchasing and procurement especially for medical devices, and (iv) to inform clinical guidance. For instance, HTA bodies with a coordination role can rarely impact coverage decisions but their recommendations can be used for the update of clinical guidelines. HTA systems across our sample could be further divided in several categories in terms of the way HTA recommendations are implemented in decision-making. We observed systems where HTA outputs provide a fundamental basis for pricing and

reimbursement; for example, in France HTA recommendations are used both for reimbursement decisions by the national insurance fund and for pricing decisions by the Transparency Committee. Other systems, such as that of England, operate in a manner where HTA body makes a recommendation which eventually might trigger negotiations if the cost-effectiveness threshold is higher than the acceptable range or when there is considerable clinical uncertainty around the technology under evaluation. In this case negotiations take place outside the remit of the HTA body between the purchaser/commissioner of care and the manufacturer. Lastly, there are HTA systems, such as that of Australia or HTA by health insurance funds, which internalise the decision-making process. Under these systems, negotiations, risk-sharing agreements, or strategic purchasing and procuring take place within the HTA body based on the HTA outcome of the body itself. Despite how HTA recommendations are implemented, it is important to highlight that the ultimate "client" of the HTA bodies is the healthcare system they operate in.

6.5.1 Study limitations

Our study is not without limitations: (a) due to unavailability of data and limited access, we were not able to identify all regional HTA bodies across study countries; (b) reliance on secondary sources has meant that it may not have been possible to capture HTA processes and implementation in detail; (c) some HTA bodies may consider additional dimensions of value beyond clinical benefit and cost-effectiveness. Nevertheless, it has not always been possible to determine whether these features have an explicit impact on HTA recommendations through literature or expert opinion; and (d) even though we tracked the HTA systems across countries, the actual implementation and uptake of HTA activities during funding decisions were not fully captured. In order to address the latter two limitations, we performed the round of consultation to improve our understanding of the role and extent of HTA at national level.

6.6 Conclusion

Based on a conceptual framework and taxonomy we outlined the main operational pillars of HTA, showcased how HTA systems are set up within countries, how well developed HTA processes are as well as identified the different facets of HTA systems across the EU, the UK, Canada and Australia. Countries may follow similar pathways in the way HTA systems are set up, their role, remit and the way HTA processes are implemented, however, there are variations in the way HTA recommendations are translated into funding decisions. These relate to how well HTA processes are developed and integrated in the decision-making and the extent to which purchasers/commissioners of care consider evidence-based information when deciding funding of technologies. While HTA processes are well-established for pharmaceuticals across the study

countries, there seems to be a need for the development of established HTA processes of medical devices and other technologies. HTA is a dynamic and transformative process which constantly adapts to new types of evidence, innovative technologies, and redefined objectives of healthcare systems. Even though HTA is now present across many settings, there is still an unmet need to make reimbursement and negotiation processes more transparent to better understand how purchasers/commissioners of care use HTA recommendations during negotiations with manufacturers, and to further investigate the extent to which HTA recommendations can influence coverage decisions.

6.7 Appendices

6.7.1 Appendix 1

HTA systems across European Union Member States, the United Kingdom, Canada and Australia, 2020

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
Austria	Gesundheit Österreich GmbH/Geschäftsbereich/ National Public Health Institute (GÖG)	Research institution	Advisory and coordination	Comparative clinical benefit assessment	Assessment	Clinicians	External experts	Non-binding	✓
	Austrian Institute for health technology assessment (AIHTA)	HTA-Research institution	Advisory and coordination	Comparative clinical benefit assessment	Assessment	Clinicians	Manufacturers	Non-binding	✓
	Hauptverband der Österreichischen Sozialversicherungsträger /Association of Austrian Social Insurance Institutions (HVB)	National insurance organisation	Regulatory	Clinical and cost-effectiveness as a criterion	Appraisal	Representatives of the Social Security Institutions, the Austrian Chamber of Commerce, the Federal Labor Board, the Austrian Medical Association, the Austrian Chamber of Pharmacists and the Federal States and academics	N/A	Binding[1]	✓
Belgium	Federaal Kenniscentrum voor de gezondheidszorg / Centre fédéral d'expertise des soins de santé / Belgian Health Care Knowledge Centre (KCE)	Research institution	Advisory and coordination	Clinical and cost-effectiveness	Assessment	Representatives of public healthcare bodies, patient associations and health insurance, healthcare professionals and healthcare experts	Public authorities such as the Ministry of Health, universities, professional associations	Non-binding	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering / Institut National d'Assurance Maladie-Invalidité/ National Institute for Health and Disability Insurance (INAMI)	National insurance organisation	Regulatory	Clinical and cost-effectiveness as a criterion	Appraisal	Representatives of insurers, the Ministry of Social Affairs, the Ministry of Health, the Ministry of Finance and the industry, healthcare professionals, academics	N/A	Non-binding	✓
Bulgaria	National Council of Pricing and Reimbursement (NCPR) of the Council of Ministers	National healthcare organisation	Regulatory	Clinical and cost-effectiveness/ MCDA	Assessment	Healthcare professionals and economists	Healthcare experts	Binding	✓[2]
Croatia	Agencija za kvalitetu i akreditaciju u zdravstvu i socijalnoj skrbi/ Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ)	National healthcare organisation	Advisory	Clinical and cost-effectiveness	Assessment	Representatives from the Ministry of Health, the Croatian Medical Chamber, the health chambers, patients, healthcare professionals and healthcare experts	Patients	Non-binding	✓
	Hrvatski zavod za zdravstveno osiguranje/ Croatian Institute for Health Insurance Fund (HZZO)	National insurance organisation	Regulatory[3]	Clinical and cost-effectiveness as a criterion	Appraisal	Clinicians	N/A	Non-binding	×
Cyprus	Pharmaceutical Committee of the Ministry of Health	Governmental institution	Regulatory	Clinical and cost-effectiveness	Assessment	Representatives from the Health Authority and Ministry of Health, ideally with some experience on pharmacology or health economics	N/A	Binding	×

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
Czech Republic	Státní ústav pro kontrolu léčiv/ State Institute of Drug Control (SUKL)[4]	Drug regulator	Regulatory	Clinical and cost-effectiveness	Assessment	Health insurance companies and manufacturers	Patient organisations and professional societies.	Binding	✗
Denmark	Central Denmark Region in collaboration with Department of Research and HTA, Odense University Hospital, Region of Southern Denmark (DEFACTUM)[5]	Research institution	Advisory and coordination	Clinical and cost-effectiveness	Assessment	N/A	Clinicians and manufacturers	Non-binding	✓
Estonia	Institute of Family Medicine and Public Health, University of Tartu (UT)	Research institution	Advisory	Clinical and cost-effectiveness	Assessment[6]	Health economists, healthcare experts and clinicians	Representatives of the Ministry of Social Affairs, the Estonian Health Insurance Fund, the State Agency of Medicines, the Estonian Society of General Practitioners, the Estonian Medical Association, the Institute for Health Development and the	Non-binding	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
							University of Tartu		
	Eesti Haigekassa/Estonian Health Insurance Fund (EHIF)	National insurance organisation	Regulatory	Clinical and cost-effectiveness as a criterion	Assessment	Health economists, healthcare experts and healthcare professionals	N/A	Non-binding	✗
Finland	Finnish Medicines Agency (FIMEA)	Drug regulator	Advisory	Clinical and cost-effectiveness	Appraisal	Health economists and healthcare experts	Healthcare Service Selection Council (PALKO), the National HTA Coordination Unit (FinCCHTA), hospital districts, clinicians, patients and other national stakeholders	Non-binding	✓
	Kansallinen HTA-koordinaatioyksikkö/ Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)[7,8]	HTA-Research institution	Coordination	Clinical and cost-effectiveness	Appraisal	N/A	Citizens	Non-binding	✓
	Pharmaceuticals Pricing Board organisation (HILA)	National healthcare organisation[9]	Regulatory	Clinical and cost-effectiveness	Appraisal	Representatives of the Ministry of Social Affairs and Health, the Ministry of Finance, the Social Insurance	N/A	Binding	✗

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
						Institution, the Pharmaceutical Safety and Development Center and the Department of Health and Welfare, experts on medicine, pharmacology and health insurance			
France	Haute Autorité de Santé/ High Authority of Health (HAS)	National HTA body	Advisory	Value-based assessment[10]	Appraisal	Healthcare professionals, specialists in methodology and epidemiology, patients and user representatives	Patients and user associations	Non-binding[11]	✓
Germany	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen /Institute for Quality and Efficiency in Health Care (IQWiG)	National HTA body	Advisory	Comparative clinical benefit assessment	Assessment	Clinicians, patient advocates and health economists	Citizens	Non-binding	✓
	Gemeinsamer Bundesausschuss/Federal Joint Committee (G-BA)	National healthcare organisation	Regulatory	Comparative clinical benefit assessment	Appraisal[12]	Representatives of National Association of Statutory Health Insurance and of the service providers, clinicians, patients and health economists	Patients and self-help organisations	Binding	✓
Greece	HTA committee of the Ministry of Health	Governmental institution	Regulatory[13]	Comparative clinical	Assessment	Healthcare professionals, health	N/A	Non-binding	×

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
				benefit assessment		economists and healthcare experts			
Hungary	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet/ National Institute of Pharmacy and Nutrition (OGYÉI)	Drug regulator	Advisory	Clinical and cost-effectiveness	Appraisal	Clinicians and health economists	N/A	Non-binding	✗
Ireland	National Centre for Pharmacoeconomics (NCPE)	National HTA body	Advisory	Clinical and cost-effectiveness	Assessment	Healthcare professionals, health economists, healthcare experts, HTA experts	Patients	Non-binding	✓[14]
	Health Information and Quality Authority (HIQA)	HTA-Research institution	Advisory and coordination	Clinical and cost-effectiveness	Appraisal	Representatives of the National Center of Pharmacoeconomics, Department of Health, Healthcare experts, patient associations and health economists	Academics and clinicians	Non-binding	✓
Italy*	Agenzia Italiana del Farmaco /Italian Medicines Agency (AIFA) (National)	Drug regulator	Regulatory	Clinical and cost-effectiveness	Appraisal	Healthcare experts	Patients	Binding	✗
	Agenzia nazionale per i servizi sanitari regionali/ Italian National Agency for Regional Healthcare Services (AGENAS) (National)	National healthcare organisation	Advisory	Clinical and cost-effectiveness	Appraisal	Clinicians and health economists	Patients, Manufacturers, healthcare experts and clinicians.	Non-binding	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
	Coordinamento Regionale Unico sul Farmaco /Regional coordination for medicines (CRU) (Regional-Veneto)	Regional healthcare organisation	Advisory	Clinical and cost-effectiveness	Assessment	Healthcare experts and patients advocates	Healthcare experts	Non-binding	✓
	Agenzia sanitaria e sociale-Regione Emilia Romagna/ Regional health agency in Emilia Romagna (ER Salute) (Regional- Emilia Romagna)	Regional healthcare organisation	Advisory	Clinical and cost-effectiveness	Assessment	Clinicians and health economists	Healthcare experts as peer reviewers	Non-binding	✓
Latvia	Nacionālais veselības dienests/ The National Health Service (NVD)	National healthcare organisation	Regulatory	Clinical and cost-effectiveness	Appraisal	Healthcare experts	Healthcare professionals	Binding	×
Lithuania	Valstybinė Akreditavimo Sveikatos Priežiūros Veiklai Tarnyba/State Health Care Accreditation Agency under the Ministry of Health (VASPVT)	National healthcare organisation	Advisory	Clinical and cost-effectiveness	Appraisal	Healthcare experts	Healthcare experts	Non-binding	✓
	Higienos institutas/ Public Health Technology Centre of the Institute of Hygiene (HI)	HTA-Research institution	Advisory	Clinical and cost-effectiveness	Appraisal	Healthcare experts	N/A	Non-binding	✓[14]
	Ministry of Health of the Republic of Lithuania	Governmental institution	Regulatory	Clinical and cost-effectiveness	Appraisal	Clinicians and healthcare experts	N/A	Binding	✓
Luxembourg	Inspection générale de la sécurité sociale, Cellule d'expertise médicale/ Cell of medical expertise of the General Inspectorate of Social Security (CEM)	Governmental institution	Advisory	Clinical and cost-effectiveness	Appraisal	Clinicians and healthcare experts	N/A	Non-binding	×

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
Malta	Health Technology Assessment Unit in the Directorate for Pharmaceutical Affairs (DPA) of the Ministry of Health	Governmental institution	Advisory	Clinical and cost-effectiveness	Assessment	Representatives of the Ministry of Health, health economist and clinicians	Relevant stakeholders	Non-binding	✗
Netherlands	Zorginstituut Nederland/The National Health Care Institute (ZiN)	National healthcare organisation	Advisory	Clinical and cost-effectiveness	Appraisal	Representatives of the Healthcare institute, healthcare professionals, health economists, HTA experts	Patient organisations, scientific associations and other interested parties	Non-binding	✓
Poland	Agencja Oceny Technologii Medycznych i Taryfikacji/ Agency for Health Technology Assessment and Tariff System (AOTMiT)	National HTA body	Advisory	Clinical and cost-effectiveness	Appraisal	Representatives of the Ministry of Health, National Health Fund, National Regulatory body, patient organisations and ethicists	N/A	Non-binding	✓
Portugal	Sistema Nacional de Avaliação de Tecnologias de Saúde/National System for the Evaluation of Health Technologies (SiNATS) under the National Authority of Medicines and Health Products (INFARMED)	Drug regulator	Regulatory[15]	Clinical and cost-effectiveness	Appraisal	Representatives of the Ministry of Health, of the Healthcare system, the industry, patient organisations, consumers, healthcare professionals,	Patients	Binding	✓
Romania	Agentia Nationala a Medicamentului si a Dispozitivelor	Drug regulator	Regulatory	Clinical and cost-effectiveness	Appraisal	Clinicians, health economists and technical experts	N/A	Non-binding[16]	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
	Medicale/National Agency for Medicines and Medical Devices (ANMDM)								
Slovakia	Health Technology Assessment Department of Ministry of Health	Governmental institution	Advisory	Value-based assessment[10]	Assessment	Representatives from the Ministry of Health, the Slovak Medical Chamber and health insurance companies, healthcare professionals, healthcare experts and academics	Patient organisations	Non-binding	✓
	Faculty of Pharmacy, Comenius University in Bratislava, Slovakia (UNIBA FoF)	Research institution	Advisory and coordination	Value-based assessment[10]	Assessment	Healthcare professionals	Academics and healthcare experts	Non-binding	×
Slovenia	Zavod za zdravstveno zavarovanje Slovenije/ Health Insurance Institute of Slovenia (ZZZS)	National insurance organisation	Regulatory[17]	Value-based assessment[10]	Assessment	Experts in the field of medicine and pharmacy, with knowledge in the field of clinical pharmacology and other experts with systemic knowledge in the field of medicinal products	Patients	Binding	×
	Health Council	Governmental institution	Advisory	Clinical effectiveness and budget impact	Appraisal	Representatives from the health organisation, healthcare professionals and health economists	N/A	Non-binding	×

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
Spain*	IInstituto de Salud Carlos III/ The Carlos III Health Institute (ISCIII) (National)	HTA-Research institution	Advisory and coordination	Clinical and cost-effectiveness	Assessment	Healthcare professionals	Healthcare professionals	Non-binding	✓
	Agència de Qualitat i Avaluació Sanitàries de Catalunya/ The Catalan Agency for Health Information, Assessment and Quality (AQuAS) (Regional- Catalonia)	Regional HTA body	Advisory	Clinical and cost-effectiveness	Assessment	Healthcare professionals	Healthcare professionals	Non-binding	✓
	Servicio de Evaluación de Tecnologías Sanitarias/Basque Office for Health Technology Assessment (OSTEBA) (Regional- Basque Country)	Regional HTA body	Advisory	Clinical and cost-effectiveness	Assessment	Healthcare professionals	Healthcare professionals	Non-binding	✓
	Agencia de Evaluación de Tecnologías Sanitarias de Andalucía /Andalusian Health Technology Assessment Department (AETSA) (Regional-Andalusia)	Regional HTA body	Advisory	Clinical and cost-effectiveness	Assessment	Representatives of the body, the Andalusian Center for Pharmacovigilance and clinical experts	Healthcare professionals and health economists	Non-binding	✓
	Servicio de Evaluacion del Servicio Canario de salud/ Service Evaluation of the Canary Islands Health Service (SECS) (Regional-Canary Islands)	Regional healthcare organisation	Advisory	Clinical and cost-effectiveness	Appraisal	Healthcare professionals	Healthcare professionals and patient advocacy groups	Non-binding	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
	Unidad de Evaluación de Tecnologías Sanitarias de la Comunidad de Madrid/Health Technology Assessment Unit of the Community of Madrid (UETS) (Regional-Madrid)	Regional governmental institution	Advisory	Clinical and cost-effectiveness	Assessment	Healthcare professionals	Healthcare professionals	Non-binding	✓
	Agencia de Evaluación de Tecnologías Sanitarias de Galicia/Health Technology Evaluation Agency of Galicia (Avalia-t) (Regional-Galicia)	Regional healthcare organisation	Advisory	Clinical and cost-effectiveness	Appraisal	Healthcare professionals	Healthcare professionals	Non-binding	✓
	Instituto Aragonés de Ciencias de la Salud /Aragonese Institute of Health Sciences (IACS) (Regional-Aragon)	HTA-Research institution	Advisory and coordination	Clinical and cost-effectiveness	Appraisal	Healthcare professionals	Healthcare professionals	Non-binding	✓
Sweden	Tandvårds- och läkemedelsförmånsverket/ Dental and Pharmaceutical Benefits Agency (TLV)	National healthcare organisation	Regulatory	Value-based assessment[10]	Appraisal[18]	Representatives from the Health Authority, clinicians and health economists, citizens, patient representatives	N/A	Binding	✓
	Statens beredning för medicinsk och social utvärdering/ Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	National healthcare organisation	Advisory and coordination	Clinical and cost-effectiveness	Assessment	Healthcare professionals, health economists and healthcare experts, ethicists	Patients	Non-binding	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
United Kingdom	The National Institute for Health and Care Excellence (NICE) (England)	National HTA body	Advisory	Value-based assessment[10]	Appraisal	Representatives from the NHS, patient and carer organisations, academics, pharmaceutical and medical devices industry representatives	Patients, carers, citizens voluntary and community sector organisations	Non-binding[19]	✓
	National Institute for Health Research (NIHR) (England)	Research institution	Coordination	Clinical and cost-effectiveness	Assessment	N/A	NHS, universities, local government, other research funders, patients, service users, carers, charities	Non-binding	✓
	Scottish Medicine Consortium (SMC) (Scotland)	National HTA body	Advisory	Value-based assessment[10]	Appraisal	Clinicians, pharmacists, NHS board representatives, the pharmaceutical industry and the public	Patient groups and clinicians	Non-binding[19]	✓
	Health Technology Wales (HTW) (Wales)	National HTA body	Advisory	Clinical and cost-effectiveness	Appraisal	NHS consultants, health economists, patients, clinicians	NHS consultants, clinicians, manufacturers, patients, carers, citizens (topic selection)	Non-binding	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
	All Wales Medicines Strategy Group (AWMSG) (Wales)	National HTA body	Advisory	Clinical and cost-effectiveness	Appraisal	NHS consultants, GPs, nurses, pharmacists, health economists, pharmaceutical industry representatives and citizens	Patients, carers, patient organisations, citizen, healthcare professionals, manufacturers	Non-binding	✓
EU level	EUnetHTA	EU HTA body	N/A	N/A	Assessment	N/A	Patients, health care professionals, payers, and industry stakeholders	Non-binding	✓
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH) (National)	HTA body	Advisory	Clinical and cost-effectiveness	Appraisal	Representatives from the federal, provincial, and territorial publicly funded drug plans, ethicists, health economists, clinicians, citizens	Health care professionals, patients, manufacturers, associations, and other interested parties	Non-binding	✓
	Institut national d'excellence en santé et en services sociaux (INESSS) (Regional-Quebec)	HTA body	Advisory	Clinical and cost-effectiveness	Appraisal	Clinicians, ethicists, managers and citizens	Healthcare professionals, researchers, health economists, ethicists, citizens	Non-binding	✓
	Health Quality Ontario (HQO) (Regional-Ontario)	HTA body	Advisory	Clinical and cost-effectiveness	Appraisal	Representatives from the Health Authority and Ministry of Health, clinicians,	Patients, families and public advisors	Non-binding	✓

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Role of HTA	Model of HTA	Assessment Vs. Appraisal	Stakeholder involvement at HTA committee	External stakeholder consultation	HTA recommendations and funding decisions	Publicly available reports
						patients, patient advocates and representatives, industry representatives, ethicists and policy advisors			
	Committee to Evaluate Drugs (CED) (Regional-Ontario)	HTA body	Advisory	Clinical and cost-effectiveness	Appraisal	Patient representatives, healthcare professionals and health economists	Advocacy group including patients and caregivers	Non-binding	✓
	Health Technology Assessment Committee (Regional-British Columbia)	HTA body	Advisory and coordination	Clinical and cost-effectiveness/ MCDA	Assessment	Representatives from the Health Authority and Ministry of Health, health economists, ethicists and scientific advisors and patients	Patients and clinicians	Non-binding	✗
Australia	Pharmaceutical Benefit Advisory Committee (PBAC)	HTA body	Advisory	Value-based assessment[10]	Appraisal	Clinicians and health economists	Healthcare professionals and patients	Non-binding[19]	✓

Notes:

**Includes both national and key regional bodies*

[1] Only for outpatient reimbursable pharmaceuticals

[2]The HTA outcome by the NCPR is binding when supported by the National Health Insurance Fund.

[3]The HZZO Committee for Medicines is advisory and provides a non-binding opinion to the HZZO management board, which makes the final reimbursement decision.

[4]With the entry into force of the Act on Quality of Health Care (Official Gazette No. 118/2018) of January 1, 2019, the Ministry of Health takes over all the activities, scanning and other documentation, resources, rights and obligations and funding of the Agency for Quality and accreditation in health and social care.

[5]*In December 2012, the Danish Health Authority stopped making health technology assessments. However, the HTA activities were reorganised into a joint regional collaboration between five Danish Regions and is managed by DEFACTUM, Central Denmark Region in close collaboration with Department of Research and HTA, Odense University Hospital, Region of Southern Denmark.*

[6]*Only occasionally public consultations with stakeholders such as specialist medical societies and manufacturers are carried out to discuss and verify the methodology of the HTA report and the conclusions drawn by the assessment team. Therefore, we consider that the University of Tartu mainly performs HTA assessments.*

[7]*FinCCHTA has replaced FinOHTA in 2018. FinCCHTA has now a national position to coordinate HTA in Finland.*

[8]*FinCCHTA responsibility is to coordinate HTA hospital activities within the national HTA-network (five university hospitals jointly producing the reviews). FinCCHTA collects all jointly produced HTA reviews and gives national recommendations based on this work.*

[9]*HILA is an independent authority whose responsibility is to confirm the pharmaceuticals to be included in the positive list of the national health insurance and their reimbursement categories. Therefore, they are not a pure national healthcare organisation.*

[10] *These HTA bodies were classified as following the value-based model of HTA as they consider explicitly other criteria of value beyond clinical and/or cost-effectiveness.*

[11]*In France, reimbursement decisions are non-binding as the Ministry of Health and Ministry of Finance are free to follow or not the opinion of the Transparency Committee. However, recommendations are binding for price negotiations.*

[12]*In Germany, assessment and appraisal of medicines treating rare diseases ('orphan medicines') are conducted by G-BA.*

[13]*The HTA Committee of the Ministry of Health in Greece has an advisory role to the Minister. Therefore, the committee provides the assessment to the Minister, which makes the final coverage decision as a regulatory body*

[14]*Only summaries are available*

[15]*SiNATS assess health technologies and have an advisory role to INFARMED, which subsequently makes coverage decisions.*

[16]*In Romania, the HTA department in ANMDM makes a recommendation to the Ministry of Health. However, in practice the Ministry of Health includes in the reimbursement list the health technologies with a positive outcome. Manufacturers of health technologies with a conditional positive recommendation submit a request to the National Health Insurance for cost-volume negotiations. This request is assessed by the negotiation commission, which decides if contract negotiations will be initiated.*

[17]*The Pharmaceutical Reimbursement Committee has an advisory role to the ZZZS. However, the committee provides the appraisal to ZZZS, which makes the final coverage decision as a regulatory body.*

[18]*In-patient pharmaceuticals undergo assessment, whereas out-patient pharmaceuticals undergo appraisal.*

[19]*HTA recommendations made by NICE, SMC and PBAC were categorised as non-binding, even though recommendations play a key role in national coverage decisions.*

Source: *The authors based on primary and secondary data collection.*

6.7.2 Appendix 2

Relationship of multiple HTA bodies within countries and their impact on coverage decisions

We identified that thirteen countries out of the 32 included have more than one body performing HTA at national level. Out of the 14 countries contacted for the expert consultation round, stakeholders from Belgium, Austria, Estonia, Slovakia, Slovenia, Sweden and Ireland, excluding Spain, provided information on how multiple national HTA bodies are set up in their country's system, how these bodies interact with each other and their impact on funding decisions.

In Belgium, a research institution (KCE) and a national insurance organisation (INAMI) are performing HTA nationally. However, their roles in the decision-making process are quite distinct. INAMI informs the Belgian Ministry of Health about their HTA recommendations within a legal time frame. INAMI critically assesses manufacturer submissions and then gives advice on reimbursement to the Ministry of Health. KCE, on the other hand, assesses health technologies independently for research purposes and not in the context of reimbursement requests. Therefore, there is no legal framework within which KCE recommendations are used in the decision-making process.

In Austria there are two formal HTA processes. First, manufacturers of outpatient pharmaceuticals submit their dossier to the national insurance organisation (HVB) which assesses the evidence, whereas the Drug Evaluation Committee, which is organised by HVB and consists of different stakeholders including academics, clinicians, pharmacists, the Social Security Institutions, the Austrian Chamber of Commerce and the Federal Labor Board performs the appraisal. HVB makes the decision to include a new product into the positive list using HTA as one of the criteria considered in the decision-making process. However, whether HTA evaluations are considered in the coverage decisions is still unclear and equivocal. Second, the HTA research institution (AIHTA) assesses manufacturers' or hospitals' submissions for in-patient medical devices and high-tech interventions. A working group of representatives, which are mainly medical experts from the federal, regional and social security level decides on topic selection. The working group further appraises the evidence and the Federal Health Commission makes the final coverage decision. HTA for other technologies such as public health interventions can be requested by the Ministry of Health, regional health insurance bodies or other decision-making bodies and could be performed by other research institutions such as the Austrian Public Health Institute (GÖG) or departments of private or public universities.

In Estonia, the research institution (UT) performs HTA assessments for the topics that are chosen by the HTA Supervisory Board. The national insurance organisation (EHIF), the Ministry of Health and the National Institute for Health Development use these HTA assessments as input for decision-making. The national insurance organisation (EHIF) critically appraises submitted cost-effectiveness analyses of health technologies which is used as one of the criteria of reimbursement during the decision-making process which is made by the Reimbursement Committee.

In Slovakia, the Ministry of Health established the Reimbursement Committee to act as an advisor for reimbursement decision-making. The Committee prepares recommendations for coverage, patient co-payments, and conditions for reimbursement. Based on the recommendations from the Reimbursement Committee, the Minister of Health issues the final funding decisions. A research institution (UNIBA FoF) is also performing HTA at national level for pharmaceuticals. Its recommendations are taken into consideration by the Union Health Insurance Fund, which is a member of the national Reimbursement Committee.

In Slovenia, the national insurance organisation (ZZZS) performs HTA and makes reimbursement decisions on which pharmaceuticals should be included in the positive list and further negotiate with manufacturers. The Health Council, which performs HTA for medical devices and other technologies but not pharmaceuticals, advises the Ministry of Health about new technologies which need to be reimbursed based on clinical effectiveness and budget impact analysis. Once a decision is made, the technology is passed into ZZZS for further negotiations with manufacturers.

In Sweden, only HTA assessments of out-patient pharmaceuticals by TLV are used directly in decision-making. Swedish regions through their national cooperative structure (NT council) use assessments of in-patient medicines performed by TLV to make regional funding decisions.

In Ireland, HTA assessments for new pharmaceuticals are mandatory and conducted by the National Centre for Pharmacoeconomics (NCPE), which acts as advisor to the Health Service Executive (HSE). HSE is the governing authority accountable to the Ministry of Health. HTA of non-pharmaceuticals including medical and surgical devices, vaccines and national screening programmes are conducted by the Health Information and Quality Authority (HIQA), which are usually commissioned by the HSE and the Ministry of Health. However, HTA of non-pharmaceuticals is not mandatory.

6.7.3 Appendix 3

Technologies undergoing HTA across Europe, United Kingdom, Canada and Australia

Country	HTA Agency/ Institution undertaking HTA activities[7]	Pharmaceuticals	Medical Devices	Other technologies*
Austria	GÖG	✓[1]	✓	✓
	AIHTA	✓	✓	✓
	HVB	✓[2]	✓	✓
Belgium	KCE	✓	✓	✓
	INAMI	✓	✓	✓
Bulgaria	NCPR	✓	×	×
Croatia	AAZ	✓	✓	✓
	HZZO	✓	×	×
Cyprus	Ministry of Health	✓	×	×
Czech Republic	SUKL	✓	×	×
Denmark	DEFACTUM	×	✓	✓
Estonia	UT	✓	✓	✓
	EHIF	✓	✓	✓
Finland	FIMEA	✓[3]	×	×
	FinCCHTA	✓	✓	✓
	HILA	✓	×	×
France	HAS	✓	✓	✓
Germany	IQWiG	✓	✓	✓
	G-BA	✓	✓	✓
Greece	Ministry of Health	✓	×	×

Country	HTA Agency/ Institution undertaking HTA activities[7]	Pharmaceuticals	Medical Devices	Other technologies*
Hungary	OGYÉI	✓	✓	✓
Ireland	NCPE	✓	✓[4]	×
	HIQA	✓	×	✓
Italy	AIFA	✓	×	×
	AGENAS	×	✓	×
	CRU	✓	×	×
	ER Salute	×	✓	×
Latvia	NVD	✓	✓	×
Lithuania	VASPVT	×	✓	✓
	Institute of Hygiene	×	×	✓
	Ministry of Health	✓	✓	✓
Luxembourg	CEM	✓	×	×
Malta	DPA	✓	×	×
Netherlands	ZiN	✓	✓	✓
Poland	AOTMiT	✓	✓	✓
Portugal	SiNATS	✓	✓	×
Romania	ANMDM	✓	×	×
Slovakia	Ministry of Health	✓	✓	×
	UNIBA FoF	✓	×	×
Slovenia	ZZZS	✓	×	×
	Health Council	×	✓	✓
Spain	ISCIII	✓	✓	✓
	AQuAS	✓	✓	✓

Country	HTA Agency/ Institution undertaking HTA activities[7]	Pharmaceuticals	Medical Devices	Other technologies*
	OSTEBA	✗	✓	✓
	AETSA	✓[5]	✓	✓
	SECS	✗	✓	✓
	UETS	✗	✓	✗
	Avalia-t	✗	✓	✓
	IACS	✗	✓	✓
Sweden	TLV	✓[6]	✓	✗
	SBU	✗	✗	✓
United Kingdom	NICE	✓	✓	✓
	SMC	✓	✓	✗
	HTW	✗	✓	✓
	AWMSG	✓	✗	✗
	NIHR	✓	✓	✓
EU level	EUnetHTA	✓	✓	✓
Canada	CADTH	✓	✓	✗
	INESSS	✓	✓	✗
	HQO	✗	✓	✓
	CED	✓	✗	✗
	Health Technology Assessment Committee (British Columbia)	✗	✓	✓
Australia	PBAC	✓	✗	✗

Notes: ** Other technologies" refer to public health interventions such as screening programmes, vaccination campaigns, evaluation of surgical and non-surgical interventional procedures, stem cell therapies, innovative cancer vaccines, cell & gene therapies, other forms of personalized treatments and screening programmes. Assessments that consider the introduction of treatments for diseases as a part of a holistic health and social intervention are included in this category.*

[1] *Outpatient pharmaceuticals.*

[2] *Pharmaceuticals are assessed only if requested by the Ministry of Health.*

[3] *Only in-patient pharmaceuticals are assessed.*

[4] *NCPE has only assessed one medical device.*

[5] *AETSA is only synthesising evidence for pharmaceuticals.*

[6] *TLV mainly assesses outpatient pharmaceuticals.*

[7] ***GÖG:*** *National Public Health Institute;* ***AIHTA****: Austrian Institute for Health Technology Assessment;* ***HVB:*** *Association of Austrian Social Insurance Institutions;* ***KCE:*** *Belgian Health Care Knowledge Centre;* ***INAMI:*** *National Institute for Health and Disability Insurance;* ***NCPR****: National Council of Pricing and Reimbursement;* ***AAZ****: Agency for Quality and Accreditation in Health Care and Social Welfare;* ***HZZO****: Croatian Institute for Health Insurance Fund;* ***SUKL****: State Institute of Drug Control;* ***DEFACTUM:*** *Central Denmark Region in collaboration with Department of Research and HTA, Odense University Hospital, Region of Southern Denmark;* ***UT****: Centre for Health Technology Assessment-University of Tartu;* ***EHIF:*** *Estonian Health Insurance Fund;* ***FIMEA:*** *Finnish Medicines Agency;* ***FinCCHTA****: Finnish Coordinating Center for Health Technology Assessment;* ***HILA****: Pharmaceuticals Pricing Board organisation;* ***HAS:*** *High Health Authority;* ***IQWiG:*** *Institute for Quality and Efficiency in Health Care;* ***G-BA:*** *Federal Joint Committee;* ***OGYÉI:*** *National Institute of Pharmacy and Nutrition;* ***NCPE:*** *National Centre for Pharmacoeconomics;* ***HIQA:*** *Health Information and Quality Authority;* ***AIFA:*** *Italian Medicines Agency;* ***AGENAS:*** *Italian National Agency for Regional Healthcare Services;* ***CRU:*** *Regional coordination for medicines;* ***ER Salute:*** *Regional health agency in Emilia Romagna;* ***NVD:*** *The National Health Service;* ***VASPVT:*** *State Health Care Accreditation Agency under the Ministry of Health;* ***HI:*** *Public Health Technology Centre of the Institute of Hygiene;* ***CEM:*** *Cell of medical expertise of the General Inspectorate of Social Security;* ***DPA:*** *Directorate for Pharmaceutical Affairs;* ***ZiN:*** *The National Health Care Institute;* ***AOTMiT****: Agency for Health Technology Assessment and Tariff System;* ***SiNATS:*** *National System for the Evaluation of Health Technologies;* ***ANMDM:*** *National Agency for Medicines and Medical Devices;* ***UNIBA FoF:*** *Faculty of Pharmacy, Comenius University of Bratislava ;****ZZZS:*** *Insurance Institute of Slovenia;* ***ISCIII:*** *The Carlos III Health Institute;* ***AQuAS:*** *The Catalan Agency for Health Information, Assessment and Quality;* ***OSTEBA****: Basque Office for Health Technology Assessment;* ***AETSA:*** *Andalusian Health Technology Assessment Department;* ***SECS:*** *Service Evaluation of the Canary Islands Health Service;* ***UETS:*** *Health Technology Assessment Unit of the Community of Madrid;* ***Avalia-t:*** *Health Technology Evaluation Agency of Galicia;* ***IACS:*** *Aragonese Institute of Health Sciences;* ***TLV****: Dental and Pharmaceutical Benefits Agency;* ***SBU:*** *Swedish Agency for Health Technology Assessment and Assessment of Social Services;* ***NICE:*** *The National Institute for Health and Care Excellence;* ***NIHR****: National Institute for Health Research;* ***SMC****: Scottish Medicines Consortium;* ***HTW:*** *Health Technology Wales;* ***AWMSG:*** *All Wales Medicines Strategy Group;* ***EUnetHTA:*** *European Network for Health Technology Assessment;* ***CADTH:*** *Canadian Agency for Drugs and Technologies in Health;* ***INESSS:*** *Institut national d'excellence en santé et services sociaux;* ***HQO:*** *Health Quality Ontario;* ***PBAC****: Pharmaceutical Benefits Advisory Committee.*

Source: *The authors based on secondary data collection.*

7 How can health technology assessment be improved to optimise access to medicines? Results from a Delphi study in Europe

This study has been published in *The European Journal of Health Economics. "Fontrier, A.M., Kamphuis, B. and Kanavos, P., 2023. How can health technology assessment be improved to optimise access to medicines? Results from a Delphi study in Europe: Better access to medicines through HTA. The European Journal of Health Economics, pp.1-16.".*

The text in this chapter has been slightly edited[11] to follow the flow of the thesis.

Key messages

- Key European stakeholders, who participated in a Delphi panel, agreed that current efforts and discussions on how HTA can be designed or adjusted at regional, national and supranational levels are likely to optimise access to medicines. And improved HTA features targeting evaluation processes are the features which are more likely to optimise access to medicines.
- 'Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence' is the HTA feature participants believed to have the most positive impact on the availability of medicines within markets. While the 'provision of scientific advice ahead of commencement of formal HTA process' showed the most positive impact on both availability of medicines and affordability of the healthcare system and of patients. 'Clarity of evidentiary requirements for value assessment in HTA' is the HTA feature that can ensure timeliness.
- HTA features showed mostly to have a positive impact on timely patient access to publicly funded medicines. However, more HTA features were expected to have a positive impact on health system and patient affordability, given that HTA processes are implemented in an effort to allocate resources efficiently considering evidence-based information, the sustainability of the healthcare system, and the finite budgets available.

[11] The numerical ordering of tables and figures have been updated to follow the flow of the thesis, and the spell out of acronyms have been removed if acronyms have been explained previously.

Abstract

Introduction: Access to medicines is a shared goal across healthcare stakeholders. Since health technology assessment (HTA) informs funding decisions, it shapes access to medicines. Despite its wide implementation, significant access variations due to HTA are observed across Europe. This paper elicited the opinions of European stakeholders on how HTA can be improved to facilitate access**.**

Methods: A scoping review identified HTA features that influence access to medicines within markets and areas for improvement, while three access dimensions were identified (availability, affordability, timeliness). Using the Delphi method, we elicited the opinions of European stakeholders to validate the literature findings.

Results: Nineteen participants from 14 countries participated in the Delphi panel. Thirteen HTA features that could be improved to optimise access to medicines in Europe were identified. Of these, 11 recorded a positive impact on at least one of the three access dimensions. HTA features had mostly a positive impact on timeliness and a less clear impact on affordability. 'Early scientific advice' and 'clarity in evidentiary requirements' showed a positive impact on all access dimensions. 'Established ways to deal with uncertainty during HTA' could improve medicines' availability and timeliness, while more 'reliance on real-world evidence' could expedite time to market access.

Conclusions: Our results reiterate that increased transparency during HTA and the decision-making processes is essential; the use of and reliance on new evidence generation such as real-world evidence can optimise the availability of medicines; and better collaborations between regulatory institutions within and between countries are paramount for better access to medicines.

7.1 Background

Access to medicines is a multifaceted concept in that it is informed or influenced by different access dimensions, such as the availability of medicines within markets and the affordability of the healthcare system, among others. The Word Health Organisation (WHO) states that access to medicines is achieved when access is affordable and the medicines are safe, of high quality and effective (75). The European Parliament (EP) has suggested that Europe should "*guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies*" (78). Even though better access to medicines might be a shared goal amongst healthcare stakeholders, its achievement has proven complicated. In Europe, a plethora of evidence showcases variability in access to medicines across countries (16,20,53,86,161,165,169,342,343). These variations can be attributed to a variety of factors: some are associated with broader-level features such as (i) the general country characteristics, including gross domestic product (GDP) per capita and the epidemiological profile; and (ii) the country's healthcare system characteristics, including healthcare expenditure, organisation of the healthcare system and clinical practices. Others are associated with more specific features such as (iii) the pharmaceutical market characteristics, including regulatory frameworks and the policies medicines undergo to become available and publicly funded in a given market (342). Regulatory frameworks and policies are of particular interest to policymakers because they are amenable to policy changes. However, they can still be further complicated by the need to find a balance across different perspectives and objectives of involved stakeholders. For instance, whilst healthcare payers are seeking ways to optimise costs and ensure the sustainability of the healthcare system, patients seek timely access to medicines without considering the likely burden on local budgets.

In recent years, health technology assessment (HTA) has become one of the most important stages for efficacious and cost-effective medicines to become available and accessible to patients (13). HTA recommendations play a crucial role in informing pricing and reimbursement decisions, facilitating negotiations, and updating national clinical guidance on disease treatment protocols, which can further impact the diffusion and uptake of new technologies (15,17,92,183,344,345). Nowadays, HTA is used across all European countries, at least to some extent (15). However, discrepancies are seen in the way HTA systems are set up, the processes that are employed, the way assessment is performed, and the extent to which HTA recommendations inform reimbursement decisions, all of which can have an impact on access to medicines (15–17,20,86,92,133,156,160,161,166–169,171,172,184,193,197,343,346).

Within the European context and in order to alleviate access inequalities occurring due to variations in the conduct of HTA, numerous efforts have been made at both EU and national levels to harmonise, simplify, and expedite HTA processes (19,164,347). Furthermore, efforts to establish collaborations between regulatory agencies and HTA bodies, such as parallel review processes and early scientific advice, are taking place to ensure that some alignment exists between what regulators and HTA agencies want, ultimately impacting patients' access to the right treatment in a timely manner (12,17,168,344). However, evidence is scarce on what features of HTA, from the way it is set up within the healthcare system to its role in funding decisions, are more likely to positively impact access to medicines beyond the details of submissions by manufacturers, including the clinical and economic evidence and their respective quality (16–18,86,129,131,174). Additionally, it is not clear whether current efforts aiming to improve HTA systems and processes, such as the harmonisation of clinical assessments through the new EU HTA regulation (19), are welcomed by both Western and Eastern European countries given differences in how well developed HTA processes are. And whether these efforts are considered as successful means to optimise access to medicines by relevant stakeholders. Finally, evidence is scarce on what dimensions of access (e.g.: availability, time to patient access, affordability) are targeted and, potentially, improved by different HTA features and components. In a nutshell, there is a gap in the literature on how HTA can be improved in a holistic way (i.e.: from its set-up to its uptake in funding decisions) to facilitate access to medicines across Europe and in light of the implementation of the new EU HTA regulation (19).

In addressing the above gaps, the objectives of this study are twofold: First, to explore how can HTA be improved to optimise access to medicines. And second, to assess levels of agreement between stakeholders from different geographic jurisdictions and/or different stakeholder groups on what features of HTA are more likely to have the most positive impact on access. To engage and elicit the views of European stakeholders, a Delphi exercise was conducted to develop an expert-based judgment (256). Contrary to simple surveys and interviews, the Delphi method structures and organises group communications while allowing for controlled feedback (243–245).

While there are studies in the literature which use the Delphi method to elicit opinions on subjects such as value assessment of medical devices (348,349), population health (251) and digital health technologies (350), to our knowledge there is only one study similar to ours in remit. This study explores how HTA for medicines can be improved across Europe, but with a different focus on the value assessment of oncology and haematology products, and the recent EU HTA regulation (347). In our study, we aimed to validate HTA features that existing studies found to have an

impact on access to medicines, and explored how a better understanding of these features through expert views can help improve HTA at national, regional and supranational levels in a holistic way (i.e.: from its set-up to its uptake in funding decisions) in order to facilitate access to medicines.

7.2 Methods

Both primary and secondary evidence was used. Secondary data collection was conducted through a scoping review of the literature to identify, first, a list of HTA features that have shown to have an impact on access or features that could be improved. And second, to identify relevant access dimensions. Primary evidence was collected through a web-based Delphi panel in European stakeholders from both Western and Eastern European countries to validate the findings of the literature.

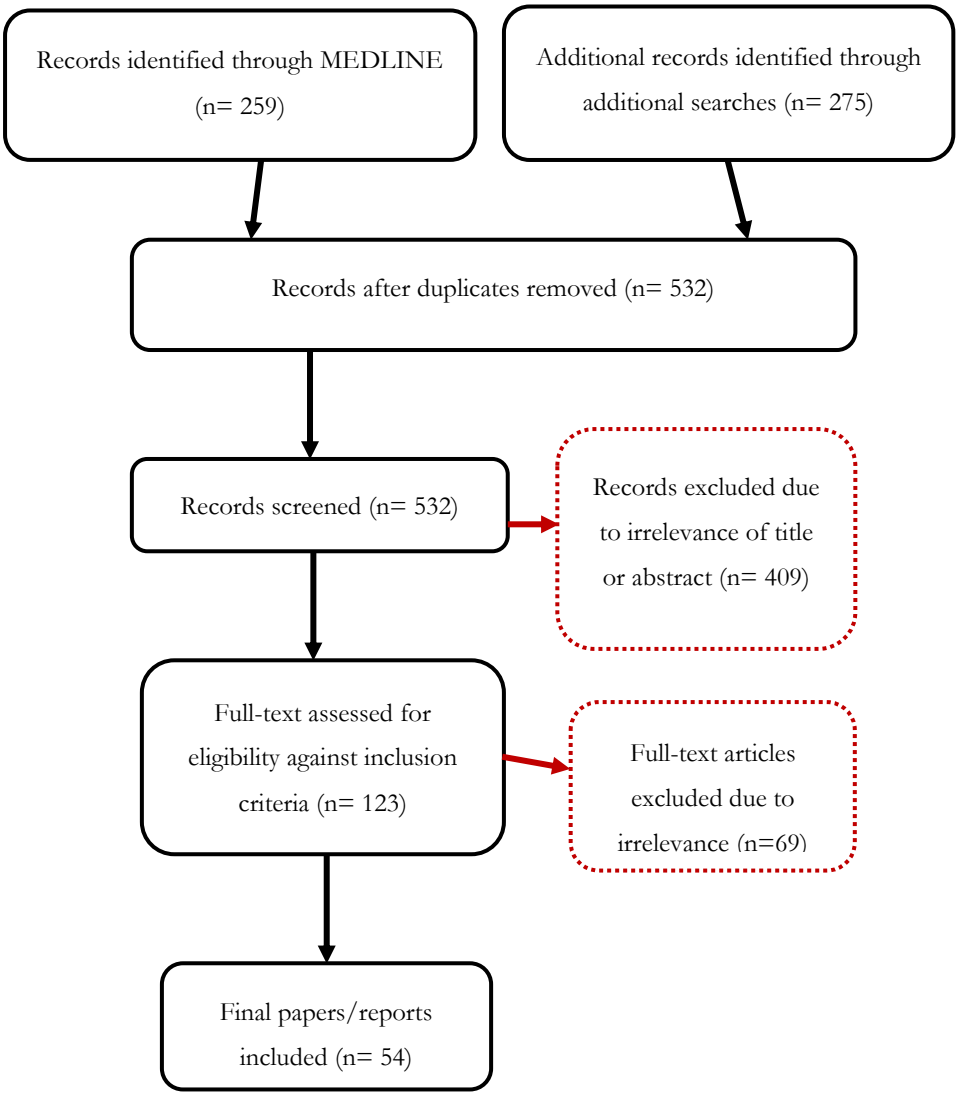
7.2.1 Scoping review: HTA features and access dimensions

A scoping review was selected over a systematic literature review, as the scope of our search and the inclusion criteria were broader than the ones usually used in a systematic literature review. Generally, scoping reviews can help identify and map available evidence that is still unclear and cannot yet be addressed through a more precise systematic review (240).

7.2.1.1 HTA features

To identify recent peer-reviewed literature on HTA features and areas for improvement, we searched the MEDLINE via the PubMed database from January 2011 to December 2021 using the keywords ('health technology assessment' OR 'HTA' OR 'value assessment') AND 'Europe'. A detailed description of the scoping review strategy including the screening process and the exclusion and inclusion criteria used is outlined in detail in Appendix 1. The titles and abstracts of the resulting papers were screened by the first two authors in a double-blind fashion. Any disputes were resolved between first two authors. Papers considered relevant to our study objectives were downloaded and screened by the first author. An additional search was conducted by the first author on the websites of the European Commission and EUnetHTA to identify relevant grey literature using 'Health technology assessment' OR 'HTA' as key terms. Reports published from 2017 and onwards were included to capture recent developments and the current landscape of HTA in Europe. Figure 11 outlines the different steps and respective search results of the scoping review.

Figure 11:Flow diagram of the scoping review process



Relevant evidence was recorded and grouped into four main categories/endpoints, following an iterative process. The identified HTA features and components related to: (i) HTA system set-up; (ii) HTA procedures; (iii) HTA evaluation processes; and (iv) HTA and funding. An additional endpoint was created to record evidence on the access dimensions used in the relevant studies. The results of the scoping review on HTA features are summarised in Appendix 2. Table 8 presents the list of HTA features considered relevant in having an impact on access to medicines in the European region (Table 8).

Table 8: Features related to HTA as shown in the web Delphi panel

No.	HTA Features
HTA system	
1	Presence of an independent HTA body
HTA procedures	
2	Scientific advice (feedback and advice on upcoming applications) provided to manufacturers ahead of commencement of formal HTA process by HTA bodies
3	Introduction of parallel review process to streamline marketing authorisation and HTA
4	Stakeholder involvement during the HTA process
5	No reliance on "HTA referencing" (requirement for positive HTA recommendations from other countries to commence or conclude the HTA process or reliance on HTA recommendations from other countries to inform decision-making)
6	Agreed-upon timelines for the completion of HTA process
HTA evaluation processes	
7	Clarity of evidentiary requirements for value assessment in HTA (e.g.: clear instructions published by the HTA body on the evidence to be submitted by manufacturers; evidentiary requirements based on a validated or publicly available framework)
8	Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence
9	Harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level
10	Coordination of HTA rules, methods and processes across national and regional level, if both co-exist
11	Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies (example dimensions include unmet medical need, impact on carers and family, impact on society, etc.)
12	Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe (e.g.: request of additional evidence, sensitivity analysis, dossier re-submission)
HTA and funding decisions	
13	Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations

7.2.1.2 Access dimensions

To provide a comprehensive definition of access to medicines, the different dimensions of access used in the resulting papers of the scoping review (described above) were explored, when available. Additional searches were conducted on the websites of international organisations such as the WHO, the United Nations and the European Commission, using the key term "access to medicines" OR "patient access" OR "access".

Three relevant dimensions of access were identified and included in this study. The dimensions and definitions of access are used for the sole purpose of this study are as follows:

- Availability of medicines: whether clinically- and cost- effective medicines are available and marketed in a given market;
- Time to patient access (timeliness): the timely access of patients to publicly reimbursed medicines, and;
- Affordability: whether the prices of clinically- and cost- effective medicines are in line with the purchasing ability of healthcare systems and of patients.

7.2.2 The Delphi process

The Delphi method can be used to fulfil a variety of research objectives such as reaching participant consensus on a complex topic, prioritisation of policies, and generation of debate among participants who might not share a common vision (246,247). The Delphi method can also be used when current knowledge is incomplete, uncertain or lacking (248). During a series of rounds (surveys), panel participants can first respond to a set of questions and, in subsequent rounds, are given the opportunity to re-consider and re-assess their initial opinions after seeing the aggregate responses of other participants (243,247,250–255). Hence, the Delphi method is an iterative process that avoids intentional and unintentional noise, such as irrelevant and non-productive communication among the participants (245,247). Panel responses are always anonymous allowing participants to express their opinion freely without introducing potential bias due to peer pressure or the presence of potentially dominant or more vocal experts (243,247,249–255).

No set minimum or maximum participant number for Delphi panels exists, with Delphi panels being conducted from five up to thousands of participants (248,256–262); an appropriate number is most likely dictated by the objectives and nature of the research, though methodological advice, and Delphi panels in practice, often range between 10 and 20 participants (252,260–262,265).

Even though Delphi panels may usually include three or more rounds to reach consensus amongst participants, in this study we deemed that two rounds were sufficient to ensure desirable completion rates, in line with other studies in the literature (256–258,264). This is because we had already compiled a list of HTA features likely to have an impact on access, thus an initial round soliciting experts' opinions was deemed unnecessary.

7.2.3 Stakeholder sample

A list of stakeholders was compiled from the authors' network, considering their knowledge and areas of expertise, country of origin/work, and affiliation. Overall, our sample followed a purposive and snowball sampling strategy targeting experts in HTA from all European Union

Member States, Norway, Switzerland, and the United Kingdom. Invited experts (n=128) were either from academic or health policy research institutions, the pharmaceutical industry, decision-making/payer bodies, or patient organisations to capture the views of relevant stakeholders. To ensure a representative sample of European stakeholders, we invited a minimum of four experts, one of each stakeholder group, across all study countries. A limitation of this study is that healthcare professionals were not included in the sample as the authors were unable to identify clinicians that were familiar with and/or involved in HTA through either their network or the sampling strategies used.

7.2.4 Study design and administration

The survey was piloted with five health economists from our institution to reflect on the structure and content prior to dissemination to external participants.

All stakeholders were invited via a personal email sent by the authors inviting them to participate in a two-round Delphi panel. Experts who indicated they were unable to participate were asked to identify a team member or colleague with similar expertise as a replacement. Where an alternate expert was identified, the original invitee was asked to provide the name, email and job title of their suggested colleague to ensure that their expertise was relevant to the research objectives of this study.

The study utilised a web platform, Welphi®, for the Delphi process. The platform ensures all experts received an automated email with a unique URL link. Participation is anonymised by Welphi® and each participant had a unique identifier containing an alphanumeric string (e.g.: 079AB). These identifiers allowed the authors to track whether the same individual participated in both Delphi rounds. Each round remained open for a month to accommodate schedules and availability. Automated reminders were sent every week to participants who had not started the survey and participants who had not yet completed their responses.

Participants were requested to complete an informed consent form to be able to continue with the Delphi process. All participants were asked to respond to demographic questions including the country they live and work in, their organisation affiliation, and their perspective selected from a list of pre-defined categories: research and policy, patient/patient organisation, industry, or decision-maker/payer. Participants were given clear definitions of all three access dimensions, and were able to rank their agreement using a 5-point Likert scale ('strongly agree' (SA), agree' (A), 'neither agree nor disagree', 'disagree' (D), 'strongly disagree' (SD)) on the positive impact of the HTA features on the three access dimensions. To ensure reliability of the panel's outcomes,

participants were given the option to select 'do not know' for instances where they did not feel confident about their response and a 'not applicable' option was also given to allow participants to indicate HTA features they felt might not be relevant to an access dimension. A single, open-ended question was available to the participants in the first round only to provide the opportunity to add any factor or HTA feature that, in their opinion, might have a positive impact on access and was not identified through our scoping review. However, these responses were used only as contextual information and were not included as statements in the second and final round of the Delphi panel for two reasons: first, the objective of the study was to validate the results of the scoping review and; second, if these new statements would have been included in the second round, the participants' ability to engage with the statements would have been limited as they would have not been able to see the aggregate responses of the participants and potentially revise or keep their initial responses in an additional round, which is a main feature of the Delphi method.

In round 2, participants were asked to rank again the value statements. In this round, participants were able to see the aggregate responses of all the participants from round 1 as percentages. Participants had the option to revise or keep their initial responses from round 1. The study received ethics approval by our institution.

7.2.5 Data analysis

The analytical methods employed were chosen considering the ordinal scale nature of our data, our study objectives and the results of a thorough search of the literature on Delphi panel methodologies (247,255,258,259,272–274) and other studies using the Delphi method (251,260,275–284). Quantitative methods were used, including both descriptive and inferential statistics, to explore (i) what features of HTA had the most positive impact against different access dimensions in the final round; (ii) the level of agreement between stakeholders about the impact and rank of different HTA features across access dimensions in both rounds, and (iii) how stable their responses were across rounds. The open-ended responses provided by the participants in the first round were used only as contextual information and were excluded from the data analysis.

Different measures and methods were used to explore the aforementioned points which are outlined in detail in Table 9. For points (i) and (iii), additional analyses were performed using more than one commonly used method to validate the robustness of our results, recognising that there is limited to no evidence on which exact method is the most suitable to use in specific circumstances, or how results can change when using different methodologies. All analysis was conducted for 39 value statements (13 HTA features across the three access dimensions).

Strongly agree (SA) and agree (A) and strongly disagree (SD) and disagree (D) responses were grouped, respectively, for the percentage agreement analysis. Median and interquartile ranges, rather than mean and standard deviation, were used for measuring central tendency and level of dispersion to avoid skewed results due to outliers. Gwet's kappa coefficient was selected to test inter-rater agreement on each round over other kappa coefficients as it allows for multiple participants and any level of measurement by applying relevant weights for the ordinal scale, and missing values due to the selection of the 'do not know' or 'not applicable' options (286–289). The 'do not know' and 'not applicable' responses were excluded from the quantitative analysis to limit analysis of agreement to participants who were confident in their responses.

Finally, since consensus is a term poorly and ambiguously defined in the literature (247) while its measurement greatly varies across studies (247,248,269), in this study, we differentiate between agreement and consensus. For consensus, stricter criteria were applied compared to group agreement to avoid inconclusive results. However, given that consensus is based on subjective criteria, it was only used for discussion purposes. All analyses were conducted in Stata SE 16.1 and SPSS Version 27.

Table 9:Summary of definitions and methods used in this study

Definition(s)		Method	Interpretation
Agreement	The group agreement on the positive impact of HTA features on access dimensions in round 2[1]	Percentage agreement	Approved by absolute majority: SA>50% and SD+D<33.3% Qualified majority: SA+A>75% Rejected by absolute majority: SD+D>50% (247,251)
		Central tendency and level of dispersion using median and the interquartile range (IQR)	Positive impact: median of 1 (SA) or 2 (A) No positive impact: median of 4 (D) or 5 (SD) Agreement: IQR ≤1 (i.e.: more than 50% of all opinions fall within 1 point on the scale) Lack of agreement: IQR >1 (247,277,279,284)
	The likelihood at which participants independently rate a given statement with the same rank in each round accounting for agreement occurring simply by chance /*Whether participants agree with each other on the ranking they gave for each value statement in each round*	Inter-rater reliability (IRR) using Gwet's kappa coefficient applying ordinal weights	Poor agreement: Gwet's kappa< 0.00 Slight agreement: 0.00 > Gwet's kappa ≤ 0.20 Fair agreement: 0.20 > Gwet's kappa≤ 0.40 Moderate agreement: 0.40 > Gwet's kappa ≤ 0.60 Substantial agreement: 0.60 > Gwet's kappa ≤ 0.80 Almost perfect agreement: 0.80 > Gwet's kappa≤ 1(305)
Stability and consistency	The stability/consistency of group responses per value statement between rounds/ *The likelihood participants changed their opinion/rankings as a group from round 1 to round 2*	Non-parametric Wilcoxon matched-pairs signed-rank test	Stable response: p value >0.05 non statistically significant change Unstable response: p value ≤ 0.05 statistically significant change(247,280,290)
		Spearman's rho coefficient	High degree of concordance: positive correlation coef. (ϱ≥0.75) with p value ≤ 0.05 showing that is statistically significant Low degree of concordance: negative correlation coef. (ϱ<0.75) with p value >0.05 showing that is non-statistically significant(247,279,290)

Consensus[2]	*Consensus was considered achieved when a value statement was approved by qualified majority or had a median of 1 and 2 and IQR≤1 in round 2 and showcased stability (non-statistically significant change) between rounds.*

Notes*:*[1] *Group agreement has been calculated for both rounds. However, in the results section, we present the value statements that reached agreement in the 2nd round. Appendix 2 includes results across all rounds.*

[2]*Since this measure is subjective, it was used only for the purposes of the discussion section.*

Source: *The Authors based on a search of the literature on Delphi panel methodologies* (247,255,258,259,272–274) *and other studies using the Delphi technique* (251,260,275–284).

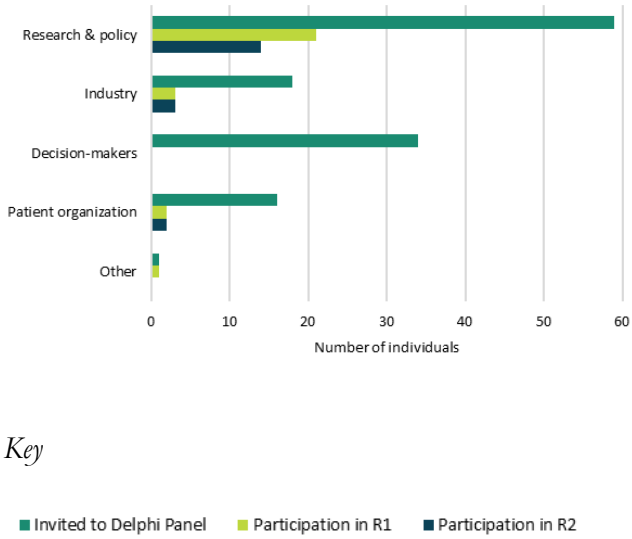
7.3 Results

7.3.1 Participation rate

A total of 128 participants across Europe were approached for involvement in the Delphi panel. Of these, 27 participants from 16 European countries took part in round 1. From the 27 participants in round 1, 19 participants from 14 countries completed round 2. Figure 12 illustrates the characteristics of the stakeholders from round 2.

Figure 12: Expertise and geographic setting for participants in round 2

Expertise areas

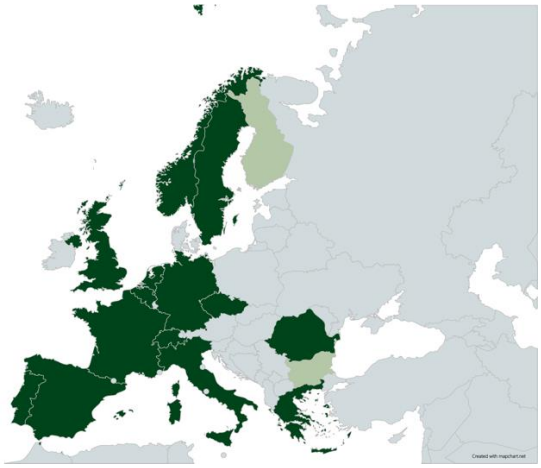


Key

Invited to Delphi Panel Participation in R1 Participation in R2

Notes: *'Research &policy'=academics, healthcare systems experts and analysts affiliated with research institutions/non-governmental organisations*
'Other' = healthcare professionals or hospital affiliated

Geographic setting



Key
Light green: participation in R1 only
Dark green: participation in R1 and R2

Notes:
Countries include Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Greece, Italy, the Netherlands, Norway, Portugal, Romania, Spain, Sweden, Switzerland and the United Kingdom

7.3.2 Delphi panel results

We present the results of all statistical analyses across 39 value dimensions (13 HTA features across three access dimensions). Appendix 3 provides the results for both rounds.

7.3.2.1 Agreement

7.3.2.1.1 Group agreement on value statements with the most positive impact on access dimensions in round 2

Table 10 summarises the group agreement on the positive impact of each HTA feature on each access dimension in round 2.

Percentage agreement: From a total of 39 value statements in round 2, 18 (46.2%) were approved by qualified majority (i.e.: SA+A>75%), including one statement ('*harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level*' on availability of medicines) which was approved by absolute majority (SA>50% and SD+D<33.3%). No value statement was rejected by absolute majority (SD+D>50%), showing that there was no HTA feature in our list that many participants felt that it cannot have a positive impact on access.

Access dimensions: Most HTA features were found to have a positive impact on time to patient access (9 out of 13 HTA features). Seven HTA features were considered to have a positive impact on availability of medicines within markets while only two features were believed to have a positive impact on affordability for patients and healthcare systems.

HTA features: One HTA feature, '*scientific advice provided to manufacturers by HTA bodies ahead of the initiation of the HTA process*', was considered to have a positive impact by qualified majority across all three access dimensions (89% on availability and 79% on both timeliness and affordability, respectively). '*Reliance on real-world (RWE) evidence in cases of limited clinical data*' was the only HTA feature that all stakeholders (100%) believed to have a positive impact on time to patient access.

Central tendency and level of dispersion: 22 (out of 39) value statements reached agreement across participants, with a median of 1 or 2 and IQR≤1 (56.4%) in round 2.

Access dimensions: Participants agreed (median:2 and IQR≤1) that most HTA features had a positive impact on time to patient access (10 out of 13 HTA features with a median of 1 and 2 and IQR≤1), while six HTA features resulted in agreement on their positive impact on availability. Six HTA features were found to have a positive impact on affordability.

HTA features: Participants strongly agreed (median:1; IQR:1) on the positive impact on availability of '*harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems*'.

7.3.2.1.2 Factors not captured by the scoping review that might have an impact on access as suggested by participants in round 1

Open-ended question: Only three participants provided factors that could potentially have an impact on access not identified through the scoping review through a response to the open-ended question in round 1. These suggested factors included: (i) choosing a cost-effectiveness approach rather than comparative clinical benefit assessment; (ii) having pre-defined criteria for which stakeholders should be involved during HTA processes (for impact on availability, not necessarily time to access), and; (iii) having a linkage between horizon scanning, budgeting and HTA. These statements were not validated by the Delphi participants in the second round.

Overall group agreement per value statement in rounds 1 and 2

Inter-rater reliability (IRR), Gwet's kappa coefficient: In round 1, low levels of agreement were observed across participants. Participants had fair or moderate agreement for 30.8% (12 out of 39) and 38.5% (15 out of 39) value statements, respectively. Substantial agreement was reached in only 15.4% (6 out of 39) of value statements, two of which had been approved by qualified majority and reached agreement through central tendency and low level of dispersion in round 1. There was no value statement with almost perfect agreement.

In round 2, agreement levels changed; 33.3% of value statements (13 of 39) resulted in substantial agreement and one value statement (on the positive impact of '*establishing procedures to deal with clinical and economic uncertainties*' on availability) reached an almost perfect agreement. Six of the value statements showcasing substantial agreement amongst participants and the one value statement with almost perfect agreement were also approved by qualified majority and showcased a median of 1 or 2 with IQR≤1 in round 2.

Table 10 summarises the overall group agreement per value statement in round 2.

Table 10: Results of agreement in round 2 using percentage agreement, central tendency and median, and inter-rater agreement

HTA Features	Availability				Time to patient access (timeliness)				Affordability			
	Agreement in round 2				Agreement in round 2				Agreement in round 2			
	% SA+A	median	IQR	Gwet's kappa (Level of agreement)	% SA+A	median	IQR	Gwet's kappa (Level of agreement)	% SA+A	median	IQR	Gwet's kappa (Level of agreement)
HTA system												
1	41%	3	1 *agreement*	0.59 *moderate*	47%	3	2 *no agreement*	0.06 *slight*	79%	2	0 *agreement*	0.42 *moderate*
HTA procedures												
2	89%	2	1 *agreement*	0.64 *substantial*	79%	2	1 *agreement*	0.52 *moderate*	79%	2	0 *agreement*	0.69 *substantial*
3	50%	2.5	2 *no agreement*	-0.07 *poor*	95%	2	1 *agreement*	0.53 *moderate*	32%	3	2 *no agreement*	0.09 *slight*
4	47%	3	1 *agreement*	0.08 *slight*	74%	2	1 *agreement*	0.64 *substantial*	63%	2	1 *agreement*	0.65 *substantial*
5	33%	3	1 *agreement*	0.59 *moderate*	35%	3	1 *agreement*	0.71 *substantial*	13%	3	0 *agreement*	0.71 *substantial*
6	63%	2	1.5 *no agreement*	0.38 *fair*	94%	2	0 *agreement*	0.72 *substantial*	12%	3	0 *agreement*	0.75 *substantial*
HTA evaluation processes												
7	76%	2	1 *agreement*	0.04 *slight*	95%	2	1 *agreement*	0.62 *substantial*	53%	2	1 *agreement*	0.50 *moderate*
8	88%	2	0 *agreement*	0.75 *substantial*	100 %	2	0 *agreement*	0.47 *moderate*	37%	3	1 *agreement*	0.44 *moderate*
9	76% *	1	1 *agreement*	0.31 *fair*	89%	2	1 *agreement*	0.49 *moderate*	37%	3	2 *no agreement*	0.11 *slight*

	Availability				Time to patient access (timeliness)				Affordability			
	Agreement in round 2				Agreement in round 2				Agreement in round 2			
10	75%	2	1.5 *no agreement*	0.37 *fair*	94%	2	1 *agreement*	0.57 *moderate*	53%	2	2 *no agreement*	0.02 *slight*
11	75%	2	1.5 *no agreement*	0.37 *fair*	72%	2	2 *no agreement*	0.24 *fair*	53%	2	1 *agreement*	0.46 *moderate*
12	94%	2	0 *agreement*	0.82 *almost perfect*	83%	2	0 *agreement*	0.78 *substantial*	61%	2	1 *agreement*	0.61 *substantial*
HTA and funding decisions												
13	65%	2	1 *agreement*	0.1 *slight*	76%	2	1 *agreement*	0.44 *moderate*	25%	3	1 *agreement*	0.67 *substantial*

Notes: SA+A: Strongly agree and agree; IQR: Interquartile range
Median: 1=strongly agree; 2=agree; 3=neither agree nor disagree; 4=disagree; 5=strongly disagree
*This value statement was approved by absolute majority (SA > 50% and SD + D < 33.3%)

7.3.2.2 Stability and consistency of responses between rounds

Non-parametric Wilcoxon matched-pairs signed-ranks test: 94.9% of the value statements were stable between rounds (i.e.: not significantly changed). Only two value dimensions had a p-value less than 0.05 which indicated that they were statistically significant, thus unstable: these two were the positive impact of '*agreed timelines for the conduct of HTA processes'* on time to patient access, and the positive impact on the '*use of established procedures to handle uncertainty*' on affordability.

Spearman's rank-order correlation coefficient (Spearman's rho): Participants' opinions had a statistically significant high degree of concordance in 69.2% (27 out of 39) of the value statements.

Table 11 presents the results of stability between rounds 1 and 2.

Table 11:Results of stability between rounds 1 and 2

HTA Features	Availability		Time to patient access (timeliness)		Affordability	
	Stability between rounds					
	Spearman's rho (Level of concordance)	Wilcoxon matched-pair signed rank test (p-value)	Spearman's rho (Level of concordance)	Wilcoxon matched-pair signed rank test (p-value)	Spearman's rho (Level of concordance)	Wilcoxon matched-pair signed rank test (p-value)
HTA system						
1	0.97 *high degree*	*1.00 stable*	0.91 *high degree*	0.50 *stable*	0.94 *high degree*	*stable*
HTA procedures						
2	0.94 *high degree*	0.50 *stable*	0.97 *high degree*	1.00 *stable*	0.85 *high degree*	1.00 *stable*
3	0.96 *high degree*	1.00 *stable*	0.96 *high degree*	0.50 *stable*	0.90 *high degree*	1.00 *stable*
4	1.00 *high degree*	1.00 *stable*	0.82 *high degree*	1.00 *stable*	0.92 *high degree*	1.00 *stable*
5	0.71 *low degree*	0.06 *stable*	0.52 *low degree*	0.17 *stable*	-0.03 *low degree*	1.00 *stable*
6	0.71 *low degree*	0.11 *stable*	0.49 *low degree*	0.00 *unstable*	0.20 *low degree*	1.00 *stable*
HTA evaluation processes						
7	0.93 *high degree*	0.50 *stable*	0.87 *high degree*	1.00 *stable*	0.79 *high degree*	0.25 *stable*
8	0.76 *high degree*	1.00 *stable*	0.77 *high degree*	0.50 *stable*	0.92 *high degree*	0.50 *stable*
9	0.99 *high degree*	1.00 *stable*	0.92 *high degree*	0.50 *stable*	0.98 *high degree*	1.00 *stable*
10	0.98 *high degree*	1.00 *stable*	0.96 *high degree*	1.00 *stable*	0.98 *high degree*	1.00 *stable*

	Availability		Time to patient access (timeliness)		Affordability	
11	0.83 *high degree*	0.50 *stable*	0.77 *high degree*	0.50 *stable*	0.99 *high degree*	1.00 *stable*
12	0.38 *low degree*	0.40 *stable*	*0.47* *low degree*	0.13 *stable*	0.55 *low degree*	0.02 *unstable*
HTA and funding decisions						
13	0.66 *low degree*	1.00 *stable*	0.16 *low degree*	0.27 *stable*	0.51 *low degree*	*0.06* *stable*

7.4 Discussion

Using the Delphi method, we explored how HTA systems, procedures and processes can be improved to optimise access to medicines by canvassing opinions and perspectives of European HTA experts. Our results have several implications for both the HTA features and the access dimensions. However, they should be interpreted with caution due to the inherit limitations of the Delphi method, such as low participation and high dropout rates. In our study, a small number of experts participated in both rounds, and responses were predominately received from research and policy makers, with no opinions from healthcare professionals and decision-makers captured.

With regards to HTA features, 11 out of the 13 showed a positive impact on at least one of the three access dimensions suggesting that participants' views are broadly aligned with current efforts and discussions on how HTA can be designed or adjusted at regional, national and supranational levels to optimise access to medicines. 'Early scientific advice' and 'clarity in evidentiary requirements' reached consensus on their positive impact on all access dimensions. Interestingly, even though many well-established HTA bodies in Europe currently provide early scientific advice to manufacturers and have published guidelines for evidence requirements, a call to action for some HTA bodies to (i) emphasise more the provision of early support to manufacturers before HTA initiation, (ii) provide more clarity on the evidence required for evaluation, and (iii) be more transparent and systematic on the way they deal with uncertainty if it arises, was identified.

'*Established ways to deal with potential uncertainty occurring during HTA assessments'* reached consensus on its positive impact on both availability and time to patient access. This HTA feature was also identified by a recent study (347) which highlighted that the management of uncertainty is one of the challenges that need to be addressed to provide an 'additional benefit' to a European HTA process.

'*Reliance on RWE in HTA'* reached 100% agreement among participants in the second round on its positive impact on timeliness, emphasizing the importance of the use of new types of evidence

beyond strict clinical studies which do not test for the clinical benefit of a medicine in a real-world setting. This has been extensively discussed across Europe, especially at regulatory and HTA levels for instances where clinical evidence might still be incomplete or of low quality. However, the use of RWE varies across countries with some HTA bodies accepting RWE data while others do not (179), and with other access implications arising due to a lack of systematic ways to collect, interpret and use these data during assessments (351).

Looking at the results of all the analytical methods used and recognising that different methods can lead to different conclusions, we can only conclude confidently (SA+A>75%, median:1 or 2 and IQR ≤1, substantial or almost perfect agreement and high degree of concordance and stable responses between rounds) that participants agreed on the positive impact of '*reliance on RWE'* on availability of medicines and of '*provision of scientific advice'* on both availability and affordability and; of '*clarity of evidentiary requirements for value assessment'* on timeliness.

Table 12 summarises the HTA features with the most positive impact on the respective access dimensions.

Table 12: HTA features with the most positive impact on access dimensions

		Availability	Time to patient access (timeliness)	Affordability
HTA system				
1	Presence of an independent HTA body			
HTA procedures				
2	Scientific advice provided to manufacturers ahead of commencement of formal HTA process by HTA bodies	✓		✓
3	Introduction of parallel review process to streamline marketing authorisation and HTA			
4	Stakeholder involvement during the HTA process			
5	No reliance on "HTA referencing"			
6	Agreed-upon timelines for the completion of HTA process			
HTA evaluation processes				
7	Clarity of evidentiary requirements for value assessment in HTA		✓	
8	Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence	✓		
9	Harmonization of rules for HTA methodologies, evidentiary requirements,			

		Availability	Time to patient access (timeliness)	Affordability
	and procedures across HTA bodies and systems at supranational level			
10	Coordination of HTA rules, methods and processes across national and regional level, if both co-exist			
11	Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies			
12	Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe.			
HTA and funding decisions				
13	Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations			

Notes: *Green coloured cells show the HTA features that reached consensus on having the most positive impact on the respective access dimension (approved by qualified majority and/or having a median of 1 or 2 with low level of dispersion (IQR≤1) and stable responses between round 1 and 2)*

✓ *show the HTA features that we can confidently conclude that they have a positive impact on the respective access dimensions according to all the analytical methods used (SA+A>75%, median:1 or 2 and IQR ≤1, substantial or almost perfect agreement of participants and high degree of concordance and stable responses between round 1 to 2).*

Across the grouping of HTA features presented in Table 1, all features targeting evaluation processes reached consensus on their positive impact on at least two access dimensions: participants agreed access to medicines could be ameliorated by having clear guidance on what evidence is required, on ways to deal with uncertainty, and on the incorporation of additional dimensions of value beyond clinical and cost-effectiveness, together with general coordination and harmonization of evaluation processes at regional, national and supernational level. The new HTA regulation of the European Commission on joint clinical assessments across European Member States, to be officially implemented in 2025, aims to address access issues arising due to discrepancies in the evaluation processes of national/regional HTA bodies. The importance of this is also reiterated in our findings, as '*harmonization of rules for HTA methodologies, evidentiary requirements, and evaluation procedures across HTA bodies and systems at supranational level*' was approved by absolute majority in both rounds for its positive impact on the availability of medicines and reached consensus on its positive impact on availability and time to patient access. Therefore, standardizing HTA evaluation processes and creating coherent and consistent scientific evidence

collection, generation and interpretation across Europe could achieve better and more controlled access to medicines within countries. On the other hand, HTA features related to procedures and set-up reached consensus mainly on their positive impact on time to patient access and affordability, rather than the availability of medicines. As both of these are more relevant to the specificities of each setting, they should still remain a country competence taking into account country-specific characteristics, objectives and values and further reflect the way the healthcare system is organized (12,15,344).

With regards to the access dimensions, Delphi participants believed that the included HTA features mostly had a positive impact on timely access to publicly funded medicines which is in line with broader HTA objectives as a tool informing reimbursement decisions within nations or healthcare systems to streamline national/regional accessibility to medicines after receiving marketing authorisation. However, a number of concerns have been raised previously that HTA processes can hinder timeliness due to assessment delays and the presence of an additional regulatory step to medicines' availability within markets (16,191,352). More HTA features were expected to have a positive impact on affordability of the healthcare system, as HTA processes are implemented in an effort to allocate resources efficiently considering evidence-based information, the sustainability of the healthcare system, and the finite budgets available. On the contrary, HTA features with the lowest percentage agreement on their positive impact were identified on the affordability dimension. And interestingly, '*legally binding HTA recommendations for reimbursement decisions and/or negotiations'* did not reach agreement or consensus amongst participants in round 2, in having a favourable effect on affordability, even though required translation of HTA recommendations into funding would mean that the most cost-effective medicine would be covered using publicly available budgets.

Our findings on affordability, however, are not conclusive because of the lack of representation of decision-makers/payers in our sample. Yet, these findings can still observe what other HTA experts believe: For instance, the '*presence of an independent body'* reached consensus on its positive impact on affordability (and not on any other access dimension), highlighting that transparency and conflict of interest concerns may remain when HTA processes are integrated within national/regional healthcare payers/ decision-makers opposed to taking place independently at arm's length (15). Therefore, more transparency might be needed to better understand how HTA recommendations are used during negotiations and price setting within jurisdictions. However, this may only apply in some cases, as HTA systems for medicines integrated to governmental institutions are rarely seen in Europe (15).

Overall, even though HTA is an essential instrument to streamline and monitor access to medicines across settings, it is important to highlight that any action to achieve better and faster patient access should be complemented by other appropriate and effective regulatory policies and procedures, which are equally important. Targeted efforts and interventions in HTA alone will not necessarily translate to better patient access without adjustments in other areas: for example, if reimbursement policies are not adjusted to align to, or at least take into consideration, HTA recommendations which promote the most cost-effective therapeutic option. Not only should each stage of the access pathway aim to maximize the effects on improving access, it may also benefit from synergies between these stages. For instance, the '*introduction of parallel review processes'* reached consensus on its positive impact on time to patient access, highlighting that collaboration between marketing authorisation and HTA bodies could improve timeliness.

7.4.1 Study limitations

Our study is not without limitations. First, our results should be interpreted with caution due to the small sample size caused by low participation and high dropout rates, limited or lack of representation of some stakeholder groups (i.e.: healthcare professionals), and limited geographical representation. Additionally, participant representation which was skewed towards policy and research experts could have introduced bias in our results. Nevertheless, the findings of this study can still be considered informative in (i) identifying how different HTA features target different access dimensions, (ii) understanding (dis-) agreement on whether current efforts to improve HTA are successful according to experts from different geographic settings, and (iii) identifying areas of HTA that might need improvement, as long as, this limitation is acknowledged in the interpretation of these three conclusions. Second, while a scoping review was conducted to create a list of HTA features that might have an impact on access, this list may not be exhaustive. To address this, participants had the opportunity to respond to an open-ended question in round 1 to share additional HTA features that might have not been included in our list. Third, our Delphi panel included two rounds rather than three rounds. However, we deemed that two rounds were sufficient as we had already conducted a scoping review and compiled a list of HTA features that were likely to have an impact on access. Finally, there are numerous definitions for agreement, stability and consensus in the literature, which are often unclear, and each of these can rely on several different methodologies for results analysis. To address this, our study defined the relevant terms in detail and conducted analysis using more than one method, when applicable and appropriate.

7.5 Conclusion

Using the Delphi method, this study found that improved HTA processes and procedures were shown to have a predominantly positive impact on timeliness, and a less clear impact on affordability despite HTA's remit to ensure efficient allocation of finite resources. The most positive impact on all three access dimensions was seen on HTA features related to more clear, consistent and harmonised evaluation processes within and across countries, which is in line with current European efforts targeting the harmonisation of clinical assessment processes. Even though our results might not be conclusive, they reiterate the following overarching themes: increased transparency during HTA and decision-making processes is essential, use of and reliance on RWE can optimise availability of medicines, while better collaborations between regulatory institutions within and between countries are paramount for better access to medicines.

7.6 Appendices

7.6.1 Appendix 1

Scoping review strategy to identify HTA features and areas for improvement to optimise access to medicines

Our objective was to identify features and components of HTA that impact access to medicines favourably or unfavourably, or areas for improvement.

An advanced search was conducted in the MEDLINE via PubMed database to identify peer-reviewed papers from January 2011 to December 2021. The following keywords were used: 'health technology assessment' OR 'HTA' OR 'value assessment' AND 'Europe'. The relevant terms were searched through the titles and abstracts of the papers and the search was limited to the English language. Initially, 'access' was used as an additional key term, however, we removed it from the search terms as it was limiting our results substantially.

Search results were downloaded using EndNote and duplicates were removed when identified. An initial screening through the titles and abstracts was conducted to identify relevant papers that focuses on HTA of in-patent medicines and study access variations due to HTA. An additional screening in the titles and abstracts was conducted by the second author. Papers were excluded from the initial screening, when they were focusing on medical devices or other technologies (i.e.: vaccines, diagnostics, biomarkers or surgical procedures) or off-patent and generic medicines or hospital-based HTA; when they were clinical and cost-effectiveness assessments conducted by the authors instead of relevant national or regional authorities which officially conduct HTA; when alternative value assessment processes than HTA were explored, such as multiple-criteria decision analysis and; when other stages of a medicine's access pathway such as regulatory and MA processes, the development phase of medicines or innovative pricing mechanisms and managed entry agreements or clinical guidelines, were studied.

The full texts of the remaining papers were screened by the first author, to identify features of HTA that facilitate or impede access or are responsible for observed variations in HTA recommendations for the same medicines across settings. Any information on current efforts to improve HTA processes at national or supranational level in Europe was also extracted.

An additional search was conducted on the website of the European Commission and EUnetHTA to identify relevant grey literature on HTA in Europe. 'Health technology assessment' OR 'HTA' were used as key terms for the search and the same inclusion and exclusion criteria as the ones used in the scoping review were used for the screening of the relevant hits. Reports published from

2017 and onwards were only included to capture recent developments and the current landscape of HTA in Europe.

Relevant information from both searches was recorded in an excel spreadsheet. Information was organised following an iterative process. Therefore, the extracted evidence was classified into the following four main categories/endpoints:

(1) ***HTA system,*** which included features related to how HTA is set up within the healthcare system;

(2) ***HTA procedures,*** which related to administrative stipulations of HTA;

(3) ***HTA evaluation process,*** which related to the assessment of the submitted evidence, and;

(4) ***HTA and funding decisions***, which reflected how and to what extent HTA is being used during funding decision-making.

Initially, information was recorded as a full text extracted from the initial source but was subsequently re-worded as statements that could improve access to medicines after three reiterations by the authors.

An additional study endpoint was used identify different access metrics. First, relevant evidence was extracted from the included studies of the scoping review. This information was further complemented with evidence from additional searches on the websites of international organisations. Through this endpoint, we were able to define access to medicines using different key metrics.

7.6.2 Appendix 2

Scoping review results on HTA features and areas for improvement to optimise access to medicines

System set-up and organization. The way healthcare and HTA systems are organised and set up can contribute to access delays (15,18,20,86,156–158,235). This can manifest itself within the HTA system, such as in Greece, where HTA is integrated within the government and the national payer and unclear or non-transparent connections and interactions between the multiple institutions involved result in unnecessary delays in funding negotiations (15,157), or in Italy, where the multi-level structure of HTA results in increased inequality of access to new medical technologies (158). Characteristics of the wider healthcare system may also create variation in patient access, such as the decentralised healthcare systems of Italy or Spain which can result in variation across regions because of divergent HTA recommendations or funding decisions due to differences in the methodologies used to assess technologies and the selection of technologies undergoing assessment (18,20,86,159,235).

HTA procedures. Extensive evidence variations in the HTA procedures employed by different HTA bodies, (such as whether HTA commences before or after MA, the actual timelines of HTA evaluations, and whether and/or to what extent external stakeholders are involved in the HTA process) might result in access delays or create unnecessary access hurdles (15–17,21,87,126,160,161,173,234,235). An example of how HTA processes can impact access negatively is seen in a few European countries: Bulgaria and Romania both rely on HTA decisions of other well-established HTA agencies, and as such, HTA processes in these countries might be delayed until HTA recommendations are published in the countries they use as a reference (169). Or, how timelines for HTA recommendations to be published after MA vary significantly across countries in practice: Spain had the longest timelines (mean time of 713 days), followed by Italy and Poland (504 and 462 days respectively), while France and Germany were the fastest, publishing HTA recommendations in 227 days and 199 days on average after MA (86). Similar results were seen in another study where France had the fastest timelines (155 days) and Italy had the slowest ones (375 days) (160). When looking at the median timelines between MA and HTA submission, timelines also differed with seven days seen on average in England, 23 days in Italy, 29 days in France, 42 days in Germany and 49 days in Spain (160). These variations in time are due to different stipulations of HTA procedures. For instance, in Germany, the HTA assessment must be initiated within three months from MA approval according to German law (160). However, in other settings, HTA processes can only be initiated by manufacturers upon dossier submission (163).

Stop-the-clock mechanisms, allowed by the English HTA for some medicines, can further lead to longer evaluation processes (160,164).

Better cooperation between regulatory and HTA bodies seems to be crucial for optimal and timely market access, with some collaborative processes being implemented in some settings to support this (172,183–186). The presence of early scientific advice from the HTA body to manufacturers before dossier submissions or during the medicine development process is a way to expedite HTA assessments (85,160,172,183–186,192). The provision of early scientific advice has aided manufacturers to generate evidence that meets the standards of both regulatory agencies and HTA bodies, however, according to key stakeholders this initiative had not yet succeeded to align regulatory and HTA requirements (85). Despite efforts to expedite assessment processes at regulatory level and harmonise assessment processes at both levels, still, a proportion of approved medicines do not result in positive HTA recommendations, and only in a few cases, HTA bodies seem to accept a lower quality of evidence which has already been approved by regulatory agencies (18,86,134,160,173,187–189).

Other elements which may have a positive impact is the stakeholder involvement in the HTA process (i.e.: for selecting which technologies should be assessed by the HTA body, during technology assessment or in the decision-making process for issuing HTA recommendation) (15,17,156,163,165–167). However, some researchers mentioned that divergent HTA recommendations for the same medicine across HTA bodies could be attributed to differences in the interpretation of the assessed evidence due to varying levels and types of stakeholders' involvement (87,129,131,163,168).

HTA evaluation processes. Differences in HTA recommendations across HTA bodies or observed access delays can also be attributed to variations in the assessment practices followed by HTA bodies such as differences in evidentiary requirements, the potential inclusion of other value dimensions beyond clinical and cost-effectiveness, divergent ways to deal with uncertainty, and acceptance of real-world evidence (16–18,21,81,86,87,129,131,136,136,160,161,170–172,174–177,183,235).

For example, HTA evaluation in Romania is mainly focused on costs rather than other additional value criteria creating challenges for patient access to innovative medicines (181), while in England a number of value and end-of-life criteria are considered explicitly in the assessment of some medicines, together with recognition of elements such as medicine innovation in deliberations on whether to accept higher willingness to pay thresholds (166,182). However, a study looking at 29 jurisdictions reported that more similarities than differences exist between major methodological

aspects used in the HTA processes of the study countries, showing room for better cross-country co-operations (175). Another study reported, though, that manufacturers had to generate local contextualised evidence, including evidence on the local comparator, to meet specific evidentiary requirements of European HTA bodies. Almost 90% of submissions in England incorporated local information such as local standard of care and clinical practice, followed by 82% of the submission in Germany, 80% in Italy, 79% in Spain and 72% in France (160). Similarly, another study discussed that country-specific practice-related factors can explain differences in HTA recommendations across settings (126).

Heterogeneity in HTA recommendations across countries might also be attributed to differences in the acceptance of evidence from observational studies and indirect comparisons (81,129,136,175,178–180). However, evidence on whether acceptance of real-world data might improve access at HTA level is not widely positive: one study discussed that generation of real-world evidence might be one of the contributing factors for longer delays of access, as setting up registries can be time-consuming and bureaucratic (161), and another study highlighted that in Bulgaria, limited epidemiological data may pose an additional challenge to manufacturers for the preparation and submission of pharmacoeconomic and HTA dossiers beyond the lack of expertise for gathering data from real-world evidence (181).

HTA and funding. The relationship between HTA recommendations and funding decisions might play an important role for patient access. The most important challenge for patient access is a lack of an explicit framework on how to use HTA evidence in the decision-making process, while the availability of such a framework is among the most important facilitators (197). Evidence from middle-income European countries showed a lack of a legal framework for the implementation of HTA recommendations in funding decision-making (196), while another study highlighted that this phenomenon is also observed in high-income countries where HTA systems are well-developed and established (168).

Across Europe, there are countries where HTA recommendations are not legally binding and, thus, not always followed during decision-making processes (15,163,168,235). A study looking at the agreement between HTA recommendations and funding decisions for oncology medicines in Central and Eastern Europe showed that there was a low level of agreement between HTA and funding in Poland where HTA recommendations are non-binding, contrary to Latvia where recommendations are binding (169). Similarly, a study in Poland, where HTA recommendations are not legally binding, showed only a fair agreement between national HTA recommendations and ministerial funding decisions between 2013 and 2015 (241). A more recent study focusing on

oncology medicines in Central and Eastern Europe showed that there was a low level of agreement between HTA and funding in Poland, contrary to Latvia where recommendations are binding (169). Therefore, in systems where HTA recommendations are binding, their implementation in funding decisions is more straightforward. For instance, the English NHS should reimburse and make available within a timeframe of three months a medicine that received a positive HTA recommendation by the English HTA body (18).

7.6.3 Appendix 3

Detailed results for rounds 1 and 2

Percentage agreement (SA+A) per value statements for rounds 1 and 2

	Percentage agreement per access dimensions		
HTA features	**Availability**	**Time to patient access (timeliness)**	**Affordability**
1.Presence of an independent HTA body	Round 1: 52% Round 2: 41%	Round 1: 44 % Round 2: 47%	✓ Round 1: 74 % Round 2: 79%
2.Scientific advice provided to manufacturers ahead of commencement of formal HTA process by HTA bodies	✓✓ Round 1: 80 % Round 2: 89%	✓ Round 1: 74% Round 2: 79%	✓ Round 1: 70 % Round 2: 79%
3.Introduction of parallel review process to streamline MA and HTA	Round 1: 64% Round 2: 50%	✓✓ Round 1: 85 % Round 2: 95%	Round 1: 42% Round 2: 32%
4.Clarity of evidentiary requirements for value assessment in HTA	✓ Round 1: 68% Round 2: 76%	✓✓ Round 1: 85% Round 2: 95%	Round 1:62 % Round 2:53 %
5.Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence	✓✓ Round 1: 76 % Round 2: 88%	✓✓ Round 1: 85% Round 2: 100%	Round 1: 44% Round 2: 37%
6.Stakeholder involvement during the HTA process	Round 1: 50 % Round 2: 47%	Round 1: 69 % Round 2: 74%	Round 1: 58% Round 2: 63%
7.Harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level	✓✓ Round 1: 75%† Round 2: 76%†	✓✓ Round 1: 81% Round 2: 89%	Round 1: 46% Round 2: 37%
8.Coordination of HTA rules, methods and processes across national and regional level, if both co-exist	✓ Round 1: 70 % Round 2: 75%	✓✓ Round 1: 88% Round 2: 94%	Round 1: 54 % Round 2: 53%
9. Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies	✓ Round 1: 71% Round 2: 75%	Round 1: 65% Round 2: 72%	Round 1: 52% Round 2: 53%
10. Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations	✓ Round 1: 83% Round 2: 65%	✓✓ Round 1: 77% Round 2: 76%	Round 1: 58% Round 2: 25%
11. No reliance on "HTA referencing"	Round 1: 64% Round 2: 33%	Round 1: 68% Round 2: 35%	Round 1:33 % Round 2: 13%
12. Agreed-upon timelines for the completion of HTA process	Round 1: 52 % Round 2: 63%	✓ Round 1: 48% Round 2: 94%	Round 1: 26% Round 2: 12%*
13.Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe	✓ Round 1: 65 % Round 2: 94%	✓✓ Round 1: 88% Round 2: 83%	Round 1: 33% Round 2: 61%

Notes:

1. ✓: Agreement was reached amongst participants with a value statement within one of the rounds: strongly agree and agree ≥ 75% approved by qualified majority
2. ✓✓: Agreement was reached amongst participants with a value statement within both rounds: strongly agree and agree ≥ 75% approved by qualified majority
3. * this statement reached a 76% of participants choosing that they are neutral (neither agree nor disagree) with the positive impact of this value dimension on affordability
4. None of the value dimensions were rejected by absolute majority (SD + D > 50%)
5. †: this statement was approved by absolute majority (SA > 50% and SD + D < 33.3%) in both round 1 and 2

Central tendency and dispersion per value statements for rounds 1 and 2

	Round 1			*Round 2*			*Change between rounds*		
HTA features	**Availability**	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**
1.Presence of an independent HTA body	Median: 2	Median:3	Median:2	Median: 3	Median: 3	Median: 2	Median:1	No change	No change
	IQR: 2	IQR:2	IQR:2	IQR: 1	IQR: 2	IQR:0	IQR: -1	No change	IQR:-2
2.Scientific advice provided to manufacturers ahead of commencement of formal HTA process by HTA bodies	Median: 2	Median:2	Median:2	Median:2	Median: 2	Median: 2	No change	No change	No change
	IQR:1	IQR:2	IQR:2	IQR: 1	IQR: 1	IQR: 0	No change	IQR:-1	IQR:-2
3.Introduction of parallel review process to streamline MA and HTA	Median:2	Median:2	Median:3	Median: 2.5	Median: 2	Median: 3	Median: 0.5	No change	No change
	IQR: 2	IQR: 1	IQR: 1	IQR: 2	IQR: 1	IQR: 2	No change	No change	IQR:-1
4.Clarity of evidentiary requirements for value assessment in HTA	Median: 2	Median: 2	Median: 2	Median: 2	Median: 2	Median: 2	No change	No change	No change
	IQR: 2	IQR: 1	IQR: 2	IQR: 1	IQR: 1	IQR: 1	IQR:-1	No change	IQR:-1
5.Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence	Median: 2	Median: 2	Median: 3	Median: 2	Median: 2	Median: 3	No change	No change	No change
	IQR: 1	IQR: 1	IQR: 1	IQR: 0	IQR: 0	IQR: 1	IQR:-1	IQR:-1	No change
6.Stakeholder involvement during the HTA process	Median: 2.5	Median: 2	Median: 2	Median: 3	Median: 2	Median: 2	Median: 0.5	No change	No change
	IQR: 1.5	IQR: 1	IQR: 1	IQR: 1	IQR: 1	IQR: 1	IQR:0.5	No change	No change
7.Harmonization of rules for HTA methodologies, evidentiary requirements,	Median: 1	Median: 2	Median: 3	Median: 1	Median: 2	Median: 3	No change	No change	No change

	Round 1			*Round 2*			*Change between rounds*		
HTA features	**Availability**	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**
and procedures across HTA bodies and systems at supranational level	IQR: 1.5	IQR: 1	IQR: 2	IQR: 1	IQR: 1	IQR: 2	IQR:-0.5	No change	No change
8.Coordination of HTA rules, methods and processes across national and regional level, if both co-exist	Median: 2	Median: 2	Median: 2	Median: 2	Median: 2	Median: 2	No change	No change	No change
	IQR: 2	IQR: 1	IQR: 2	IQR: 1.5	IQR: 1	IQR: 2	IQR:-0.5	No change	No change
9. Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies	Median: 2	Median: 2	Median: 2	Median: 2	Median: 2	Median: 2	No change	No change	No change
	IQR: 2	IQR: 2	IQR: 2	IQR: 1.5	IQR: 2	IQR: 1	IQR:0.5	No change	IQR:-1
10. Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations	Median: 2	Median: 2	Median: 2	Median: 2	Median: 2	Median: 3	No change	No change	Median:-1
	IQR: 0	IQR: 0	IQR: 0	IQR: 1	IQR: 1	IQR: 0.5	IQR:-1	IQR:-1	IQR:-0.5
11. No reliance on "HTA referencing"	Median: 2	Median: 2	Median: 3	Median: 3	Median: 3	Median: 3	Median:- 1	Median:-1	No change
	IQR: 2	IQR: 2	IQR: 1	IQR: 1	IQR: 1	IQR: 0	IQR: -1	IQR: -1	IQR:- 1
12. Agreed-upon timelines for the completion of HTA process	Median: 2	Median: 2	Median: 3	Median: 2	Median: 2	Median: 3	No change	No change	No change
	IQR: 1	IQR: 1	IQR: 1	IQR: 1.5	IQR: 0	IQR:0	IQR: -0.5	IQR:-1	IQR:-1
13.Established procedures on how uncertainties resulting from submitted	Median: 2	Median: 2	Median: 3	Median: 2	Median: 2	Median: 2	No change	No change	Median: -1

	Round 1			*Round 2*			*Change between rounds*		
HTA features	**Availability**	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**
evidence are managed and resolved within an agreed-upon timeframe	IQR: 2	IQR: 1	IQR: 1	IQR: 0	IQR: 0	IQR: 1	IQR: -2	IQR:-1	No change

Note: *No value statements received strong agreement (median 1), disagreement (median 4) and strong disagreement (median 5) by the participants in any round.*

Group agreement: Gwet's coefficient

	Round 1			*Round 2*		
HTA features	**Availability**	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**
1.Presence of an independent HTA body	0.20 slight	0.38 fair	0.15 slight	0.59 moderate	0.06 slight	0.42 moderate
2.Scientific advice provided to manufacturers ahead of commencement of formal HTA process by HTA bodies	0.51 moderate	0.46 moderate	0.47 moderate	0.64 substantial	0.52 moderate	0.69 substantial
3.Introduction of parallel review process to streamline MA and HTA	-0.05 poor	0.26 fair	0.34 fair	-0.07 poor	0.53 moderate	0.09 slight
4.Clarity of evidentiary requirements for value assessment in HTA	0.38 fair	0.61 substantial	0.29 fair	0.04 slight	0.62 substantial	0.50 moderate
5.Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence	0.54 moderate	0.60 moderate	0.43 moderate	0.75 substantial	0.47 moderate	0.44 moderate
6.Stakeholder involvement during the HTA process	0.05 slight	0.45 moderate	0.55 moderate	0.08 slight	0.64 substantial	0.65 substantial
7.Harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level	0.52 moderate	0.52 moderate	0.37 fair	0.31 fair	0.49 moderate	0.11 slight
8.Coordination of HTA rules, methods and processes across national and regional level, if both co-exist	0.39 fair	0.38 fair	0.14 slight	0.37 fair	0.57 moderate	0.02 slight
9. Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the	0.43 moderate	0.10 slight	0.46 moderate	0.37 fair	0.24 fair	0.46 moderate

HTA features	*Round 1*			*Round 2*		
	Availability	**Time to patient access (timeliness)**	**Affordability**	**Availability**	**Time to patient access (timeliness)**	**Affordability**
evaluation of health technologies						
10. Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations	0.70 substantial	0.59 moderate	0.51 moderate	0.10 slight	0.44 moderate	0.67 substantial
11. No reliance on "HTA referencing"	0.33 fair	0.23 fair	0.65 substantial	0.59 moderate	0.71 substantial	0.71 substantial
12. Agreed-upon timelines for the completion of HTA process	0.24 fair	0.67 substantial	0.70 substantial	0.38 fair	0.72 substantial	0.75 substantial
13.Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe	0.40 fair	0.41 moderate	0.65 substantial	0.82 Almost perfect	0.78 substantial	0.61 substantial

Stability

HTA features	*Wilcoxon matched-pair signed rank test*		
	Availability	**Time to patient access (timeliness)**	**Affordability**
1.Presence of an independent HTA body	P=1 Z=1 N=17	P=0.500 Z= 1.414 N=19	P=1 Z=-1 N=19
2.Scientific advice provided to manufacturers ahead of commencement of formal HTA process by HTA bodies	P=0.5 Z= 1.414 N=17	P=1 Z=1 N=19	P=1 Z= 0.577 N=19
3.Introduction of parallel review process to streamline MA and HTA	P=1 Z=-1 N=18	P=0.5 Z= 1.414 N=19	P=1 Z=-1 N=19
4.Clarity of evidentiary requirements for value assessment in HTA	P=0.5 Z= 1.414 N=17	P=1 Z= 0.038 N=19	P=0.25 Z= -1.731 N=18
5.Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence	P=1 Z= -0.577 N=17	P=0.5 Z=0.641 N=19	P=0.500 Z= -1.414 N=19
6.Stakeholder involvement during the HTA process	P=1 Z=0 N=17	P=1 Z= -0.513 N=19	P=1 Z=0 N=19
7.Harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level	P=1 Z=1 N=17	P=0.5 Z= 1.414 N=19	P=1 Z=-1 N=19
8.Coordination of HTA rules, methods and processes across national and regional level, if both co-exist	P=1 Z=1 N=16	P=1 Z=1 N=17	P=1 Z=-1 N=17
9. Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies	P=0.5 Z= 1.413 N=16	P=0.5 Z= 1.414 N=18	P=1 Z=1 N=17
10. Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations	P=1 Z= -0.378 N=16	P= 0.2656 Z= 1.342 N=16	P= 0.0625 Z= -2.138 N=15
11. No reliance on "HTA referencing"	P= 0.0625 Z= -2.138 N=15	P= 0.1719 Z= -1.501 N=15	P=1 Z= -0.116 N=13
12. Agreed-upon timelines for the completion of HTA process	P= 0.1094 Z= 1.911 N=15	P= 0.0020 Z= 3.109 N=17	P=1 Z= -0.180 N=15
13.Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe	P= 0.3984 Z= 1.076 N=16	P= 0.1250 Z= -1.890 N=18	P=0.0156 Z= 2.636 N=17

HTA features	*Spearman correlation coefficient*		
	Availability	**Time to patient access (timeliness)**	**Affordability**
1.Presence of an independent HTA body	0.9678 P< 0.001 high	0.9083 P< 0.001 high	0.9434 P< 0.001 high
2.Scientific advice provided to manufacturers ahead of commencement of formal HTA process by HTA bodies	0.9430 P< 0.001 high	0.9670 P< 0.001 high	0.8507 P< 0.001 high
3.Introduction of parallel review process to streamline MA and HTA	0.9602 P< 0.001 high	0.9575 P< 0.001 high	0.9035 P< 0.001 high
4.Clarity of evidentiary requirements for value assessment in HTA	0.9255 P< 0.001 high	0.8668 P< 0.001 high	0.7947 P< 0.001 high
5.Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence	0.7564 P< 0.001 high	0.7721 P< 0.001 high	0.9221 P< 0.001 high
6.Stakeholder involvement during the HTA process	1.0000 P< 0.001 high	0.8239 P< 0.001 high	0.9244 P< 0.001 high
7.Harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level	0.9891 P< 0.001 high	0.9242 P< 0.001 high	0.9825 P< 0.001 high
8.Coordination of HTA rules, methods and processes across national and regional level, if both co-exist	0.9767 P< 0.001 high	0.9575 P< 0.001 high	0.9764 P< 0.001 high
9. Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies	0.8297 P< 0.001 high	0.7725 P=0.002 high	0.9862 P=0.002 high
10. Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations	0.6580 P=0.056 low	0.1552 P= 0.5660 low	0.5079 P= 0.0533 low
11. No reliance on "HTA referencing"	0.7114 P= 0.0029 low	0.5236 P= 0.0452 low	-0.0309 P= 0.9201 low
12. Agreed-upon timelines for the completion of HTA process	0.7050 P= 0.0033 low	0.4876 P= 0.0471 low	0.1967 P= 0.4822 low
13.Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe	0.3817 P= 0.1446 low	0.4669 P= 0.0508 low	0.5508 P=0.0219 low

8 Market access for medicines treating rare diseases: Association between specialised processes for orphan medicines and funding recommendations

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The text in this chapter has been slightly edited[12] to follow the flow of the thesis.

Key messages

- Canada approved more orphan medicines through specialised pathways than Scotland
- Less negative HTA outcomes for medicines with specialised MA in both countries
- Less negative HTA recommendations for orphan medicines in Scotland than Canada
- Low levels of agreement in HTA for orphan medicines between Scotland and Canada
- Time to market access occurred considerably faster in Canada than Scotland

[12] The numerical ordering of tables and figures have been updated to follow the flow of the thesis, and the spell out of acronyms have been removed if acronyms have been explained previously.

Abstract

Access to medicines treating rare diseases ('orphan medicines') has proven challenging due to high prices and clinical uncertainty. To optimise market access to these medicines, some healthcare systems are implementing specialised pathways and/or processes during MA and/or HTA. Comparing one setting where these medicines are classed as "orphan" (Scotland) to another where they considered "non-orphan" (Canada), this study aims to explore whether the presence of specialised pathways and processes at MA and HTA levels is associated with more favourable funding recommendations and faster time to market access. A matched sample of 116 medicines-indication pairs with MA approval from 2001 to 2019 in Europe and Canada was identified, and publicly available sources were used for data extraction. Descriptive statistics were used for data analysis. All medicines were commercially marketed in both countries, except one instance in Scotland. In Scotland, slightly more orphan medicines (68.1%) had a favourable HTA recommendation than in Canada (60.4%), while Canada issued more negative HTA recommendations (20.7%) than Scotland (15.5%). Low levels of agreement on HTA recommendations and the main reasons driving recommendations were found between settings. In both countries, medicines with specialised MA approval were less likely to receive negative HTA recommendations than medicines with standard MA. Time to market access was faster in Canada than Scotland, though medicines with specialised MA approval had slower timelines than medicines with standard MA approval in both countries. However, it is unclear whether the presence of orphan designation and HTA specialised processes alone could result in favourable funding recommendations without accounting for other healthcare system-related factors and differences in the decision-making processes across settings. Holistic approaches and better alignment of evidentiary requirements across regulators are needed to optimise access to orphan medicines.

8.1 Background

Safe and effective medicines contribute to longer, better lives. Promoting access to medicines is, therefore, essential for well-functioning and efficient healthcare systems. There are several steps before patients have access to a new therapy: a product must receive marketing authorization (MA), obtain coverage from the healthcare insurance (market access), and subsequently reach patients through appropriate prescribing and care provisions (patient access). MA is based on a risk-benefit assessment of clinical trial data, while health technology assessment (HTA) bodies consider clinical and economic evidence, often alongside other socioeconomic factors, to decide whether a new medicine offers good value for money (15,17). Institutions responsible for making these decisions face particular challenges when dealing with medicines used to treat rare diseases ('orphan medicines'). Guaranteeing access to orphan medicines is usually more complex than for non-orphan medicines, as orphan medicines are more challenging to develop because of small populations sizes and frequently carry high price tags (4,5), in part due to the institutionalised market exclusivity granted to their manufacturers in some settings (5,22,69,70,209). Recent studies have highlighted delays in access and inequalities in several high-income countries, owing primarily to high prices and poor cost-effectiveness (4,79,80,208).

To ensure market access for treatments that address high unmet need, such as orphan medicines, some healthcare systems implement specialised pathways and/or processes for MA and/or HTA. These pathways exist, first, to mitigate high levels of uncertainty resulting from limited clinical data (due to reasons such as small sample sizes, lack of active comparators, reliance on short-term studies and often on surrogate outcomes) and typically high prices, and, second, to reflect societal values around equity (5,23,193,211). Additionally, an orphan designation may be given during MA in some settings to encourage manufacturers to invest in research and development (5,22,70,209).

There is substantial controversy around whether orphan medicines should be treated differently than other medicines, as increasing MA approvals and funding for these medicines puts pressure on health care budgets and means that there is less money available to treat other patient populations suffering from more common diseases (4,14,22,23,71,80,207,215,226–228,353). There is conflicting evidence on whether the use of specialised pathways and/or orphan status at MA and designated HTA processes contribute to improving market access for orphan medicines. Some studies (22,80,207,224,225) suggest that the presence of such policies during MA have been successful in ensuring more MA approvals for orphan medicines. However, a recent study (213) showed no differences in MA approvals, time spent during the regulatory process, and marketing delays for orphan medicines between countries which differ in terms of whether they grant orphan

designation. At HTA level, some studies have found a positive correlation between specialised HTA processes for orphan medicines and positive HTA recommendations for funding (4,80,211,212,219,220).

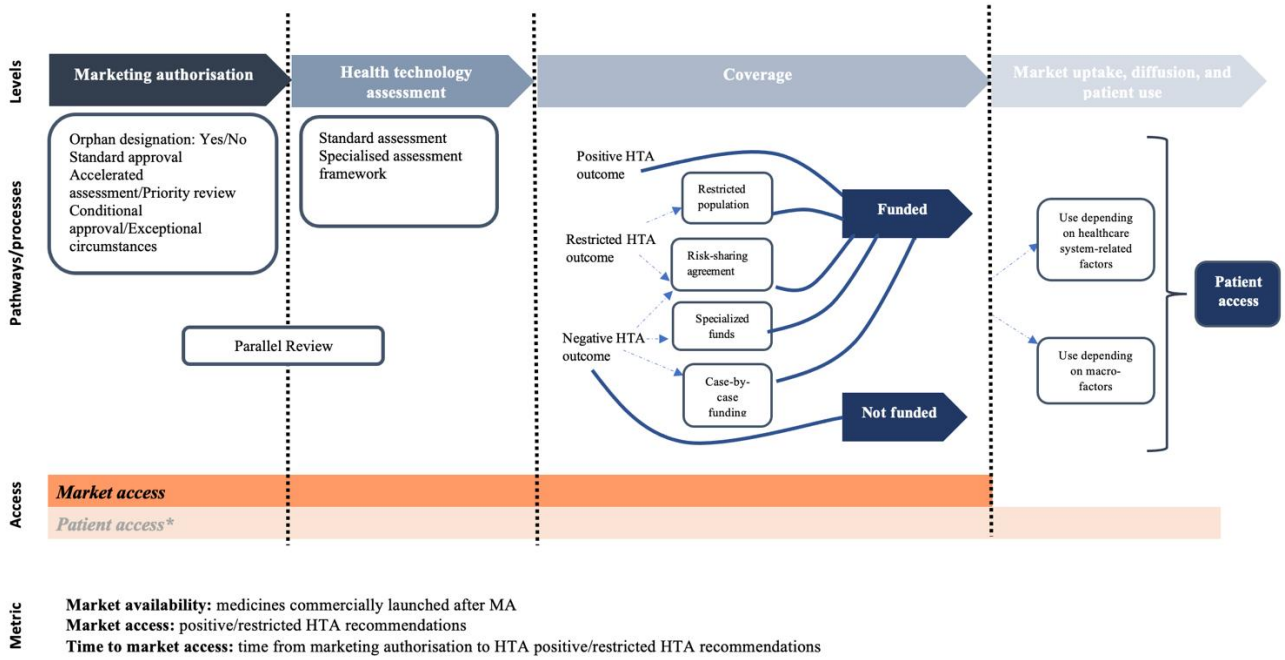
No study has examined whether both specialised MA and HTA policies targeting medicines for high unmet need have a positive impact on funding recommendations and time to market access for orphan medicines. Even though the evidence submitted for MA through these specialised pathways might be sufficient for regulatory agencies to authorise these products, the same evidence could be insufficient for HTA where decision-makers have different trade-offs to make (79,188,193).

This paper compares two settings - one of which has clear and well-established evaluation processes for orphan medicines during MA and HTA (Scotland), and another which has no orphan designation at MA and no designated HTA process for orphan medicines (Canada) – to study differences in HTA recommendations for funding for medicines classed as "orphan" in one setting and "non-orphan" in another. The aim is to evaluate whether the presence of orphan designation at MA and specialised HTA processes might be associated with a larger percentage of favourable funding recommendations and faster time to market access. Additionally, in recognition of the fact that many orphan medicines are likely to be approved through specialised MA pathways in both settings (due to factors such as low quality clinical trial data and unmet need), regardless of presence of orphan medicines regulations (213), this study also compares HTA recommendations and time to market access between orphan medicines with a MA through a specialised pathway and orphan medicines approved through the standard pathway.

8.2 Conceptual framework

This study focuses on market access, rather than patient access, to allow for systematic comparisons of market availability and HTA recommendations for funding. Patient access depends, in part, on other system and macro-related factors and could be challenging to quantify, especially in the case for orphans where access may be granted on a case-by-case basis or through dedicated funds (79,80). A conceptual framework showcases the different levels and metrics used to assess market access (Figure 13).

Figure 13:Analytical framework of access to medicines for rare diseases



*Note: *Patient access is out of the remit of this study.*
Sources: The author.

8.2.1 Levels

Medicines undergo several steps to achieve market access. MA is a regulatory process which allows for the use of specialised pathways if the product is a therapeutic innovation or addresses high unmet need or serious and life-threatening conditions for which there is no therapeutic alternative. Some countries have also specialised processes for the value assessment of orphan medicines to capture the needs of small, vulnerable populations and account for the unique nature of these medicines (23,79,212,219,220,226). Some settings further optimise market access through parallel review processes allowing HTA to commence prior to MA approval. Coverage is determined after HTA outcomes are issued. However whether HTA recommendations translate into funding depends on the HTA system, the role of the HTA body, and whether HTA recommendations are legally binding or not, amongst other factors (15). Generally, positive HTA outcomes result in positive funding decisions.

8.2.2 Metrics of market access

This study uses the following points to observe key trends in time: *market availability* defined as whether a medicine has been commercially launched in markets after MA and *market access* when a positive/restricted HTA recommendation for funding is issued. This definition of market access was chosen to partially account for patient access, which is more likely to be achieved if medicines

are publicly funded. However, it recognises that negative HTA recommendations do not necessarily translate into no funding, particularly in the case of orphan medicines. *Time to market access* was determined by the time (in months) between MA approval to the issue of a positive/restricted HTA recommendation.

8.3 Methods

8.3.1 Country setting

Scotland and Canada were selected for their similarities in HTA set-up, the cost-effectiveness assessment model employed, and how HTA decisions may inform funding decisions. However, there are three fundamental differences: (i) the existence of orphan designation at MA level, (ii) the presence of dedicated processes for assessment of orphan medicines, and (iii) availability of parallel review processes at MA and HTA. Table 13 summarises the main features of the two settings.

Table 13: Key characteristics of MA and HTA in Canada and Scotland

	Scotland	Canada
MA		
MA agency	European Medicines Agency (EMA)[1]	Health Canada
Orphan designation	Yes	No
Specialised regulatory pathways for MA	Yes	Yes
HTA		
HTA body	Scottish Medicines Consortium (SMC)	Canadian Agency for Medicines and Technologies in Health (CADTH) (including the Common Drug Review (CDR) and the pan-Canadian Oncology Medicine Review (pCODR))[2]
Geographical coverage of the HTA body	National	National
Role of HTA on reimbursement decisions[3]	Advisory	Advisory
Type of HTA recommendation[4]	Non-binding	Non-binding
HTA model	Comparative clinical benefit and cost-effectiveness model	Comparative clinical benefit and cost-effectiveness model
Designated assessment frameworks for orphan medicines	▪ Orphan designation ▪ Pricing agreements: Patient Access Scheme ▪ Patient and Clinician Engagement (PACE) group process ▪ SMC modifiers	No
Parallel review of MA and HTA evaluation	No	Yes

Notes: *[1] Until December 2020 following Brexit.*

[2] CADTH makes federal reimbursement recommendations to provinces, having set up two different committees (and a subcommittee for plasma protein products) that are responsible for the evaluation of medicines depending on the disease area (oncology and non-oncology medicines). These two committees follow two different and independent review processes: The Canadian Drug Expert Committee (CDEC) is evaluating medicines that are non-oncology medicines and follow the Common Drug Review (CDR); whereas the pan-Canadian Oncology

Drug Review Expert committee (pERC) evaluates oncology medicines though the pan-Canadian Oncology Drug Review (pCODR). HTA recommendations for both pCODR and CDR are published by CADTH(293).
[3]HTA agencies that act as advisors make reimbursement or pricing recommendations to the national or regional government, a ministerial department or a self-governing body.
[4] HTA recommendations can either be binding or non-binding for the final funding decision. When the HTA recommendation is non-binding, a negative recommendation is not necessarily translated into a negative coverage decision(15).
Source: *The author.*

8.3.2 Sample identification

A matched sample of orphan medicines that were available both in Scotland and Canada was identified through four steps.

First, orphan medicines were identified using both the FDA and the EMA websites; the FDA served as a proxy for Canada (where no orphan designation exists). The US FDA and EMA orphan designations were used to account for differences in the definition of rare diseases across settings (4,22,203,213,228). The FDA Orphan Medicine Product designation database was used to identify orphan medicines approved for use from January 2000 to December 2018, a timeline set to include a comprehensive sample of orphan medicines and allow sufficient time for these medicines to undergo MA in both Europe and Canada. First indication(s) at MA approval and extension of indication(s) with orphan destination, if applicable, were included in the sample. The FDA was the starting point for sample selection as it tends to have more MA approvals than the EMA (101), and includes products which had orphan designation at the time of their MA, generally providing a broader sample.

Second, EMA-approved medicines with the same therapeutic indication (henceforth referred to as medicine-indication pairs) were identified through the European public assessment reports database and additional searches in the EMA website and were matched with the orphan medicine-indication pairs from the FDA. FDA medicine-indication pairs which never had an orphan designation from the EMA were excluded. Medicine-indication pairs with a withdrawn orphan designation by the EMA or which were later withdrawn from the EU market were included in the sample, in case they had undergone HTA assessment under the orphan/ultra-orphan equivalent process of the Scottish Medicines Consortium (SMC). Inclusion of these medicine-indication pairs did not have an impact on the study's analysis which looked at the funding recommendations at the time where the products had an orphan status and were available within markets.

Third, the matched medicine-indication pairs by the EMA and the FDA were reviewed for MA by Health Canada. Medicine-indication pairs which were not approved by Health Canada or orphan medicines with a different approved indication in Canada were excluded from the sample. Again,

medicine-indication pairs where the product was later withdrawn from the Canadian market but had undergone HTA assessment by CADTH (including the CDR or pCODR) were included in the sample.

Finally, the medicine-indication pairs which were not assessed or for which there was no HTA dossier submission by the manufacturer in both Scotland and Canada were excluded. Medicine-indication pairs which were assessed at least by one of the two agencies were included in the final sample. All HTA assessments performed up until December 2019 were included.

8.3.3 Data sources and extraction

Relevant information was extracted from publicly available sources. For MA endpoints, data were extracted from the EMA website and Health Canada's notice of compliance database. For market availability, information for commercially marketed products was extracted through the Drug Product Database of Health Canada and the SMC website. An additional search was carried through the BNF, under the assumption that the formulary contains medicines which have been commercially marketed in UK since they have been funded through the NHS. For HTA endpoints, information was collected through HTA reports published on the websites of the HTA agencies in Scotland (SMC) and Canada (CADTH). Endpoints of interest were grouped and categorised as follows:

MA dates**:** The MA dates of the matched medicine-indication pairs were recorded for the first indication and the extension of indication, when applicable.

Specialised pathways at MA: The presence of specialised regulatory pathways was recorded at the time of MA of the relevant indication. Orphan medicines were categorised into those which received MA through standard approval pathways and those which received MA through specialised pathways including (i) conditional MA, and (ii) accelerated assessment/priority review. Appendix 1 outlines all the available MA specialised pathways in Europe and Canada.

HTA dates: The dates of the latest HTA recommendations were recorded, in case of re-submission. However, for medicines with a previous assessment which had resulted in a favourable recommendation, the date of the first positive/restricted recommendation was recorded, when available.

HTA recommendations: HTA outcomes were collected for the most recent assessment (including resubmissions). HTA outcomes were grouped into four main categories: positive; positive with

restrictions; negative; not assessed. In case of non-submission by the manufacturer, medicines in both settings have an unfavourable HTA recommendation.

HTA restrictions: Listed with restrictions outcomes were recorded for clinical and economic restrictions. Clinical restrictions included limited access to specific populations, restrict monitoring or prescription only to specialists, restrict medicine administration, or suggestions on when treatment should be initiated, continued and/or discontinued. Economic restrictions included funding mechanisms such as PAS (applicable only in Scotland), reductions in price of the medicine, and reimbursement in some jurisdictions only (applicable to a few cases in Canada).

Main reasons for recommendation: The main reasons for recommendations were recorded and categorised into four options: clinical achievement in terms of significant improvement in the clinical benefit; optimal cost-effectiveness; achievement of both (clinical and cost-effectiveness); failure to achieve both clinical and cost-effectiveness. Medicines with no dossier submission and those not assessed by the HTA agency were excluded from analysis on this endpoint.

Parallel review: Medicines where HTA started prior to MA in Canada were noted to examine whether time from MA to favourable HTA was faster.

8.3.4 Statistical analysis

Descriptive statistics were used to establish key trends across the two settings. Chi-square and Fisher's exact test were used to identify statistically significance (p-value ≤0.05 was considered statistically significant). Kappa scores were calculated to examine agreement for HTA recommendations and main reasons for recommendation issued in Scotland and Canada. Results were interpreted using the benchmark scale suggested by Landis and Koch (1977)(305). Concordance in recommendations between the two settings was measured by looking at the proportion of reviews with identical decisions, as done in a previous study (220).

Kaplan-Meier curves were used to estimate time to market access in both countries across the entire sample and for subsamples of orphan medicines which were granted MA through a specialised pathway and those who underwent standard MA. A subgroup analysis was performed for Canada for medicines with pre-MA submissions (parallel review) and medicines which underwent standard HTA. The Mann-Whitney U test was used to assess the equality of distributions for Scotland and Canada and Welch's t-test was used to test the statistical significance of mean times.

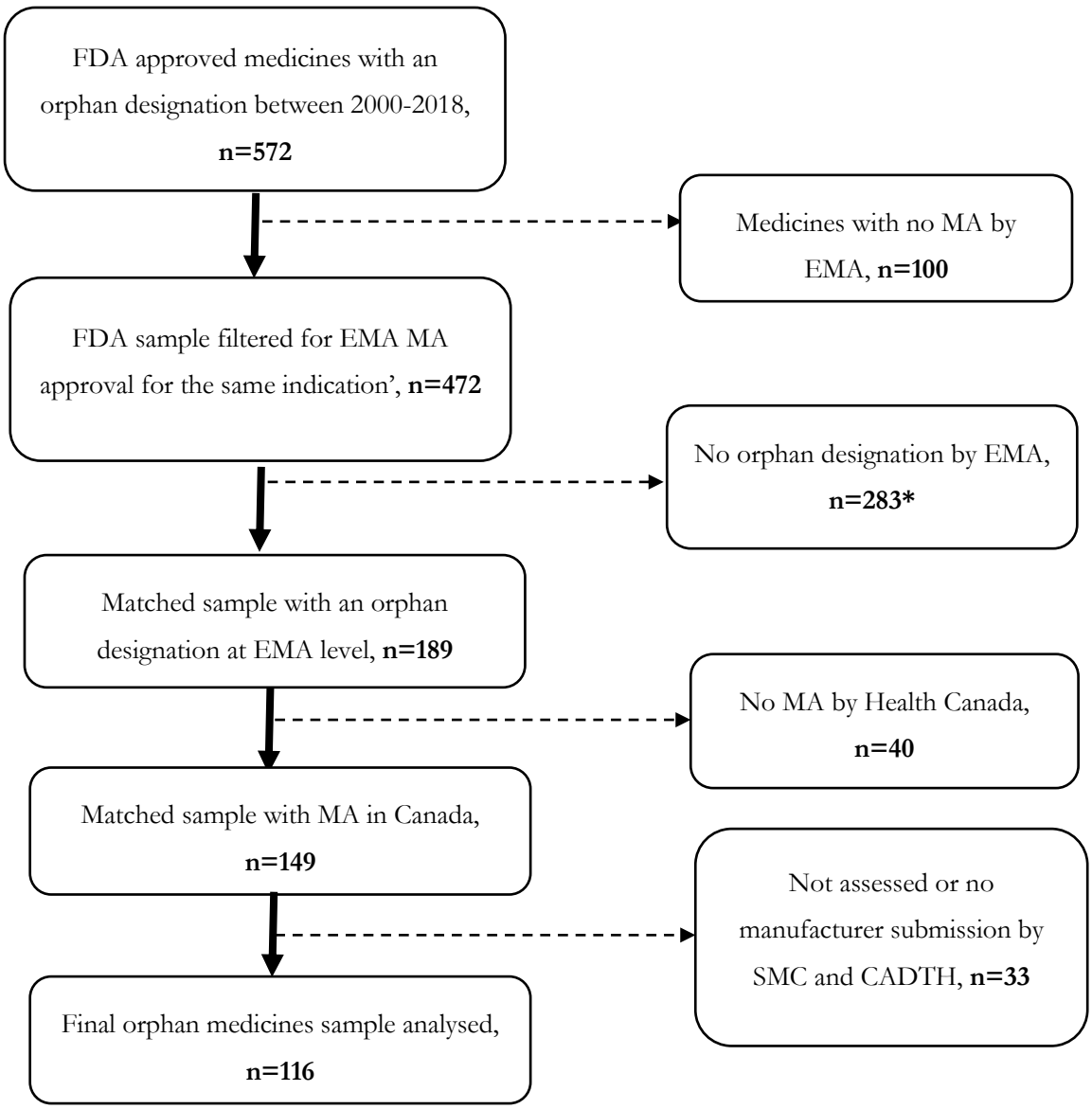
The data were analysed using Stata version 16.

8.4 Results

8.4.1 Sample of orphan medicines

Figure 14 outlines the results of the sample selection process. 116 orphan medicines-indication pairs approved by FDA, EMA and Health Canada and assessed by SMC and/or CADTH before December 2019 were included in the final sample. A full list of the sample is provided in Appendix 2.

Figure 14: Flow chart of sample selection



Note: *Differences in the definition of rare diseases in Europe and the USA, in disease prevalence, and in the time orphan designation incentives entered into force might reflect the large number of medicines with no orphan status at the EMA compared to the FDA.*

In Scotland, 38.8% of included medicines received MA through a specialised pathway. In Canada, 61.2% of the medicines had been granted MA through a specialised pathway, with 42.3% through accelerated assessment/priority review. 21.7% of the medicines in Scotland and 11.7% in Canada had a dossier resubmission. Table 14 provides statistics about the sample.

Table 14: Orphan indication-pair sample characteristics

	Canada		Scotland	
	Entire sample (N=116)			
	n	**%**	**n**	**%**
Conditional MA[1]	26	22.4%	32	27.6%
p=0.363				
Accelerated MA [2]	49	42.3%	15	12.9%
p<0.001				
MA through specialised pathways [3]	71	61.2%	45	38.8%
p<0.001				
MA through standard pathway	45	38.8%	71	61.2%
p<0.001				
Orphans with positive/restrictive HTA outcomes	70	60.4%	79	68.1%
p=0.27				
Medicines assessed by HTA	**N=94, 81.0%**		**N=97, 83.6%**	
p=0.606				
HTA resubmission	11	11.7%	21	21.7%
p=0.095				
Parallel review submission	32	34.4%	N/A	
p<0.001				

Notes:[1] *Includes both conditional MA (CMA) and authorisation under exceptional circumstances (AEC) from the EMA. In Canada, this relates to conditional notice of compliance (NOC/c) by Health Canada.*

[2] *Includes both MA with accelerated access and PRIME at the EMA and priority review in Health Canada. From the study sample, only one medicine in Europe underwent MA through PRIME.*

[3] *Includes both conditional and accelerated MAs. Seven medicines (three in Europe and four in Canada) have been both granted conditional MA and underwent an accelerated assessment review. Therefore, the sum of conditional and accelerated MA do not match to the total number of medicines with MA through specialised pathways.*

[4] *N/A: Not applicable*

8.4.2 Market availability

All the included medicine-indications pairs (n=116) were commercially marketed in Canada after MA. In Scotland, out of 97 medicine-indication pairs assessed by SMC, information on market availability was not available for eight. Searching through the BNF, four medicine indication pairs were not listed (out of the 116), including one that was also identified through the SMC search. Combining the SMC and BNF searches, only one medicine-indication pair was identified with no clear information on marketing status after MA.

8.4.3 HTA recommendations for funding

Differences in HTA recommendations, the main reasons for the recommendation and, when applicable, the type of restrictions showed statistical significance according to chi-square and fisher's exact test (see Appendix 3).

(i) HTA outcomes and level of agreement between Scotland and Canada

Positive HTA recommendations**:** Scotland had more positive HTA recommendations than Canada (10.4% vs. 2.6%, respectively). However, proportion of positive recommendations was low in both settings. In Scotland, half of positive HTA recommendations were made when medicines were proven to be both clinically and cost-effective, similar to all positive recommendations in Canada. The other half of positive recommendations in Scotland were made based on proven clinical benefit only, without being cost-effective.

Positive with restrictions HTA recommendations: More than half of orphan medicines had restricted recommendations in both Canada and Scotland (57.8%). In Canada, the majority of medicines with a restricted HTA recommendation (80.6%) had both clinical and economic restrictions for reimbursement. In Scotland, economic restrictions (46.3%) were more prevalent than only clinical restrictions (22.4%) or both clinical and economic restrictions (31.4%). While in Canada, most of the clinical restrictions imposed multiple conditions, 77.8% of the restrictions in Scotland limited the use of these medicines in certain patient populations. All the economic restrictions in Scotland suggest funding these medicines through PAS, a type of pricing agreement between manufacturers and payers. In Canada, the most common type of economic restrictions were requests for price reductions to improve cost-effectiveness (86.7%). Most medicines with restricted recommendation (83.6%) in Canada only proved a significant clinical benefit, similar to Scotland (86.2%).

Negative HTA recommendations: CADTH issued more negative HTA outcomes (20.7%) than SMC (15.5%). In Canada, the main reasons for a negative recommendation were because CADTH was not able to conclude the medicine was both clinically and cost-effective (91.7%). In Scotland, the majority of negative HTA recommendations (72.2%) were made even when medicines were proven to be clinically effective. Only 27.8% of the medicines with negative recommendations in Scotland were neither clinically nor cost-effective.

Level of agreement on HTA recommendations and main reasons for recommendation: The Kappa score analysis suggested that there was only fair agreement on HTA recommendations (kappa= 0.33, $p<0.001$), on whether the orphan medicines undergoing assessment had achieved a clinical

benefit (kappa= 0.29, p=0.003) and whether the medicines assessed were cost-effective (kappa= 0.29, p=0.003). However, no agreement (kappa=-0.02, p=0.581) was observed when looking at whether additional dimensions of value, such as other socioeconomic criteria, were considered for the recommendation.

The degree of concordance/identical HTA recommendations in Scotland and Canada was 66.2% for HTA outcomes, 70.8% on whether the clinical benefit was achieved, 87.7% on whether the medicine was cost-effective and 43.8% for consideration of other socioeconomic criteria when decisions are being made.

(ii) HTA recommendations and HTA restrictions for orphan medicines with MA through specialised pathways versus orphan medicines with standard MA

Differences in the HTA recommendations and types of restrictions for orphan medicines which were granted MA through specialised pathways across the two settings did not show statistical significance. In Scotland, more positive recommendations without restrictions were observed for medicines which underwent standard MA compared to those with MA through a specialised pathway (standard approval: 12.7% vs. specialised approval: 6.7%), whilst in Canada the opposite was observed (standard approval: 2.2 % vs. specialised approval: 2.8%). Medicines approved through specialised MA pathway were more likely to have a favourable recommendation with restrictions than those undergoing standard MA in Canada (standard approval: 54.9% vs. specialised approval: 62.2%), whilst in Scotland the exact opposite was observed (standard approval: 62.2% vs. specialised approval: 54.9%). Both clinical and economic restrictions were more likely to be recommended in Canada for medicines with standard MA than medicines with specialised MA (standard: 82.2% vs. specialised approval: 79.5%). In Scotland the type of restrictions for medicines undergoing MA through specialised pathways were broadly similar to the types of restrictions applied to medicines with standard approval (clinical restrictions only: 25.0% vs. 20.5%; economic restrictions only: 42.9% vs. 48.7%; both clinical and economic restrictions: 32.2% vs. 30.8%, respectively). Negative recommendations for medicines approved through specialised pathways were less in both settings compared to medicines approved through standard MA. However, in Scotland negative HTA recommendations for medicines with standard approval (21.1%) were significantly higher than for medicines approved through specialised pathways (6.7%). In Canada, differences in negative HTA recommendations between medicines with standard vs. specialised approval were smaller (standard approval: 24.5% vs. specialised approval: 18.3%).

8.4.4 Time to access

68.1% of medicines in Scotland and 60.4% in Canada had a positive/restricted HTA recommendation (see Table 14). The results for the time to market access analysis are summarised in Table 15.

Table 15: Time to market access in months from MA to positive/restricted recommendation in Canada and Scotland

	Minimum	Maximum	Median	Mean
All sample				
Canada	5	19	8	10.5
Scotland	7	28	13	19
		p= 0.0234		**p= 0.002**
Medicines in Canada only undergoing parallel review vs. standard HTA				
Pre-MA HTA submission	3	6	4	5.1
Standard HTA submission	8	22	14	13.3
		p < 0.001		**p < 0.001**
Medicines with standard MA Vs. medicines with MA through specialised pathways				
Canada: Standard approval	4	21	8	10
Canada: Specialised MA pathway	6	17	9	10.9
		p= 0.6322		**p= 0.6747**
Scotland: Standard approval	6	25	12	16.9
Scotland: Specialised MA pathway	7	33	14	22.1
		p= 0.3293		**p= 0.3938**

(i) Time from MA to positive/restricted HTA recommendations

Figure 15 (panel A) shows the months elapsed from a MA approval to a positive/restricted HTA recommendation. Canada (median: 8 months; mean: 10.5 months) showed considerably faster access compared to Scotland (median: 13 months; mean: 19 months).

Parallel review: In Canada, access to orphan medicines for which HTA assessment started prior to MA approval was much faster than those which were assessed after MA was granted (

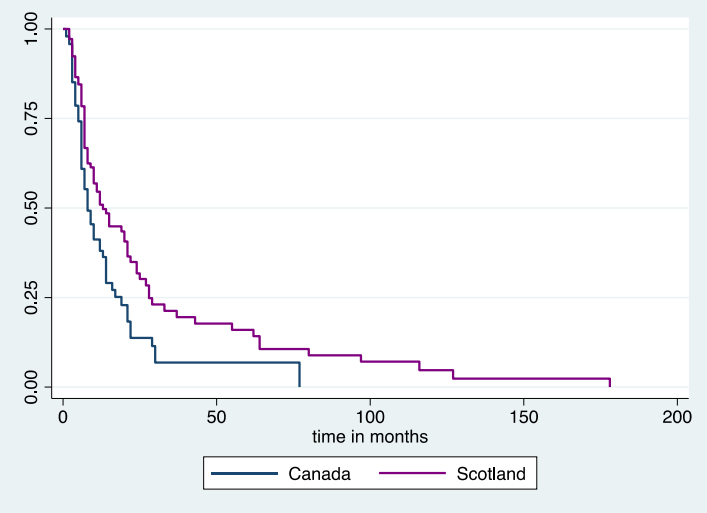
Figure 15([panel B]).

(ii) Time from MA to positive/restricted HTA recommendations depending on the presence of MA specialised pathways

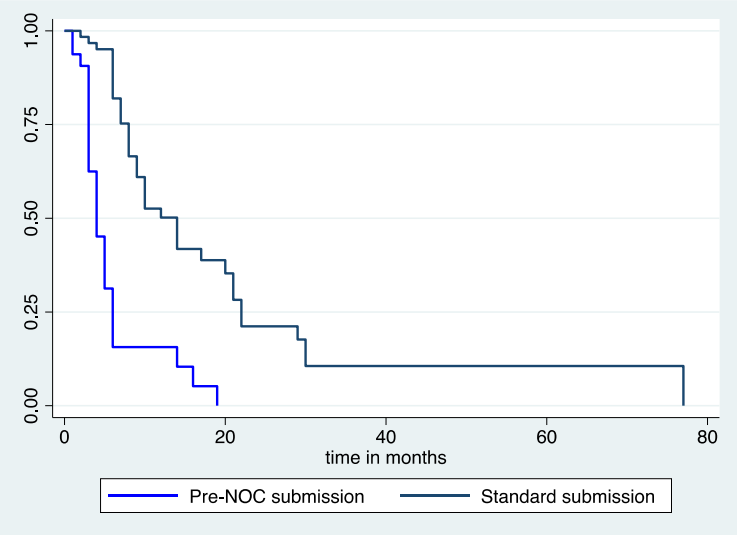
Figure 15 (panel C) shows that within both countries time to access was faster for medicines which underwent standard approval than those which granted MA through specialised pathways.

Figure 15: Kaplan–Meier curves for time to market access

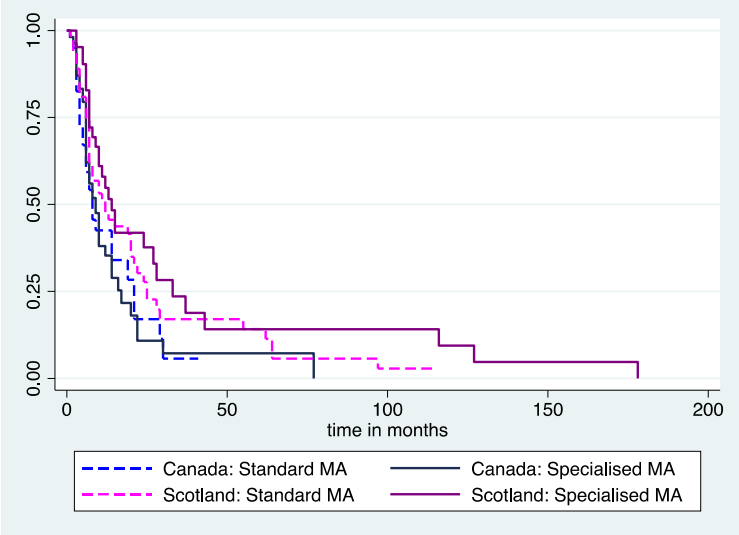
Panel A: Time to market access for all the sample



Panel B: Time to market access in Canada for medicines undergoing parallel review vs. medicines with standard HTA submission



Panel C: Time to market access for medicines undergoing MA through standard vs. specialised pathways



8.5 Discussion

Scotland, where orphan designation and specialised HTA processes for orphan medicines exist, showed slightly more positive/restricted and fewer negative HTA recommendations than Canada, where these processes are not implemented. However, in both settings proportion of positive HTA recommendations with no restrictions was very low. In Canada, orphan medicines were more likely to be approved through a specialised MA pathway than Scotland despite lack of an orphan designation. In both settings, medicines which received MA through specialised pathways were less likely to receive an unfavourable funding recommendation than medicines with standard MA. Across all time to market access analyses, Scotland had slower time to access than Canada.

Nevertheless, conclusions on whether the presence of specialised pathways for orphan medicines results in better market access cannot be drawn based only on the data used in this study. Differences in the decision-making process and value assessment methods employed in the two settings (highlighted from the low levels of agreement seen in this study), as well as other system related factors might further impact patient use and market uptake of orphan medicines.

8.5.1 Market availability

All medicine-indication pairs were commercially marketed in both settings, except for one instance in Scotland. Thus, the presence of orphan designation at MA did not seem to have an impact on the commercial availability of orphan medicines.

8.5.2 HTA recommendations for funding

Percentages of positive recommendations without restrictions were low in both countries, which could have further implications for market, and ultimately patient access. In Scotland, orphan medicines had less negative recommendation for funding compared to Canada. Funding recommendations for orphan medicines in Scotland were more likely to be accompanied by economic restrictions only, whereas in Canada funding recommendations were often subject to both clinical and economic restrictions, potentially limiting patient access to a greater extent. Clinical and economic restrictions are predominately suggested by HTA agencies to mitigate affordability concerns regarding efficient allocation of finite healthcare recourses. In fact, positive recommendations with restrictions were most often issued in both countries due to failure in proving cost-effectiveness. Thus, the high presence of economic restrictions in the form of price reductions (Canada: 86.7%) or funding mechanisms (Scotland: 100%) was expected due to the associated high costs of orphan medicines.

Negative recommendations for funding in Scotland were made even when medicines were proven to be clinically effective (n=13). Interestingly, of these 13 medicines, eight underwent assessment through the Patient and Clinician Engagement (PACE) process, which reflects on opinions of clinicians, patients, and patient organisations before a final HTA recommendation is issued (295). For these eight medicines, manufacturers failed to justify their cost in relation to health benefits. In six of these cases, PAS were proposed by the companies which may imply that the suggested discounted prices were not low enough to justify the high cost per quality-adjusted life years (QALY).

Negative recommendations in Canada were most often made when CADTH was not able to conclude that the medicine was both clinically- and cost-effective. This is contradictory to recent studies, which concluded that the main reason for a negative HTA recommendation in Canada was lack of observed clinical benefit (220,354).

The low levels of agreement between the two countries on HTA recommendations and the main reasons for final recommendations may suggest discrepancies in the way clinical benefit and cost-effectiveness are assessed, and whether other value dimensions, such as unmet need, and burden of disease among others, have an impact on the final recommendation. In fact, the level of concordance/identical outcomes between the two settings on whether other value dimensions had a positive impact on the final recommendation was low (43.8%) and might reflect the absence of a specialised assessment process for orphan medicines in Canada. The results of this study are in

alignment with findings of a previous study which showed that the level of agreement in HTA recommendations between Canada and other settings, including Scotland, was low (220).

8.5.3 Market access

Market access was measured through positive/restricted HTA recommendations. While evidence from Canada shows that there is not always alignment between CADTH recommendations and provincial reimbursement decisions (198) and medicines with negative HTA recommendations can still be found reimbursed in provinces (199,220), recommendations can generally be considered "equally impactful as binding " in both settings as national/regional healthcare systems will provide funding to medicines with favourable HTA recommendations (15,199,355).

Scotland (68.1%) showed slightly better market access to orphan medicines than Canada (60.4%). This could be in part, because certain processes in Scotland are implemented to account for high clinical uncertainty, such as SMC accepting more uncertainty in the economic case analysis or a higher cost per QALY for orphan medicines by applying modifiers which account for additional value dimensions such as whether the medicine treats a life-threatening disease or substantially improves patients' quality of life (294), a practice not seen in Canada. Another example is the explicit patient and clinician consultation through the PACE process (23,295). PACE was introduced in response to criticism from key stakeholders as a high proportion of medicines treating end-of-life and rare diseases were receiving unfavourable HTA recommendations based only on cost-effectiveness criteria. Since its introduction in 2014, favourable HTA recommendations for orphan medicines have increased (229). The current study provides further evidence in support of this finding: after introduction of the PACE process, positive HTA recommendations increased from 74.2% to 84.4%, while negative recommendations decreased from 25.8% to 15.6%. HTA recommendations of almost 91% orphan medicine-indications pairs assessed by SMC after 2014 considered the views expressed during the PACE meeting. Stakeholder consultation is part of assessments in Canada, but the type of participant may differ across health technologies or assessments, thus the potential impact to the final recommendation is hard to be established.

The larger number of dossier re-submissions in Scotland than in Canada could also contribute to slightly better market access in Scotland, as submission of new and/or additional information could be likely to change previously negative HTA outcomes (126).

Finally, favourable HTA recommendations may be more prevalent in Scotland than Canada because of price negotiations through PAS during HTA process. Companies can suggest a

discount from the NHS list price or submit new or revised PAS to SMC for previously negative HTA recommendations to improve the cost-effectiveness of medicines (302). On the contrary, negotiations or managed entry agreements take place at provincial level in Canada, after national HTA recommendations are issued (198). Thus, more negative recommendations in Canada could be expected based on potentially high prices and poor cost-effectiveness associated with orphan medicines which are not mitigated during the HTA process.

Similar to these findings, another study also concluded that a causal relationship between the presence of special HTA criteria for orphans and positive/restricted HTA recommendations cannot be established (200). However, other evidence showed no difference between positive/restricted HTA recommendations in Canada and Scotland (220).

As a final note, access to medicines cannot only be determined by looking at commercial market availability and HTA recommendations: evidence showcased a high rate of reimbursement in Europe for ultra-orphan medicines which had not undergone an HTA assessment (200). Thus, the access metrics used in this study can only signal whether the medicine is available within markets and potentially publicly funded.

8.5.4 Time to market access

Canada has shorter time periods between receiving MA to a positive/restricted HTA recommendation than Scotland across both the entire sample and the subsection of medicines which underwent MA through specialised pathways. This might be explained by additional steps in the Scottish assessment process, such as the PACE and consideration of PAS and/or the implementation of parallel review in Canada aiming to tackle delays occurring when MA and HTA assessments take place consecutively.

Beyond the remit of this study, further delays to time to access are expected after issue of HTA recommendations such as time for pricing and reimbursement negotiations between national and/or provincial payers with manufacturers. A recent study (207) showed that, in Canada federal pricing negotiations have been shown to add a median of 9.9 months after CADTH recommendations, with another 1.2 months for provincial funding (207). Usually, commercial market availability occurs earlier than publication of HTA recommendations and delays in time to access are not often due to this (see Appendix 4 for additional results on time to market access).

8.5.5 Specialised pathways for MA beyond orphan designation

Since orphan medicines are likely to be approved through specialised pathways at MA, this study explored whether market access to orphan medicines is delayed at the HTA stage due to

discrepancies in the remits of and the factors driving decision-making in MA and HTA stages. Until recently with the introduction of interim acceptance in Scotland (Scottish Medicines Consortium, 2018), there were no specific dedicated processes for the evaluation of medicines granted MA through specialised pathways in either setting which allow us to compare HTA recommendations with medicines granted standard MA. No interim acceptance was recorded in Scotland for this study's sample.

More than half of the sample was granted MA through specialised pathways in Canada while less than half of the sample received MA through specialised pathways in Europe. Interestingly, even in the absence of an orphan designation in Canada, orphan medicines were more likely to be approved through specialised pathways than Scotland. In both Scotland and Canada, medicines with MA through specialised pathways were less likely to receive a negative HTA recommendation. In Canada, those medicines were almost equally likely to receive a positive HTA recommendation (without restrictions) than those with standard approval. The oppositive was observed in Scotland, where more unrestricted favourable recommendations were recorded for medicines with standard MA. However, the difference between the percentage of negative recommendations for medicines with standard approval vs. those with specialised approval was considerably larger in Scotland than in Canada, potentially suggesting that access to medicines with MA through a specialised pathway is not halted at HTA level when specialised HTA processes are in place.

These findings are contradictory to previous studies considering access to non-orphan medicines undergoing MA through specialised pathways. One study found half of HTA recommendations for conditionally approved medicines were negative (193). Another study reported that there was no difference in positive recommendations for medicines with conditional MA and medicines with standard MA (194). A study focusing on the English HTA body showcased that the proportion of positive recommendations for medicines undergoing MA through specialised pathways was similar to overall recommendations of the technology appraisals program (188).

In the time to market access analysis, orphan medicines with MA through specialised pathways took more time to market access compared to medicines undergoing standard approval in both countries. Evidence on non-orphan medicines concluded similarly that expedited assessments for MA did not lead to earlier access because of later unfavourable funding recommendations (193). A possible reason for this finding could be that HTA agencies might be unprepared to assess medicines which are approved through conditional MA. However, Scotland had slower time to market access than Canada despite the implementation of a specialised assessment framework for

orphan medicines which may lead to the suggestion that SMC should actually be more prepared to assess medicines with high clinical uncertainty. However, in both countries, HTA processes might take more time regardless of the implementation of a specialised assessment framework to mitigate higher levels of uncertainty. In addition, as 42.3% of the sampled orphans undergoing accelerated assessment were in Canada, it is apparent that Health Canada is making considerable efforts to accelerate MA assessments to allow the HTA process to commence as quickly as possible. However, this was not reflected in the time analysis where medicines with standard MA showed faster timelines in comparison to medicines with MA through specialised pathways. In an additional time to market access analyses in Appendix 4, when the date of manufacturer's submission for MA to the regulatory body was used (instead of MA date), orphan medicines with a specialised MA showed faster timelines compared to those with standard MA in both settings.

8.5.6 Policy implications

Whether specialised assessment processes and orphan designation status can ensure better and faster access to orphan medicines is still unclear.

On one hand, the presence of processes and policies targeting orphan medicines might emphasize affordability issues. Even though these processes may be considered critical in motivating manufacturers to invest in research and development, they may contribute to why orphan medicines are now amongst the most expensive and profitable medicines worldwide (65,215). The policy environment for rare diseases in some countries has given leeway to manufacturers of orphan medicines to make considerable profit, as they are able to exercise monopolistic power to request and retain high price tags while testing the flexibility of healthcare systems in accepting higher costs per QALY (53,60,65,71,80,215,227,356,357). For example, despite the positive impact of the Scottish PACE process, concerns remained as to whether it might reduce manufacturers' incentives to lower prices, and further weakened the negotiation position of the Scottish NHS (23,229,358). Even though manufacturers take risks in investing in the development of orphan medicines, the prices charged may not be always based on the actual cost of their production or development but on a profit-maximizing price (65). Affordability concerns are not limited to price: policies for rare diseases have also been criticized for taking up finite resources of healthcare systems that could have been redirected to other diseases (60,80,215,227,357). For instance, the Dutch Healthcare Insurance Board made tough decisions regarding the reimbursement of enzyme replacement therapy for Fabry and Pompe diseases in 2012, as favourable funding decisions would have resulted in limited resources not being available for the funding of other, more cost-effective, medicines (357).

On the other hand, dedicated assessment processes for orphan medicines ensure that the patient's voice is considered during the assessment process (229), or even during medicine development such as in the case of ivacaftor where trials were conducted with the help of the Cystic Fibrosis Foundation (71). This may be particularly important for rare diseases: as the number of patients with these diseases is smaller, the resources available to, and power of, patient organisations for rare diseases to influence a negative HTA recommendation may be limited in the absence of dedicated processes (230). Additionally, specialised assessment processes increase the readiness of HTA agencies to handle submissions where high uncertainty due to limited clinical evidence exists (23). This is illustrated by the Scottish HTA recommendations, as positive restrictions were mainly limited to funding mechanisms.

Different ways forward can be pursued to find the right balance between the aforesaid points, accounting for sustainability of healthcare systems and a public health desire to drive prices of orphan medicines down and continuing to incentivise manufacturers to develop these medicines. Introduction of competitive pricing negotiations (i.e.: potentially through pricing schemes or specialised funds) as part of the value assessment process, could be considered to aid in the mitigation of cost-effectiveness concerns during the HTA process. For instance, since the implementation of the new CDF in England, in 2016, all oncology medicines undergo HTA assessment. In cases where high clinical uncertainty is established, oncology medicines can be recommended for use within the CDF by the English HTA body to avoid long delays until more evidence is gathered(145,359). Use of MCDA tools could also be considered in HTA to account for the unique nature of orphan medicines, diverging views of key stakeholders, other value criteria along with clinical benefit and cost-effectiveness, and the quality of the submitted evidence, as seen in the Netherlands and the UK (53,54,218). In addition, new value assessment systems could inform both pricing and funding of orphan medicines based on pre-defined evaluation criteria including, amongst others, the level of research undertaken by the developer including manufacturing complexity, and follow-up measures required by regulatory or other authorities (60). Alternatively, a value-based pricing policy based on HTA recommendations could be used for pricing of orphan medicines to link prices to added clinical benefit and cost-effectiveness (53). Another possibility could be for medicines with conditional MA to become available through compassionate use schemes, similar to the temporary authorisation programme (ATU) in France, though this solution should apply to products with MA, and not just pre-MA medicines as is the case in the ATU (360,361). Furthermore, requirements for additional data collection should be aligned between MA and HTA bodies to reduce further complexity, such as seen in the new SMC

interim acceptance decision option (140). In addition, use of performance-based managed entry agreements which rely on real world evidence can be explored to optimise access to medicines with uncertain clinical evidence (24,54).

Yet, these suggestions are not the panacea to access challenges observed in the case of orphan medicines. Introduction and use of programmes such as the ones mentioned above and other regulatory and value assessment policies targeting orphan medicines should be thoroughly assessed before their introduction and during their implementation. Specialised processes for orphan medicines should be accompanied by strict and transparent guidelines regarding the safety, clinical effectiveness, pricing of eligible medicines, and appropriate mechanisms to prevent potentially catastrophic costs should be in place. Implementation of processes should also reflect on lessons learned from existing programmes. For instance, the French ATU scheme was recently reformed after criticism for possible interference and delays of formal pricing and reimbursement decisions after MA, and allowing manufacturers to set high initial prices due to its free pricing period coupled with purchasers' low price sensitivity (20,361,362). Similarly, the old English CDF was heavily criticised due to a lack of transparency on how the fund operates, miscalculations of true costs of funding unapproved cancer medicines, high levels of usage of cancer medicines undermining care for other diseases, and diversion from funding recommendations by the English HTA body (363).

Important concluding messages are that (i) efforts focusing on access should take both patient and market access into account; (ii) increased transparency is needed on research and development costs and pricing of orphan medicines; (iii) better collaboration between key stakeholders can help in achieving better and timely access to orphan treatments, and; (iv) targeted efforts at different stages in the access pathway should be aligned to achieve their aims jointly. Where there are discrepancies, such as in varying clinical evidentiary requirements at MA and HTA levels, the presence of specialised pathways for MA cannot ensure better and faster access to medicines with poor clinical evidence within countries. Where the remits of MA processes and HTA agencies are different, intermediate processes or collaborative efforts could be established or strengthened.

8.5.7 Study limitations

First, Canada and Scotland differ in country size, population, and gross domestic product, as well as their willingness-to-pay thresholds per QALY and where funding decisions are made (i.e.: in Canada, funding of medicines is the competence of provincial jurisdictions), among other factors which can impact access to orphan medicines. However, these settings serve as good examples to explore whether differences in how medicines for rare diseases are treated at MA and HTA level

are highlighted in funding recommendations and time to market access, given their similarities in the role of, and assessment model followed by the HTA body. Second, positive/restricted HTA recommendations can only be used as an approximation of market access. Manufacturers can still decide not to market a product despite a favourable HTA recommendation and other system related factors might impact funding decisions. Third, the time to market access analyses measure the time from MA to favourable HTA recommendations. However, any further delays after HTA that might occur during subsequent pricing and reimbursement negotiations, or market launch are not captured. Fourth, the FDA was used as a surrogate for Canada for the sample selection as there is no orphan designation in Canada at MA level. However, there is an established collaboration and exchange of information between the FDA and Health Canada (299). Fifth, the methodology used for the sample identification was used to ensure a wider range of products were included from the outset, though all possible sampling strategies will have had an impact on the number and products included in the sample. Sixth, data on previous submissions for medicines with resubmission in Scotland were not always available, limiting our data on whether a positive/restricted HTA recommendation had been issued previously. Instead, the HTA dates of the latest submission for positive/restricted recommendations were used when this information was not available. The impact of this is considered minimal as re-submissions in Scotland usually take place to change previously negative HTA recommendations (355). Seventh, Scotland has local formularies which are not publicly available, therefore information on market availability for Scotland was extracted from the BNF, among other sources, assuming that medicines included in the BNF would have been marketed across the UK. Finally, due to lack of a comparative group of non-orphan medicine-indications pairs, it cannot be determined with certainty whether more favourable HTA recommendations in Scotland are seen due to the presence of specialised pathways only and not due to other system related factors or differences in the way medicines are assessed in these two settings.

8.6 Conclusion

Scotland, with specialised processes at MA and HTA levels for orphan medicines, showcased only slightly more favourable funding recommendations than Canada, where these medicines are assessed as any other medicine. Low level of agreement between the two agencies suggests discrepancies in their clinical- and cost-effectiveness assessments and consideration of other societal value dimensions during HTA. In Canada, orphan medicines were more likely to be granted MA through specialised pathways than Scotland. In both settings, these medicines were less likely to receive an unfavourable funding recommendation in comparison to orphan medicines

with standard MA. However, from the findings of this study, it is unclear whether the presence of orphan designation and HTA specialised processes for orphan medicines alone could result in more favourable funding recommendations, and it is not possible to suggest a single remedy for achieving better access to orphan medicines. Holistic approaches at all levels of the access pathway are necessary, together with better collaboration across respective agencies and relevant stakeholders while use of innovative pricing and assessment mechanisms for orphan medicines are needed to make these medicines more affordable while mitigate high levels of uncertainty.

8.7 Appendices

8.7.1 Appendix 1

Specialised pathways at MA in Europe and Canada

European Medicines Association (EMA)				Health Canada		
Aim of the pathway	***Scheme***	***Description***	***Eligible medicines***	***Scheme***	***Description***	***Eligible medicines***
Shortened timelines	Accelerated Assessment	Shorten review for MA	Major public interest Therapeutic innovation	Priority Review	Shorten review for MA	Serious, life-threatening or severely debilitating diseases: a) there is no alternative therapy b) significant improvement in the benefit/risk profile over existing products.
	Priority Medicines (PRIME)	Optimise development plans and speed up MA evaluation	Unmet need Major therapeutic advantage compared to existing medicines			
Deal with limited clinical data	Conditional MA	MA for medicines with less limited clinical data than normally required given that additional data will be provided once acquired	Seriously debilitating or life-threatening diseases	Notice of Compliance with conditions (NOC/c)	MA with the condition that the manufacturer will undertake additional studies	Serious, life-threatening or severely debilitating diseases: a) there is no alternative therapy b) significant improvement in the benefit/risk profile over existing products.
	Exceptional Circumstances	MA for medicines where the applicant is unable to provide comprehensive clinical under normal circumstances	Orphan medicines			

Sources: *The author.*

8.7.2 Appendix 2

Full list of the final matched indication pair sample of orphan medicines

Molecule's name	Indication	ATC code
alglucosidase alfa	For the treatment of Pompe disease (acid a-glucosidase deficiency).	A16
ambrisentan	For the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.	C02
arsenic trioxide	In combination with all-trans-retinoic acid (ATRA [tretinoin]) for the induction of remission, and consolidation in adult patients with newly diagnosed, low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤10 x 103/µl), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.	L01
asfotase alfa	Enzyme replacement therapy in patients with a confirmed diagnosis of pediatric-onset hypophosphatasia (HPP).	A16
avelumab	For the treatment of metastatic Merkel cell carcinoma.	L01
axicabtagene ciloleucel	For the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	L01
azacitidine	For treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with intermediate-2 and high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML).	L01
aztreonam	To improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa.	J01
blinatumomab	For the treatment of patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL).	L01
bosentan	For the treatment of pulmonary arterial hypertension in patients with WHO functional class III or IV primary pulmonary hypertension.	C02
bosutinib	For 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.	L01
brentuximab vedotin-1	For the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1. following autologous stem cell transplant (ASCT) or 2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.	L01
brentuximab vedotin-2	For the treatment of adult patients with CD30+ Hodgkin lymphoma at increased risk of relapse or progression following autologous stem cell transplant.	L01
brentuximab vedotin-3	For the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).	L01
canakinumab-1	For the treatment of Cryopyrin associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including	L04

Molecule's name	Indication	ATC code
	• Familial Cold Autoinflammatory Syndrome (FCAS) • Muckle-Wells Syndrome (MWS).	
canakinumab-2	For the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 through 16 years.	L04
carfilzomib	For the treatment of patients with multiple myeloma who have received at least two prior therapies, including treatment with Velcade (bortezomib) and an immunomodulatory.	L01
carglumic acid-1	For the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.	A16
carglumic acid-2	For the treatment of hyperammonaemia due to isovaleric acidaemia, methylmalonic acidaemia and propionic acidaemia.	A16
cerliponase alfa	For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency	A16
clofarabine	For the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.	L01
daratumumab-1	As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.	L01
daratumumab-2	In combination with bortezomib, melphalen, and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.	L01
daratumumab-3	In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.	L01
dasatinib-1	For the treatment of adults with chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.	L01
dasatinib-2	For the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.	L01
deferasirox	For the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.	V03
defibrotide	Treatment of severe hepatic veno-occlusive disease (VOD) also known as sinusoidal obstructive syndrome (SOS) in haematopoietic stem-cell transplantation (HSCT) therapy.	B01
dinutuximab beta	For the treatment of pediatric patients with high-risk neuroblastoma.	L01
eculizumab	For the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.	L04
eliglustat	For the long-term treatment of adult patients with the Type 1 form of Gaucher disease.	A16
elosulfase alfa	For patients with mucopolysaccharidosis VI. Galsulfase has been shown to improve walking and stair-climbing capacity.	A16
eltrombopag olamine	For the treatment of chronic idiopathic thrombocytopenic purpura to increase plate let counts in splenectomized patients who are refractory to first-line treatments (e.g .,corticost eroids, immunoglobulin). As second-line treatment for adult non-splenectomized patients where surgery is contraindicated.	B02

Molecule's name	Indication	ATC code
everolimus-1	For the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease	L01
everolimus-2	For the treatment of adult patients with progressive, well-differentiated, non-functional, neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin, (excluding pancreatic) with unresectable, locally advanced or metastatic disease.	L01
everolimus-3	For the treatment of adults with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery.	L04
everolimus-4	For the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection.	L04
galsulfase	For the treatment of patients with Mucopolysaccharidosis VI (MPS VI).	A16
glycerol phenylbutyrate-1	Use as a nitrogen-binding adjunctive therapy for chronic management of adult and pediatric patients at least 2 years of age with urea cycle disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.	A16
ibrutinib-1	For the treatment of patients with mantle cell lymphoma (MCL), a rare and aggressive type of blood cancer.	L01
ibrutinib-2	For the treatment of patients with Waldenström's Macroglobulinemia who have received at least one prior therapy.	L01
ibrutinib-3	For the treatment of adult patients with chronic lymphocytic leukaemia (CLL) (previously treated)	L01
ibrutinib-4	For the treatment of adult patients with chronic lymphocytic leukaemia (CLL) (previously untreated)	L01
idursulfase	For the treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).	A16
imatinib-1	For the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy	L01
imatinib-2	Adjuvant treatment of adult patients following complete resection Kit (CD 117) positive gastrointestinal stromal tumors (GIST).	L01
inotersen	For the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).	N07
inotuzumab ozogamicin	For the treatment of adults with relapsed or refractory acute lymphoblastic leukemia/.	L01
isavuconazole	For the treatment of adults with invasive aspergillosis and invasive mucormycosis, rare but serious infections.	J02
ivacaftor-1	For the treatment of a rare form of cystic fibrosis (CF) in patients ages 6 years and older who have the specific G551D mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene.	R07
ivacaftor-2	For the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.	R07
ivacaftor-3	For the treatment of cystic fibrosis (CF) in patients ages 2 to less than 6 years who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H.	R07
ixazomib	For the treatment of people with multiple myeloma who have received at least one prior therapy.	L01

Molecule's name	Indication	ATC code
lanadelumab	For the treatment of types I and II hereditary angioedema.	B06
laronidase	For the treatment of mucopolysaccharidosis I.	A16
lenalidomide -1	For the treatment of patients with transfusion dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5 q cytogenetic abnormality with or without additional cytogenetic abnormalities.	L04
lenalidomide-2	In combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy.	L04
lenalidomide-3	For the treatment of multiple myeloma (MM), as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT).	L04
lenalidomide-4	In combination with low-dose dexamethasone, for treatment of newly diagnosed multiple myeloma patients who are not candidates for stem cell transplantation.	L04
lenvatinib-1	For the treatment of patients with progressive, differentiated thyroid cancer (DTC) whose disease progressed despite receiving radioactive iodine therapy (radioactive iodine refractory disease).	L01
lenvatinib-2	First-line treatment of patients with unresectable hepatocellular carcinoma (HCC).	L01
letermovir	Treatment of prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT).	J05
liposomal irinotecan	In combination with 5-fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas that has progressed following gemcitabine-based therapy.	L01
lumacaftor-ivacaftor-1	For the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.	R07
lumacaftor-ivacaftor-2	For the treatment of cystic fibrosis (CF) in patients age 6-11 year old who are homozygous for the F508del mutation in the CFTR gene.	R07
lutetium (177Lu) oxodotreotide	For the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropancreatic neuroendocrine tumors (GEP-NETs).	V10
macitentan	For the treatment of adults with pulmonary arterial hypertension (PAH), a chronic, progressive and debilitating disease that can lead to death or the need for lung transplantation.	C02
mercaptopurine	For the treatment of patients with acute lymphoblastic leukemia as part of a combination regimen.	L01
midostaurin	In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FMS like tyrosine kinase 3 (FLT3) mutation-positive.	L01
migalastat	For the treatment of adults with Fabry disease.	A16
miglustat	For the treatment of mild to moderate Type I Gaucher disease in adults for whom enzyme replacement therapy is not a therapeutic option .	A16
nelarabine	For the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.	L01

Molecule's name	Indication	ATC code
nilotinib	For treatment of chronic phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib.	L01
nintedanib	For the treatment of idiopathic pulmonary fibrosis (IPF).	L01
nitisinone	For adjunctive therapy to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1.	A16
nusinersen	To treat children and adults with spinal muscular atrophy (SMA).	M09
obeticholic acid	For the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid in adults with an inadequate response to ursodeoxycholic acid or as monotherapy in adults unable to tolerate ursodeoxycholic acid.	A05
obinutuzumab-1	In combination with chlorambucil to treat patients with previously untreated chronic lymphocytic leukemia (CLL).	L01
obinutuzumab-2	For the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen.	L01
obinutuzumab-3	In combination with chemotherapy, followed by obinutuzumab maintenance therapy in patients achieving a response, for the treatment of patients with previously untreated advanced follicular lymphoma.	L01
ofatumumab-1	In combination with chlorambucil, for the treatment of patients with chronic lymphocytic leukemia (CLL) who have not received prior therapy and are inappropriate for fludarabine-based therapy.	L01
olaparib-1	As monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy, until disease progression or up to 2 years if no evidence of disease.	L01
olaparib-2	As monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.	L01
olaratumab	In combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery and for whom treatment with an anthracycline-containing regimen is appropriate.	L01
pasireotide-1	For the treatment of cushing's disease patients who cannot be helped through surgery.	H01
patisiran	For the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adult patients.	N07
pegvisomant	For the treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate.	H01
pirfenidone	For the treatment of idiopathic pulmonary fibrosis (IPF).	L04
plerixafor	In combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.	L03
pomalidomide	In combination with low-dose dexamethasone for patients with multiple myeloma for whom both bortezomib and lenalidomide have failed and who have received at	L04

Molecule's name	Indication	ATC code
	least two prior treatment regimens and have demonstrated disease progression on the last regimen.	
ponatinib	For the treatment of adults with chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), two rare blood and bone marrow diseases.	L01
riociguat-1	For the treatment of chronic thromboembolic pulmonary hypertension (CTEPH).	C02
riociguat-2	For the treatment of pulmonary arterial hypertension (PAH).	C02
romiplostim	To increase the platelet levels in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): • who are non-splenectomized and have had an inadequate response or who are intolerant to corticosteroids and/or immunoglobulins • who are splenectomized and have had an inadequate response to splenectomy	B02
rufinamide	For adjunctive therapy of seizures associated with Lennox-Gastaut syndrome in patients 4 years of age or older.	N03
ruxolitinib-1	For the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.	L01
ruxolitinib-2	For the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.	L01
sapropterin dihydrochloride	For the treatment of patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU).	A16
sebelipase alfa	For the treatment of patients with a rare disease known as lysosomal acid lipase (LAL) deficiency.	A16
siltuximab	For the treatment of patients with multicentric Castleman's disease (MCD), a rare disorder similar to lymphoma (cancer of the lymph nodes).	L04
sodium oxybate	For the treatment of cataplexy associated with narcolepsy.	N07
sorafenib-1	For the treatment of patients with advanced renal cell carcinoma.	L01
Sorafenib-2	For the treatment of unresectable hepatocellular carcinoma.	L01
sorafenib-3	For the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DCT) that is refractory to radioactive iodine treatment.	L01
stiripentol	For the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.	N03
teduglutide	For the treatment of adults with short bowel syndrome (SBS) who need additional nutrition from intravenous feeding (parenteral nutrition).	A16
telotristat ethyl	For the treatment of carcinoid syndrome diarrhoea.	A16
tezacaftor-ivacaftor	For the treatment of cystic fibrosis in patients age 12 years and older.	R07
Thalidomide	In combination with melphalan and prednisone, as first line treatment of patients with untreated multiple myeloma, aged 65 years or over or ineligible for high dose chemotherapy.	L04
Thiotepa	In combination with other chemotherapy medicinal products: 1) with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;	L01

Molecule's name	Indication	ATC code
	2) when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.	
tisagenlecleucel-1	For the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.	L01
tisagenlecleucel-2	For the treatment of patients with diffuse large B-cell lymphoma, high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma who received two or more lines of systemic therapy.	L01
tolvaptan	To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).	C03
velaglucerase alfa	For long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease.	A16
venetoclax-1	As monotherapy for the treatment of patients with chronic Lyrnphocytic leukemia.	L01
venetoclax-2	In combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.	L01

8.7.3 Appendix 3

HTA outcomes in Canada and Scotland

	Canada		Scotland	
	Entire sample (N=116)		**Entire sample (N=116)**	
HTA recommendations on entire sample				
	%	**n**	**%**	**n**
Listed	2.6	3	10.4	12
Listed with restrictions	57.8	67	57.8	67
Do not list	20.7	24	15.5	18
No submission/do not list	2.6	3	9.5	11
Not assessed	16.4	19	6.9	8
N	**100**	**116**	**100**	**116**
P= 0.004 Fisher's exact = 0.004				
Type of restrictions for listed with restrictions outcomes				
	%	**n**	**%**	**n**
Clinical only	10.5	7	22.4	15
Economic only	9.0	6	46.3	31
Both clinical and economic	80.6	54	31.4	21
N	**100**	**67**	**100**	**67**
P< 0.001 Fisher's exact< 0.001				
Type of clinical restrictions for listed with restrictions outcomes				
	%	**n**	**%**	**n**
Population	19.7	12	77.8	28
Administration	1.7	1	0.0	0
Specialist prescription/care	9.5	6	16.7	6
Treatment initiation/continuation/ discontinuation	4.9	3	2.8	1
Multiple clinical restrictions	63.9	39	2.8	1
N	**100**	**61**	**100**	**36**
P<0.001 Fisher's exact<0.001				
Type of economic restrictions for listed with restrictions outcomes				
	%	**n**	**%**	**n**
Price reduction	86.7	52	0	0
Funding mechanism	0.0	0	100	52
Similar funding with therapeutic equivalents	11.7	7	0.0	0
Reimbursement only in some provinces	1.7	1	N/A	N/A
N	**100**	**60**	**100**	**52**
P<0.001 Fisher's exact<0.001				
Medicines with MA through (a) specialised pathways and (b) standard MA, (N=114)				
HTA recommendations (for medicines with MA through a specialised pathway)				
	%	**n**	**%**	**n**
Listed	2.8	2	6.7	3
Listed with restrictions	54.9	39	62.2	28
Do not list	18.3	13	6.7	3
No submission/do not list	2.8	2	13.3	6
Not assessed	21.2	15	11.1	5
N	**100**	**71**	**100**	**45**
P=0.042 Fisher's exact = 0.040				
HTA recommendations (for medicines with standard MA)				
	%	**n**	**%**	**n**
Listed	2.2	1	12.7	9
Listed with restrictions	62.2	28	54.9	39
Do not list	24.5	11	21.1	15
No submission/do not list	2.22	1	7.1	5
Not assessed	8.9	4	4.2	3

	Canada		Scotland	
N	**100**	**45**	**100**	**71**
P=0.185 Fisher's exact = 0.189				
Type of restrictions when outcome is listed with restrictions (for medicines with MA through a specialised pathway)				
	%	**n**	**%**	**n**
Clinical only	12.8	5	25.0	7
Economic only	7.7	3	42.9	12
Both clinical and economic	79.5	31	32.2	9
N	**100**	**39**	**100**	**28**
P<0.001 Fisher's exact<0.001				
Type of restrictions when outcome is listed with restrictions (for medicines with standard MA)				
	%	**n**	**%**	**n**
Clinical only	7.2	2	20.5	8
Economic only	10.7	3	48.7	19
Both clinical and economic	82.2	23	30.8	12
N	**100**	**28**	**100**	**39**
P<0.001 Fisher's exact<0.001				

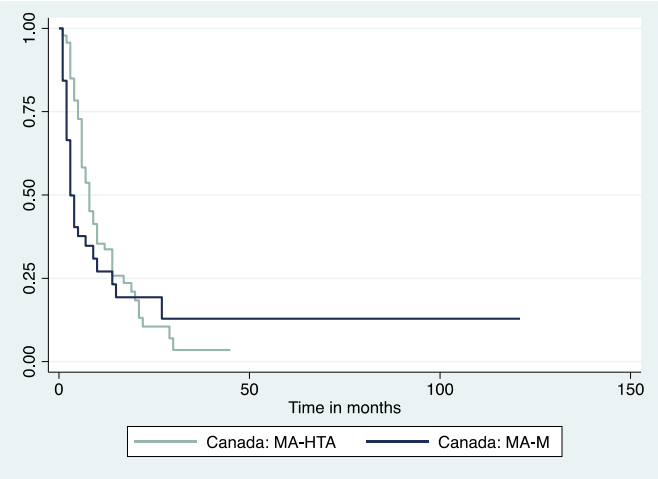
Main reasons for HTA recommendations in Canada and Scotland (all sample)

	Clinically effective	Cost-effective	Both clinically- and cost-effective	None
Canada, % (n)				
Listed	(0)	(0)	100% (3)	(0)
Listed with restrictions	83.6% (56)	3.0% (2)	7.5% (5)	6.0% (4)
Do not list	8.33% (2)	(0)	(0)	91.7% (22)
P<0.001 Fisher's exact<0.001				
Scotland, % (n)				
Listed	50% (6)	(0)	50% (6)	(0)
Listed with restrictions	86.2% (58)	1.5% (1)	4.5% (3)	7.5% (5)
Do not list	72.2% (13)	(0)	(0)	27.8% (5)
P<0.001 Fisher's exact<0.001				

8.7.4 Appendix 4

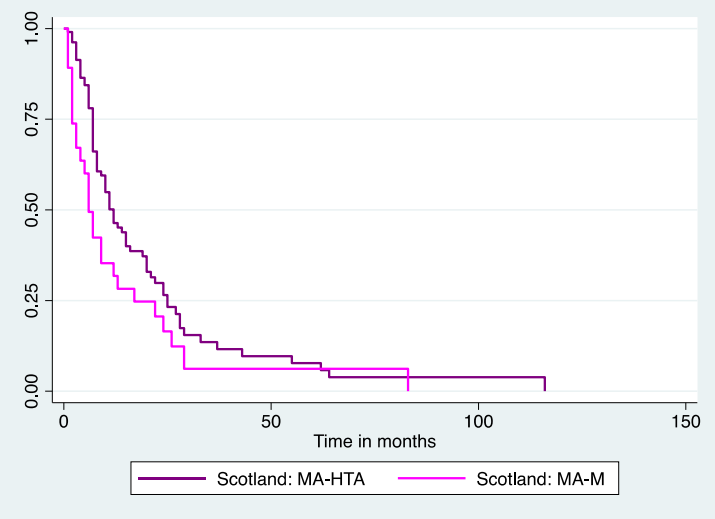
Time analysis 1: Time to market launch vs. time to a positive/restricted HTA recommendation

Canada: Market launch (M) dates were collected through the Drug Product Database (DPD) of Health Canada. All dates, but one, were available and recorded. From the 70 medicine indications pairs with a positive/restricted HTA recommendations, 6 were marketed later than the issue of the HTA recommendation.



Notes: *This data collection comes with the limitation that in the DPD database, we were not able to identify the exact indication the medicine was marketed for in Canada, in case of multiple indications. However, we were able to approximate the marketing date using the NOC date as a benchmark.*

Scotland: Market launch (M) dates were collected through SMC. From the 79 medicine indications pairs with a positive/restricted HTA recommendations, the availability date in SMC was not available for 8 medicine indication pairs. Only, three medicine was marketed later than the publication of the HTA recommendation.



In both countries, time from MA to market launch(M) occurred faster than the time from MA to positive/restricted HTA recommendations, except some few occasions. However, in Canada differences in time were smaller compared to Scotland.

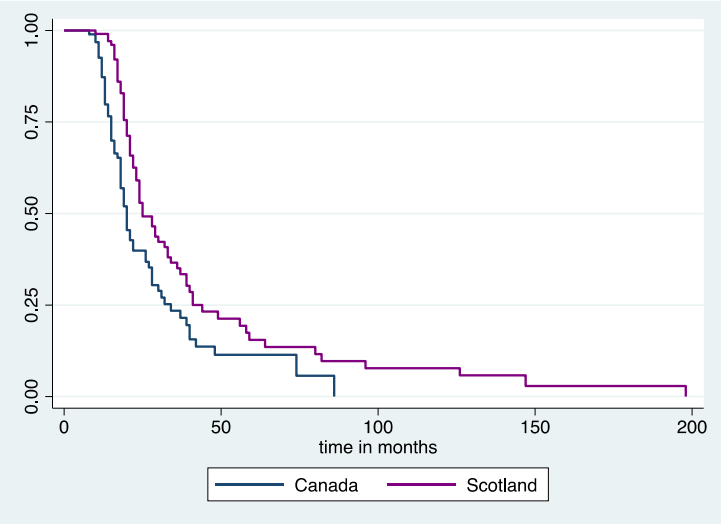
Time analysis 2: Time in months from MA application to the regulatory agency vs. time to a positive/restricted HTA recommendation

The date of submission for MA by the manufacturer to the regulatory body was extracted from the European public assessment reports (EPAR) in the EMA website for Europe and from the Drug and Health Product Register database of the Health Canada for Canada for the respective indication. Additional information was requested to and provided by the Information Dissemination Unit of the Pharmaceutical Drugs Directorate of Health Canada. Information was not found for 3 medicine-indication pairs in Europe, all of which had a positive/restricted HTA recommendations by SMC.

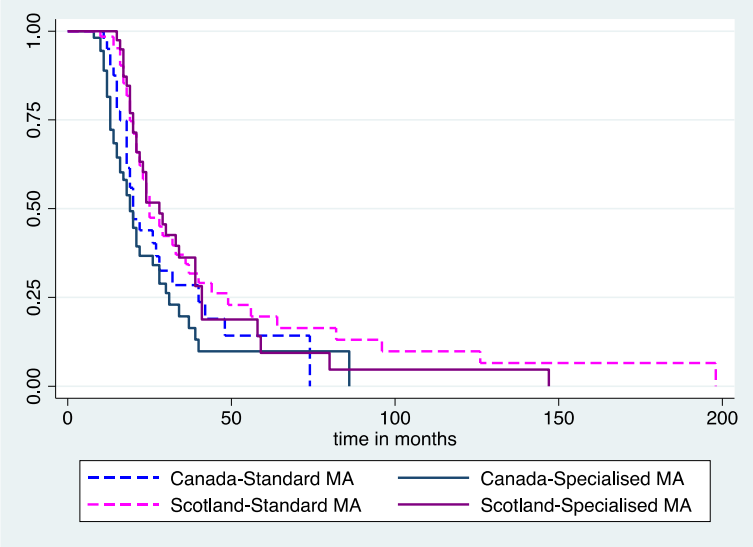
Similar to the results of the current study (where time to access is measured by the time of MA to market access defined a positive/restricted HTA recommendation), more time from MA application to positive/restricted HTA recommendations was observed in Scotland than Canada. However, in this time analysis, medicines which underwent MA through a specialised pathway had shorter timelines compared to those medicines with a standard MA approval and reached a positive/restricted HTA recommendation faster from the time of manufacturers' application for MA.

	Minimum	Maximum	Median
Canada	15	34	20
Scotland	20	44	25
Medicines with standard MA Vs. medicines with MA through specialised pathways			
Canada: Standard approval	16	40	20
Canada: Specialised MA pathway	13	31	19
Scotland: Standard approval	19	49	25
Scotland: Specialised MA pathway	20	41	28

Panel A: Time from MA application to a positive/restricted HTA recommendation for all the sample



Panel B: Time from MA application to a positive/restricted HTA recommendation for medicines undergoing MA through standard vs. specialised pathways



9 Do reimbursement recommendations by the Canadian Agency for Drugs and Technology in Health translate into coverage decisions for orphan drugs in the Canadian province of Ontario?

This study has been published in *Value in Health." Fontrier, A.M. and Kanavos, P., 2023. Do reimbursement recommendations by the Canadian Agency for Drugs and Technology in Health translate into coverage decisions for orphan drugs in the Canadian province of Ontario?. Value in Health, 26(7), pp.1011-1021."*

The text in this chapter has been slightly edited[13] to follow the flow of the thesis.

Key messages

- Recommendations by the Canadian Agency for Drugs and Technology in Health (CADTH) do not always translate to provincial coverage decisions for new drugs.
- We explored whether CADTH's recommendations are aligned with coverage decisions for orphan drugs in Ontario.
- Negative HTA recommendations did not necessarily translate to no pan-Canadian pricing negotiations.
- More than half the drugs with negative HTA recommendations were available in Ontario through specialised funds.
- A national strategy for orphan drugs could prioritise access to these treatments at a national level and harmonise access, at least to some extent, across Canada.

[13] The numerical ordering of tables and figures have been updated to follow the flow of the thesis, and the spell out of acronyms have been removed if acronyms have been explained previously.

Abstract

Objective: Unlike other high-income countries, Canada has no national policy for medicines treating rare diseases ('orphan medicines'). However, in 2022, the Canadian government committed to creating a national strategy to make access to these medicines more consistent. Our aim was to study whether recommendations made by the Canadian Agency for Drugs and Technology in Health (CADTH) translated into coverage decisions for orphan medicines in Ontario, the largest Canadian province. This study is the first to look at this question for orphan medicines which are at the centre of policy attention.

Methods: We included 155 orphan medicine-indication pairs approved and marketed in Canada between 2002 and 2022. Cohen's kappa was used to test agreement across HTA recommendations and coverage decisions in Ontario. Logistic regression was used to test which factors, relevant to decision-makers, might be associated with funding in Ontario.

Results: We found only fair agreement between CADTH's recommendations and coverage decisions in Ontario. Whilst a positive and statistically significant association between favourable HTA recommendations and coverage was found, more than half of medicines with a negative HTA recommendation were available in Ontario, predominately through specialised funds. Successful pan-Canadian pricing negotiations were a strong predictor of coverage in Ontario.

Conclusions: Despite efforts to harmonise access to medicines across Canada, considerable room for improvement remains. Introducing a national strategy for orphan medicines could help increase transparency, consistency, promote collaborations and make access to orphan medicines a national priority.

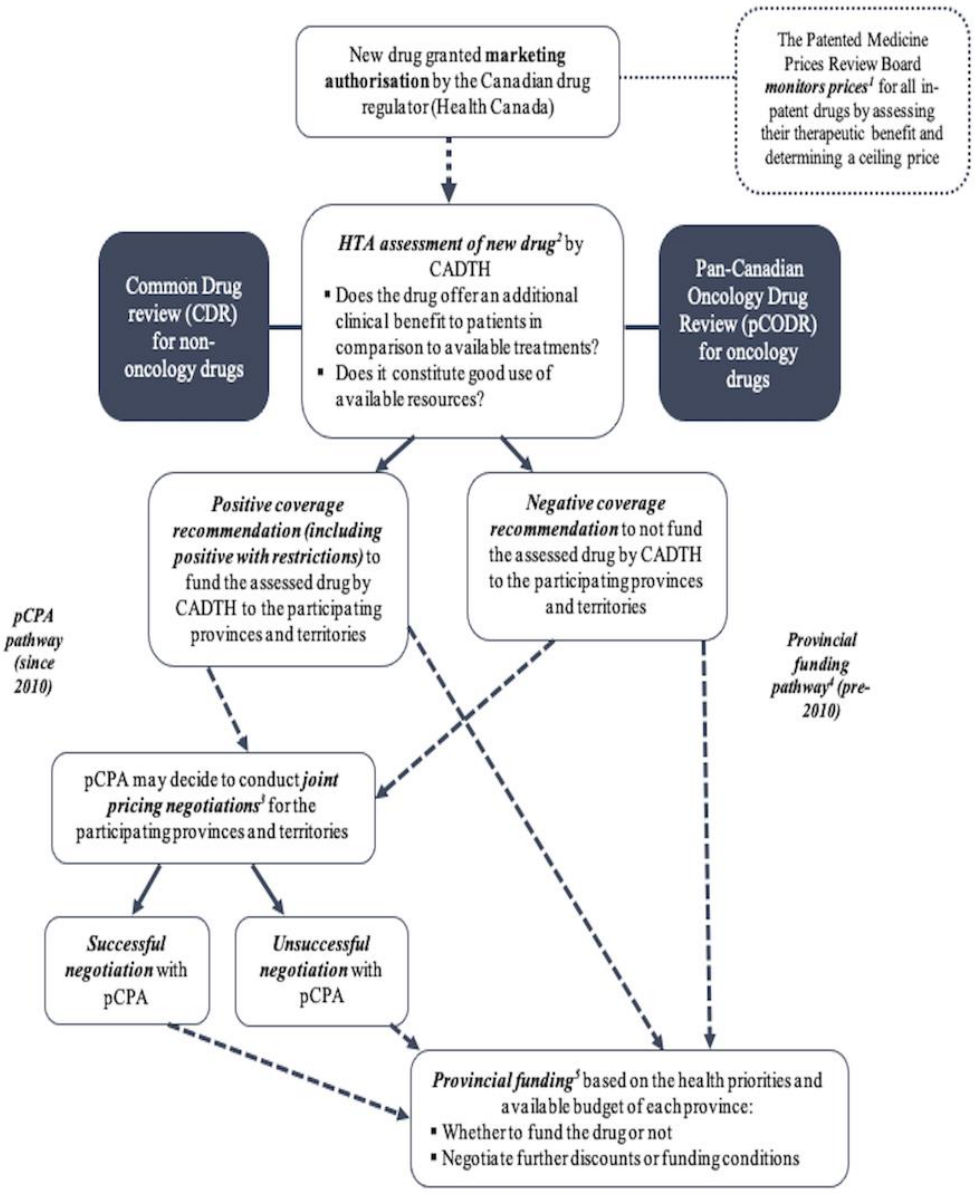
9.1 Background

Allocating resources in the context of limited budgets is one of the biggest challenges facing healthcare systems globally. Increases in pharmaceutical prices and associated expenditure further strain finite budgets, leaving decision-makers with tough coverage decisions (214). In Canada, pharmaceutical expenditure has increased by approximately CAD1 billion annually over the last decade (364). To optimise medicine expenditure, health technology assessment (HTA) is conducted through Canada's Drug and Health Technology Agency (CADTH). Since the early 2000s (365), CADTH has assessed newly approved medicines and provided coverage recommendations to the Canadian provinces and territories (apart from Quebec, which has its own HTA body). However, funding decisions remain a provincial competency.

There have been both national and provincial efforts to harmonise access to medicines across Canada: in August 2010, the pan-Canadian Pharmaceutical Alliance (pCPA) was established to perform joint pricing negotiations with manufacturers on behalf of participating provinces/territories, aiming to achieve a single medicine price across Canada (366,367). In 2016, a collaboration between CADTH and the pCPA was initiated to formally engage the pCPA during CADTH's assessments and ensure timely information exchange (368). Since April 2016, medicines assessed by CADTH are no longer required to undergo routine review by the Committee to Evaluate Drugs (CED) of the Ontario Ministry of Health (369,370).

Figure 16 summarises the pricing and reimbursement process for new medicines in Canada (excluding Quebec).

Figure 16: Pricing and reimbursement process for new medicines in Canada (excluding Quebec)



Notes: Dotted arrows indicate processes that might occur, but it is either upon the discretion of the competent authority or do not necessarily occur in routine basis.
[1]The Patented Medicine Prices Review Board monitors prices of in-patent drugs upon entry in the Canadian market and in an on-going basis. [2]CADTH assesses new drugs including drugs with a new indication, new combination products, new drug formulations and subsequent-entry non-biological complex drugs[9]. Not all drugs approved by Health Canada undergo assessment by CADTH. Assessment is initiated upon request of manufacturers or of drug programs.[3]Not all drugs reviewed by CADTH may undergo negotiations through the pCPA. After publication of a recommendation by CADTH(either positive or negative)[10], pCPA can decide whether to initiate a negotiation or not. Since 2015, Quebec is also participating in joint pricing negotiations by the pCPA. [4]Given that not all drugs will undergo negotiations through the pCPA, and it is on the discretion of the provinces/territories to participate or not in joint negotiations, provinces have the option to negotiate individually rather than jointly, after issue of HTA recommendation. Before the establishment of the pCPA, in 2010, this was the pathway followed. [5]Provinces are not mandated to follow the outcome of the pCPA negotiation or CADTH's recommendation. Funding remains a provincial competency[4,11,12]. Source: The author adapted by the literature [4,11,13–18]

Evidence has shown that the degree of alignment between CADTH's recommendations and coverage decisions varied across provinces and was dependent on whether HTA recommendations were positive (i.e.: listed and listed with restrictions) or negative (i.e.: do not list) (199,220,371–373). In Ontario, more than 90% of new medicines assessed by CADTH between 2009-2015 with positive recommendations were funded, while half of the medicines with negative recommendations still received funding (198,199,220). However, in British Columbia, fewer than the half of medicines with negative recommendations received funding (199).

9.1.1 The case of orphan medicines

Access variations are further highlighted in the case of orphan medicines. These medicines treat rare diseases (207) and usually carry high price tags despite their associated high clinical uncertainty (4,5). Therefore, in HTA terms, these medicines are generally cost-ineffective (4,13,23).

Contrary to other healthcare systems (23), Canadian national authorities do not treat orphan medicines differently than non-orphan medicines: the Canadian medicine regulator, Health Canada, does not offer orphan designation at marketing authorisation (MA), CADTH does not implement a specialised value assessment framework, and the pCPA does not apply special criteria during pricing negotiations. However, specialised funds for medicines of high unmet need and cost are available in the Canadian provinces.

Sub-group analyses on orphan medicines conducted by existing studies (198,220,310) showed larger variability in agreement between CADTH's recommendations and provincial funding, than the variability seen for non-orphan medicines. Other studies (207,367) showed that positive HTA recommendations did not necessarily translate to successful pricing negotiations for non-oncology orphan medicines, nor did they guarantee that provinces funded these medicines.

9.1.2 National strategy for medicines for rare diseases in Canada

The reasons why Canada has so far failed to implement a national orphan medicine strategy remains unclear. One contributing factor might be the presence of the Special Access Programme which allows patient access to non-approved medicines through clinical studies (214,216). In addition, Canada's close proximity to the United States (US) (where there is an orphan medicine regulation), might allow Canada to indirectly benefit from the increased research and development stimulus for orphan medicines seen in the US (214).

Currently, the Canadian government is trying to establish a national strategy for orphan medicines (217). The strategy aims to address the following issues: (i) how to improve access to these treatments and make access more consistent, (ii) how to ensure that funding decisions are informed

by the best available evidence, and (iii) how to ensure that spending on orphan medicines does not threaten the sustainability of the healthcare system (297,374,375). Even though funding for its materialisation has been secured (376), the national strategy remains in a developmental stage and the exact activities have not been outlined yet. However, key Canadian stakeholders have suggested some potential options that could be part of the national strategy. For example, they have called for a national framework for coverage decision-making, which will entail a single approach and common principles for deciding which orphan medicines should be publicly covered and under what conditions (i.e.: identifying patient populations that would be more likely to benefit from them (375)). In addition, stakeholders have suggested the establishment of a coordinating body that would improve communication and collaboration across all key Canadian stakeholders, and would provide a better evidence-base for decision-making through both consistent evidence collection (including infrastructure for collection of real-world evidence) and evaluation of a medicine's added clinical benefit (297,375,377). Finally, Canadian stakeholders have called for the explicit involvement of patients and clinicians in the decision-making process (297,374,374).

Given continuous efforts to harmonise access across Canada, our study is the first to explore whether CADTH's recommendations for orphan medicines translate into coverage decisions in Ontario, the most populous Canadian province. Unlike existing evidence that comes either from sub-group analyses or from studies with small sample sizes and/or limited timeframes (198,199,378), we used a large sample of orphan medicines approved and marketed in Canada between 2002 to 2022. Finally, to test what other factors might be associated with funding in Ontario, we performed a logistic regression analysis.

9.2 Methods

9.2.1 Sample selection

Given that Canada does not have an orphan designation nor an official definition of rare diseases (with the recent exception of Quebec (379)), we recognise that selecting a sample of orphan medicines in Canada comes with inherent limitations. To ensure that an appropriate sample of orphan medicines has been selected insofar possible, we used both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to account for differences in the jurisdictional definitions of rare diseases(203). Even though more commonality between Canada and the US may have been expected, both Health Canada and the Canadian Organization for Rare Disorders (217,296) unofficially use EMA's definition of rare disease (i.e.: a disease that affects <5 in 10,000 people (380)), rather than the FDA definition (i.e.: a rare disease affects <200,000 people of the general population (381)).

The sample selection process followed is similar to an earlier study (13) with adjustments based on this study's objectives. First, we identified all orphan medicines approved by the US FDA between January 2000 and December 2021 through the FDA Orphan Drug Product designation database, including first indication(s) at MA and extension of indication(s) with an orphan designation.

Second, we checked whether the set of FDA-approved orphan medicines-indications were granted an orphan designation by the EMA using the full list of the EMA's orphan designations and additional searches on the EMA website. As Canada unofficially uses the EMA's definition of rare diseases (217,296), we excluded medicine-indications pairs with no orphan designation in Europe. However, orphan medicine-indication pairs which were not approved by the EMA (but had been granted an orphan designation) were included in our sample: evidence has shown that more orphan medicines were granted MA by the FDA than the EMA (101). Medicine-indication pairs with a withdrawn or expired orphan designation in Europe were included to not limit the sample size.

Third, we checked whether the matched medicine-indication pairs were marketed in Canada (i.e.: were granted MA and were commercially launched according to the Health Canada's Drug Product Database). Medicine-indication pairs with no MA by Health Canada, medicines with a different approved indication than that of FDA and that granted an orphan designation by the EMA, and medicine-indication pairs which were not marketed in Canada (or were subsequently withdrawn from the market) were excluded.

Finally, the medicine-indication pairs which did not have a reimbursement review by CADTH, or for which there was no manufacturer dossier submission before June 2022 (when the data collection was completed), were excluded.

9.2.2 *Data collection and study variables*

MA: Information on whether the medicine-indication pairs had been granted standard MA or conditional MA and/or had undergone priority review at the time of approval was recorded through the Notice of Compliance-Drug Products database of Health Canada. Appendix 1 provides a detailed description of the two specialised pathways for MA.

HTA: Information on HTA recommendations, the main reasons for recommendation, the reported incremental cost-effectiveness ratio (ICER), the annual costs per patient, the date of HTA assessment, whether there has been an HTA re-submission and whether the medicine-indication treated patients younger than 18 years old was collected through the reimbursement reviews of CADTH for the most recent assessments (in cases of re-submissions).

Recommendations were categorised into: "list" (L); "list with restrictions" (LwR) and "do not list" (DNL). LwR recommendations were divided by clinical and economic restrictions and further subgroups, following the classification used in an earlier study (13) and by CADTH (293). Recommendations issued by both the Common Drug Review (CDR) and the pan-Canadian Oncology Drug Review (pCODR) have changed overtime (198), while CADTH harmonised all recommendations and procedures in 2020 (293). The main reasons for HTA recommendations were categorised following the classification used in an earlier study (13). Appendix 2 provides information on how the recommendations issued by CDR and pCODR have evolved and illustrates examples of the restrictions and main reasons for recommendation provided by CADTH.

For the logistic regression and the kappa analyses, HTA recommendations were grouped into: (i) positive HTA recommendation (including L and LwR), and (ii) negative HTA recommendation. The reported ICERs were grouped following the categorisation used in another study (318).

Pricing negotiations: The outcomes of pricing negotiations were extracted by the Brand Name Drug Negotiations Status database of the pCPA. Pricing negotiations were categorised in: (i) "successful negotiations" (i.e.: resulting in a letter of intent), (ii) "unsuccessful negotiations" (i.e.: when an agreement was not reached or when a negotiation was not pursued), and (iii) no information available (i.e.: when a medicine-indication pair was not found in the database (n=21) or when negotiations were active or under consideration at the time of data collection (n=13)). The negotiation status was recorded for the most recent negotiation (in cases of re-negotiations). For the logistic regression and the kappa analyses, negotiations with no information were recorded as "unsuccessful" as their outcomes were unknown.

Coverage: Information on funding status in Ontario was extracted from the general formulary database of the Ontario Drug Benefit Formulary/Comparative Drug Index, the drug formulary of the Cancer Care Ontario, the Ontario Drug Benefit Program, the Exceptional Access Program Reimbursement, the List of Disorders, Covered Drugs, and Supplements and Specialty Foods of the Inherited Metabolic Diseases Program. Additional searches were performed on the Ministry of Health of Ontario and the Ontario Public Drug Programs webpages.

Coverage decisions were grouped into (i) "funded" and (ii) "not funded". For funded medicine-indication pairs, we recorded whether the medicine-indication pairs were available through a specialised fund(s). Medicine-indication pairs suggested for limited use in the Ontario Drug Benefit Formulary were considered as "funded" (n=1).

Additional study variables: The 2nd level Anatomical Therapeutic Chemical code (ATC) was extracted using the ATC/DDD Index 2020 of the World Health Organisation Collaborating Centre to identify cancer and non-cancer indications and availability of therapeutic alternatives within our sample. We recorded whether a recall or safely alert has been issued using the Recalls and Safety Alerts database of Health Canada. To identify medicine-indication pairs designed to treat ultra-orphan diseases (prevalence of 1 in 50,000 or 2 in 100,000 (315–317)), we used the Prevalence and Incidence of Rare Diseases data from Orphanet (382). Finally, we recorded first-in-class medicines-indication pairs (i.e.: the first medicine approved within a therapeutic class or a medicine using new mechanisms of action (313,314)) using the FDA's Novel Drug Approvals reports and a previous study (314).

9.2.3 *Statistical analysis*

Descriptive statistics were used to analyse trends in HTA recommendations, outcomes of pricing negotiations, and coverage decisions in Ontario.

Cohen's kappa scores were used to test the level of agreement between (i) HTA recommendations and coverage decisions in Ontario; (ii) HTA recommendations and outcomes of pricing negotiations; and (iii) outcomes of pricing negotiations and coverage decisions in Ontario. Results were interpreted following the Landis and Koch (1977) benchmark scale (305).

We performed a binary logistic regression analysis to test the relationship between coverage decisions in Ontario (dependent variable) and various covariates relevant to decision-makers (318). These included: (i) HTA recommendation; (ii) whether the medicine-indication pairs had a conditional MA or (iii) had undergone priority review, given that these medicines are responding to high unmet need and, therefore, likely to be prioritised for coverage; (iv) whether the medicine-indication pairs were first-in-class, as a proxy for market competition; (v) whether there has been a recall or safety alert given that this might trigger de-listing (however, evidence from 2015 showed that serious safety alerts did not have an impact on funding status in Ontario (319)); (vi) whether the medicine-indication pairs had a cancer indication, as cancer medicines are assessed by a different committee (pCODR) within CADTH; (vii) whether the medicine-indication pairs were used to treat paediatric patients; (viii) whether they are considered ultra-orphan, as decision-makers might show greater flexibility; (ix) whether there has been an HTA re-submission, which usually is triggered when additional evidence has been generated to revert previously negative recommendations; (x) whether pricing negotiations by the pCPA were successful or not, and; (xi) the ICER reported by CADTH as funding of orphan medicines can be sensitive to the medicine's

cost-effectiveness (318). To account for other factors that might influence our dependent variable we controlled for (i) the year of the HTA recommendation and (ii) the year of MA, as changes in the assessment processes or administrative changes might have occurred over time.

Finally, to test the robustness of our results, we performed a sensitivity analysis exploring the impact of therapeutic alternatives within our sample, and the annual medicine costs per patient on funding in Ontario. A description of how we estimated annual medicine costs, when unavailable by CADTH, is presented in Appendix 3.

Chi-square and Fisher's exact tests were used to test statistical significance with a p-value of ≤0.05 indicating statistical significance. All data analysis was performed using STATA SE.17.

9.3 Results

155 medicine-indication pairs were included in our sample. Figure 17 outlines the results of the sample selection process.

Figure 17: Flow chart of sample selection

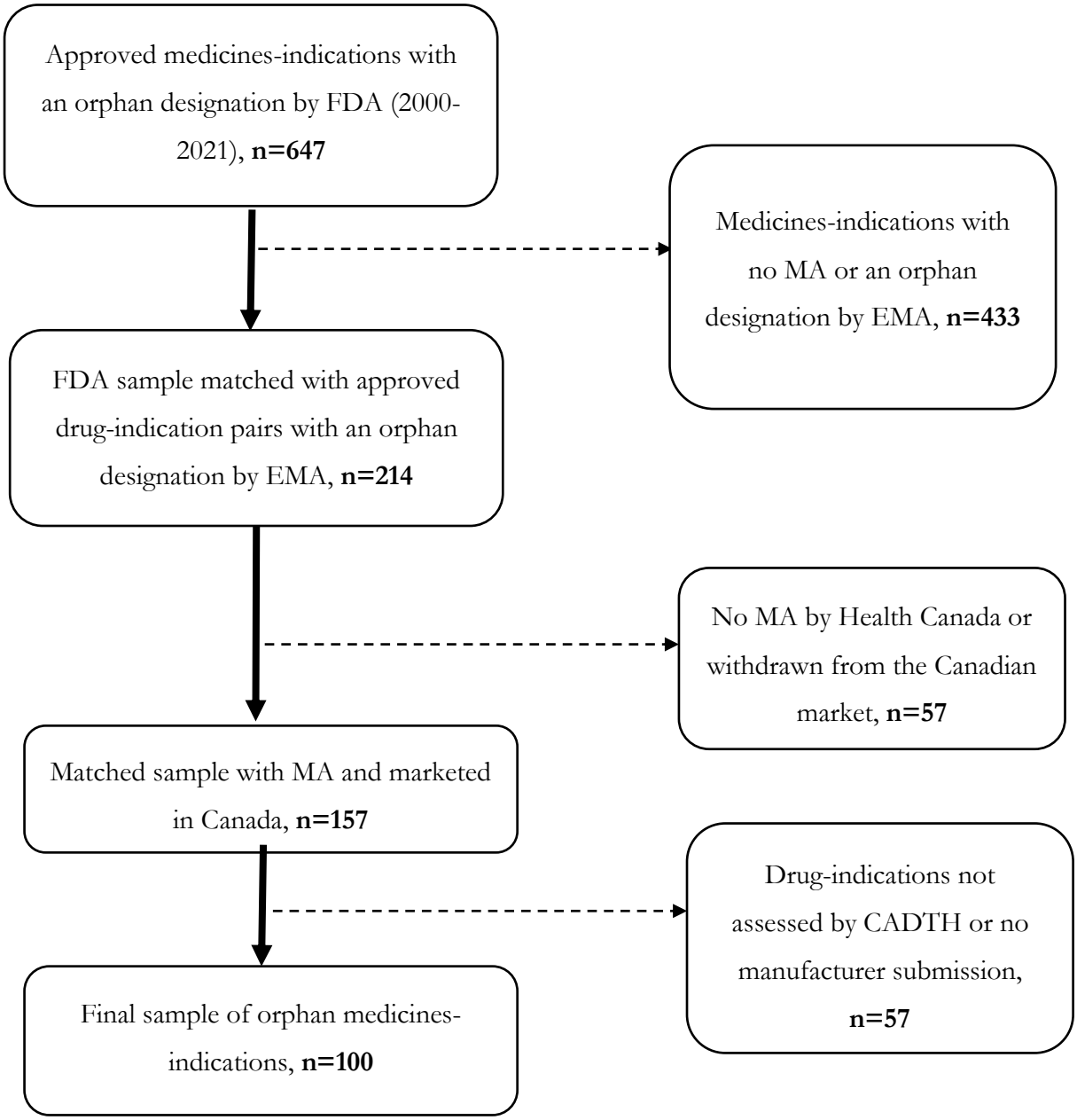


Table 16 summarises the sample characteristics and the results of HTA recommendations, outcomes of pricing negotiations, and coverage decisions in Ontario across our sample. Appendix 4 provides information on these results for different sub-groups including medicine-indication pairs treating cancer, ultra-rare diseases and first-in-class medicines.

Table 16: Sample characteristics and descriptive statistics results

Sample characteristics	n	%
Cancer indication	71	45.81
Treating patients <18 years old	40	25.81
Ultra-orphan	64	41.29
First-in-class	61	39.35
Specialised marketing authorisation[1]	92	59.35
Conditional marketing authorisation	25	16.13
Priority review at marketing authorisation	70	45.16
HTA re-submission	18	11.61
HTA recommendations		
Positive HTA recommendation (L&LwR)	122	78.71
Negative HTA recommendation	33	21.29
Listed (L)	3	1.94
Listed with restrictions (LwR)	119	76.77
Do not list (DNL)	33	21.29
HTA recommendations (for kappa and regression analyses)		
Positive HTA recommendation (L&LwR)	122	78.71
Negative HTA recommendation	33	21.29
Type of restrictions for LwR recommendations		
Clinical only	11	9.24
Economic only	4	3.36
Both clinical and economic	104	87.39
Type of clinical restrictions for LwR recommendations		
Population	15	13.04
Administration	1	0.87
Specialist prescription/care	10	8.7
Treatment initiation/continuation/discontinuation	5	4.35
Multiple clinical restrictions	84	73.04
Type of economic restrictions for LwR recommendations		
Price reduction to improve cost-effectiveness	99	91.67
Similar funding with therapeutic equivalents	8	7.41
Reimbursement only in some provinces	1	0.93
Incremental cost-effectiveness ratio (ICER)		
< CAD50,000/QALY	7	4.52
CAD50,000-CAD175,000/QALY	39	25.16
CAD175,000-CAD500,000/QALY	38	24.52
> CAD500,000/QALY	45	29.03

Not reported	26	16.77
Outcomes of pricing negotiations		
Successful	102	65.81
Unsuccessful	19	12.26
No information[2]	34	21.94
Outcomes of pricing negotiations (for kappa and regression analyses)		
Successful	102	65.81
Unsuccessful	53	34.19
Coverage decisions in Ontario		
Funded	112	72.26
Do not fund	43	27.74

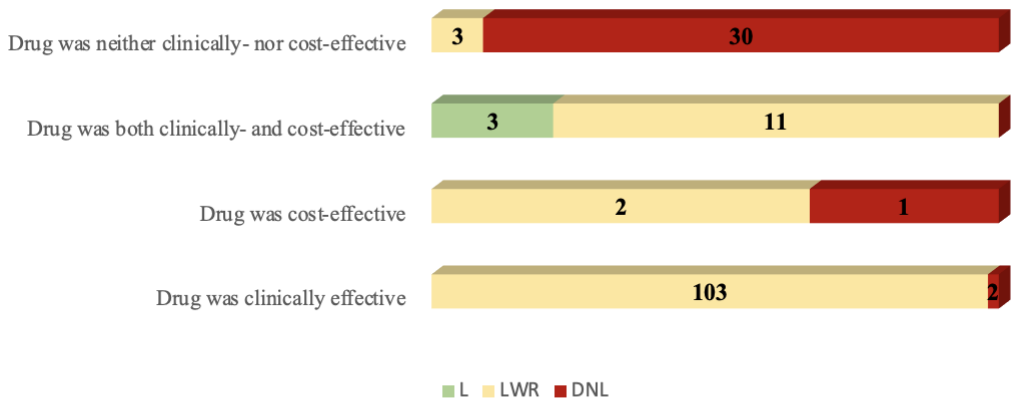
Note: *[1]Three medicine-indication pairs had both conditional marketing authorisation and undergone priority review.*

[2]It is important to highlight that the medicine-indication pairs not found in the pCPA database had been assessed by CADTH between 2004 to 2022. Therefore, the lack of data in the pCPA database cannot necessarily be attributed to pCPA's establishment in August 2010. In addition, pricing negotiations (either successful or not) have been recorded in our sample for medicines assessed prior to August 2010.

9.3.1 *HTA recommendations issued by CADTH*

HTA recommendations are summarised in Table 1 and the main reasons for recommendations per HTA outcome are presented in Figure 18.

Figure 18: Main reason for recommendation across HTA outcomes by CADTH



Notes: Data labels show the number of drug-indication pairs.
Abbreviations: CADTH: Canadian Agency for Drugs and Technologies in Health; L: Listed; LwR: Listed with restrictions; DNL: Do not list

9.3.2 Pricing negotiations conducted by the pCPA

Outcomes of the pricing negotiations by the pCPA are summarised in Table 1.

9.3.2.1 HTA and pricing negotiations

From the medicine-indication pairs with a positive HTA recommendation (both L and LwR) (n=122), 78% (n=95) resulted in successful pricing negotiations while only 3% (n=4) resulted in unsuccessful negotiations.

From the medicine-indication pairs with a negative HTA recommendation (n=33), 46% (n=15) resulted in an unsuccessful pricing negotiation. However, 21% (n=7) still resulted in successful pricing negotiations (p and fisher's exact ≤ 0.01).

9.3.3 *Coverage decisions in Ontario*

Coverage decisions in Ontario are summarised in Table 1. Appendix 5 provides information on the orphan medicine-indication pairs funded in Ontario and the specialised funds these medicines are available through.

9.3.3.1 HTA and coverage in Ontario

Ninety-five medicine-indication pairs (78%) with a positive recommendation by CADTH (including L and LWC) and 17 medicine-indication pairs (52%) with a negative recommendation were funded in Ontario (p and fisher's exact ≤ 0.01).

Twenty-seven medicine-indication pairs with a LwR HTA recommendation (23%) and 16 with DNL HTA recommendation (49%) did not receive funding in Ontario (p and fisher's exact ≤ 0.01).

9.3.3.2 DNL HTA recommendations with coverage in Ontario (n=17)

In 15 cases out of the 17 medicine-indication pairs with DNL recommendations but funded in Ontario, CADTH could not deem them as either clinically- or cost-effective. Fourteen medicine-indication pairs had undergone assessment prior to April 2016 when Ontario stopped routine assessments for medicines assessed by CADTH. However, we were able to identify only three value assessment reports from the Ontario Ministry of Health which included both the CED's recommendations and the decision of the Executive Officer. One medicine-indication pair had initially an unfavourable recommendation from the CED because it was not considered good value for money. However, the Executive Officer decided to reimburse the medicine-indication pair in question as it underwent review through the Ontario's Drugs for Rare Diseases evaluation framework (311,312). The other two medicine-indication pairs both had a favourable funding recommendation by the CED and a favourable funding decision by the Executive Officer. Examples of the language used in these reports are presented in Appendix 2.

Four (out of 17) had an unsuccessful pricing negotiation by the pCPA and five had a successful negotiation. For the remaining eight, information was not found in the pCPA database.

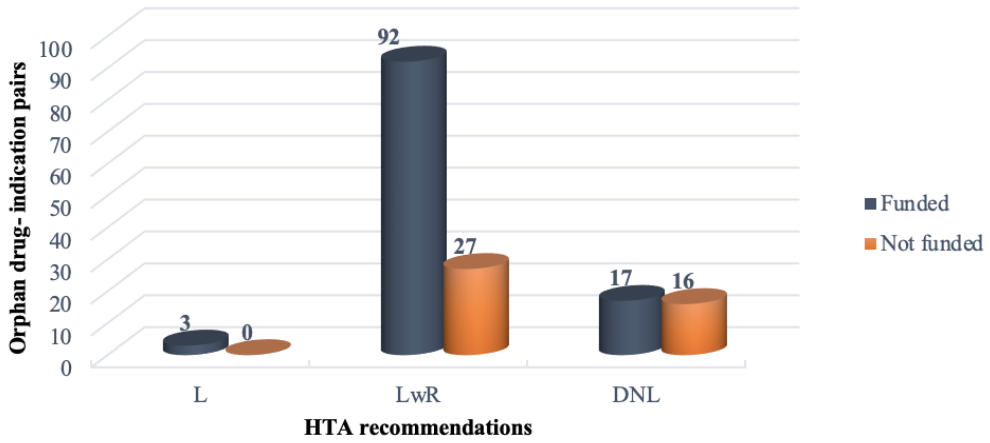
Seven of the 17 DNL medicine-indication pairs treated ultra-rare diseases, five treated paediatric patients and 12 were first-in-class. Most of these medicine-indication pairs (n=13 out of 17) were available through the Exceptional Access Program.

9.3.3.3 Positive HTA recommendations with no coverage in Ontario (n=27)

From the 27 medicine-indications pairs with LwR HTA recommendations not funded in Ontario, CADTH deemed that all of them had a significant clinical benefit but were not cost-effective. In 26 cases, both clinical and economic restrictions were suggested by CADTH. Ten had successful pricing negotiations, four had unsuccessful negotiations, and eleven had an active negotiation status. Ten of the pairs treated ultra-rare diseases, seven targeted paediatric patients and nine were first-in-class.

Figure 19 showcases coverage in Ontario across different HTA recommendations.

Figure 19: Coverage decisions in Ontario by HTA recommendation (p=0.01)



Notes: Data labels show the number of drug-indication pairs.
Abbreviations: L: Listed; LwR: Listed with restrictions; DNL: Do not list

9.3.3.4 Pricing negotiations and coverage in Ontario

From 102 medicine-indication pairs with successful pricing negotiations, 88% (n=90) received funding in Ontario while 12% (n=12) did not (p and fisher's exact ≤ 0.01). From the 19 medicine-indication pairs with unsuccessful pricing negotiations, 21% (n=4) were funded in Ontario and

79% (n=15) were not. From the 34 medicine-indication pairs for which the outcome of the pCPA negotiation was not found or negotiations were still active, 18 were funded in Ontario (53%) and 16 were not (47%). The two medicine-indication pairs (from the 34) which had an active negotiation status by the pCPA were already funded in Ontario.

9.3.4 *Level of agreement*

(i) HTA and pricing negotiations

There was moderate agreement between HTA recommendations and the outcomes of pCPA negotiations (kappa= 0.464), while the degree of concordance (i.e.: proportion of the same HTA recommendations and outcomes of pricing negotiations) was 78% ($p \leq 0.01$).

(ii) HTA and coverage in Ontario

There was fair agreement between HTA recommendations and coverage decisions in Ontario (kappa= 0.237) and the degree of concordance was 72% ($p \leq 0.01$).

(iii) Pricing negotiations and coverage in Ontario

There was moderate agreement between the outcomes of pCPA negotiations and coverage decisions in Ontario (kappa= 0.4894). The degree of concordance was 78% ($p \leq 0.01$).

9.3.5 Association between coverage decisions in Ontario and covariates

Table 17 summarises the results of the logistic regression analysis. Receiving funding in Ontario was increasingly likely, and statistically significant, to occur when there was a successful pricing negotiation by the pCPA (OR=17.23 [95% CI: 3.77, 78.73], $p \leq 0.0001$), and when a positive HTA recommendation had been issued by CADTH (OR=7.25 [95% CI: 1.11, 47.33], p=0.04).

Funding in Ontario was also likely when a medicine-indication pair had received conditional MA, underwent priority review, and had a cancer indication. Contrary, first-in-class and ultra-orphan medicine-indication pairs were less likely to receive funding in Ontario. However, all these results were not statistically significant.

Table 17: Results of the logistic regression model of predictors of funding in Ontario

Variables	p value	Odds ratio (OR)	Lower	Upper
Successful pCPA pricing negotiation	≤0.001****	17.23	3.77	78.73
Positive HTA recommendation	0.04*	7.25	1.11	47.33
Conditional MA	0.14	4.70	0.60	36.82
Priority Review MA	0.09	2.46	0.87	6.97
Cancer indication	0.08	3.42	0.88	13.33
Paediatric indication	0.40	1.71	0.49	5.95
Ultra-rare indication	0.67	0.79	0.27	2.32
First-in-class	0.36	0.54	0.14	2.02
Safety recall and alerts	0.54	2.15	0.19	23.75
Cost-effectiveness ratio				
< CAD50,000/QALY	Reference			
CAD50,000 to CAD175,000/QALY	0.05*	0.13	0.02	0.96
CAD175,000 to CAD500,000/QALY	0.05*	0.12	0.01	1.02
≥ CAD500,000/QALY	0.12	0.24	0.04	1.41
Not reported[1]	0.12	0.12	0.01	1.70
With an HTA re-submission	0.23	0.25	0.03	2.41
MA year	0.93	0.98	0.54	1.75
HTA year	0.09	0.61	0.34	1.07

Notes:
*p ≤ 0.05;****p≤ 0.0001
[1]: CADTH did not report the cost-effectiveness ratio for 27 medicine-indication pairs in our sample.
Pseudo R2 = 0.4550
Abbreviations: HTA: Health Technology Assessment; MA: Marketing Authorisation; QALY: Quality adjusted life years

9.3.5.1 Sensitivity analysis

Our results did not change significantly in the sensitivity analysis. However, the likelihood of receiving funding in Ontario for medicine-indication pairs with a conditional MA or those who had undergone priority review was statistically significant. Results of the sensitivity analysis are presented in Appendix 6.

9.4 Discussion

We found that positive HTA recommendations were a good predictor of funding in Ontario for orphan medicines. However, we observed only fair agreement between CADTH recommendations and coverage decisions in Ontario. Our results broadly align with older studies in Canada on non-orphan medicines (198,199,220,371,373). However, they are not aligned with the results of a more recent study (383), which showed a substantial agreement between recommendations by CADTH's CDR and listing decisions in Ontario for non-orphan medicines. In comparison to older studies (198,199,220,371,373) , our percentage agreement was higher, signalling that efforts to improve alignment between HTA recommendations and funding decisions in Canada might have been successful to some extent.

Similar to other studies in non-orphan medicines, more than half (52%) of the medicine-indication pairs with a negative HTA recommendation were available in Ontario, predominately through specialised funds. Even though these medicines received DNL recommendations, pan-Canadian pricing negotiations were held, and these medicines received funding in Ontario. Interestingly, most of these medicine-indication pairs were deemed as neither clinically- nor cost-effective by CADTH, while some of them also had unsuccessful pricing negotiations by the pCPA. Therefore, a question arises as to how medicines that have not shown a significant therapeutic benefit and have not gone through successful pricing negotiations are still being offered to patients in Ontario.

This might be due to the ability of each province to decide whether to fund a medicine considering their budget, health priorities and needs, and the possibility to further negotiate prices and conditions of use. In addition, Ontario, like some other Canadian provinces (i.e.: Alberta and Quebec), implements its own value assessment framework to evaluate orphan medicines in alignment with its strategic priorities (384,385). Medicines eligible for review, through the Ontario framework, include those which: (i) treat a disease with incidence rate of <1 in 150,000 live births or new diagnoses annually, and (ii) demonstrate no availability or feasibility of adequately powered randomized controlled trials (201,386). Available clinical evidence is then assessed to establish the added clinical benefit while identifying patients that are likely to benefit the most from the

treatment. Therefore, conditions of medicine use are more limited and efficient for the local context (310–312). However, cost-effectiveness is not used as a criterion during assessments (318,386). Therefore, recommendations through this framework are expected to differ from those issued by CADTH. In addition, the Ontario value assessment framework differs from frameworks implemented in other provinces, such as in Alberta (310).

Positive HTA recommendations did not always translate to successful pricing negotiations by the pCPA or funding in Ontario. This finding was only broadly in line with previous findings for non-oncology orphan medicines in Canada (207,367). However, in our sample, the percentage of positive HTA recommendations with unsuccessful pricing negotiations was still very low (3.28%). This was further highlighted in both the kappa and regression analyses: the pCPA pricing negotiations with both HTA recommendations and coverage in Ontario showed moderate agreement. Successful pan-Canadian pricing negotiations were the strongest predictor of coverage in Ontario. However, we still observed medicines with unsuccessful or absent/incomplete pricing negotiations that received funding in Ontario. This is in line with previous studies highlighting that Ontario, as the most populous province, has the greatest negotiation power and a larger proportion of medicines funded through the use of product listing agreements when compared to other provinces (198,310,372).

There is international debate on whether specialised processes for orphan medicines should exist (4,5,14,22,23,71,80,207,213,218,226,227,353). Based on our findings, we can only conclude that a national strategy for orphan medicines in Canada is needed to alleviate 'postal-code lottery' and make access to orphan medicines a national priority. Bearing in mind that these very costly treatments can add tremendous financial pressures to provincial budgets and threaten the sustainability of the healthcare system, better uptake of HTA recommendations should be ensured and further contingency steps should be adopted.

First, Canada could benefit from a single definition of rare diseases. Currently, different orphan medicines are subject for assessment through provincial specialised frameworks, which could immediately result in access variations. Second, in line with the suggestions of Canadian stakeholders (377), a national and systematic approach for the value assessment of orphan medicines (post-approval) could be a part of a national framework for more consistent coverage decision-making across Canada. Taking into account that orphan medicines are inherently different than medicines treating more common diseases, value assessment could further consider that the balance between their potential benefits and funding risks will be different than that of

medicines for more common diseases (375). A national approach to collecting and assessing real-world evidence could also be paramount to complement limited clinical evidence and assist in assessments on whether the added therapeutic benefit of orphan medicines, when used in a real-world setting, could outweigh the associated costs and risks. Clinical evidence could be further supplemented through the explicit and consistent involvement of patients and clinicians during value assessments and coverage decision-making. However, it is important to highlight that involved patient groups should have no potential conflicts of interest. By having a national approach for the assessment of orphan medicines, increasing reliance on real-world evidence, and involving patients and clinicians more explicitly, issues around clinical uncertainty could be effectively addressed and clinical conditions regarding the use of these medicines could be homogenised across provinces. Previous evidence suggested that provincial criteria for the use of orphan medicines are not always consistent with the clinical restrictions suggested by CADTH (387), contributing further to access variations. Third, it would be beneficial for all provinces/territories to actively participate in the national strategy for orphan medicines to contribute to cooperative work and knowledge sharing, potentially through the establishment of a co-ordination body as suggested by key Canadian stakeholders (375). Similarly, active participation of all jurisdictions/territories during joint pricing negotiations could further increase their negotiating power and lead to higher price reductions (currently, only one or two jurisdictions or the pCPA, as a representative of participating jurisdictions, may take the lead during price negotiations (366,388)). Fourth, better alignment in the efforts of all the involved authorities (i.e.: Health Canada, CADTH, pCPA and the provincial Ministries of Health) could be encouraged through joint initiatives to increase consistency, information exchange, and timely access, and ensure that efforts to optimise access are successful across the access pathway (from MA to coverage decisions). Examples of such initiatives are the parallel review process (which allows HTA to commence prior to MA approval), as already seen in Canada, or the new HTA interim acceptance decision in Scotland for medicines granted a conditional MA (13). Finally, having consistent and clear pre-specified criteria for funding decision-making of orphan medicines across all provinces could alleviate access discrepancies and increase transparency in the decision-making. For instance, stakeholders would have a better understanding on how HTA recommendations are being used, and to what extent they inform pricing negotiations and coverage decisions. However, we remain partly sceptical on having common funding decisions for orphan medicines across Canada: first, due to the decentralised nature of the Canadian healthcare system and differences in the available local resources, and second, due to potential inter-jurisdictional variations in the needs

of patients (310) which might result in undue pressures on certain provinces to fund therapies, that might not be required simply due to epidemiological reasons.

9.4.1 *Limitations*

First, our sample might not be as accurate and inclusive as possible given that Canada has no orphan designation nor an official definition of what is considered a rare disease (203). However, by using both the FDA and the EMA definition of rare diseases, we tried to control for jurisdictional differences in the definitions used and any potential limitations that might have arisen by only comparing Canada with either Europe or the US. Second, medicine-indication pairs with an active pCPA negotiation at the time of data collection were categorised as unsuccessful for the kappa and regression analyses as we were unaware of their outcomes. Third, our study focused on coverage using public resources, and so coverage of these medicines through private health insurance was not captured. Fourth, to establish associations between HTA recommendations and coverage decisions, we controlled for covariates that were relevant to decision-makers and, in our opinion, were more likely to have an impact on funding. However, other system- and macro-factors might have an impact on coverage outcomes. Finally, our sample is limited to orphan medicines and one Canadian province. A lack of a control group of non-orphan medicines and other provincial coverage decisions did not allow us to explore whether the orphan status of medicines and/or the province in question might have had an impact on the associations seen in our results.

9.5 Conclusion

There was only fair agreement between CADTH's recommendations and coverage in Ontario. Whilst positive HTA recommendations were strongly associated with coverage in Ontario, a negative HTA recommendation did not necessarily result in no pan-Canadian pricing negotiations and no funding in Ontario. As available budgets and health priorities may vary across provinces, the introduction of a national strategy for orphan medicines could harmonise, at least to some extent, access to these treatments across Canada.

9.6 Appendices

9.6.1 Appendix 1

Conditional marketing authorisation and priority review by Health Canada

Conditional marketing authorisation (known as notice of compliance with conditions) may be granted for medicine products which treat serious, life-threatening or severely debilitating diseases, and have no alternatives available in the market with a similar therapeutic profile or demonstrate a significant improvement in the benefit/risk profile over alternate therapies(110). Even though these medicines might have limited clinical data, they should show a promising clinical benefit beyond an acceptable safety profile. The aim of conditional marketing authorisation is to allow for earlier marketing authorisation submissions than normally and facilitate earlier access to patients. Manufacturers who have been granted conditional marketing authorisation should pursue enhanced post-market monitoring and carry out confirmatory trials to prove the clinical benefit of the medicine and fulfil the conditions of the marketing authorisation (110).

Priority review shortens review timelines compared to non-priority reviews by prioritising marketing authorisation assessments. However, assessments follow the same criteria and requirements as non-priority reviews. Eligible medicines are intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses or conditions and they have no alternatives available in the market with a similar therapeutic profile or they demonstrate a significant improvement in the benefit/risk profile over alternate therapies (111).

9.6.2 Appendix 2

The evolution of the Common Drug Review and the pan-Canadian Oncology Drug Review

In August 2003, the permanent Common Drug Review (CDR) was established, and new medicines were assessed at pan-Canadian level (except for Quebec) through a single process. In 2011, the pan-Canadian Oncology Drug Review (pCODR) was established to assess new oncology medicines(389). Since its introduction, pCODR has been using the following recommendation scale: List (full approval); List with conditions (conditional approval), and; Do not List (rejection)(389). List with conditions recommendations is suggested by pCODR when the medicine could potentially be reimbursed subject to some conditions to be fulfilled such as price reductions or use in certain populations that are not specified by the marketing authorisation indication(389–391). Similarly, the CDR was using a similar recommendation scale according to their framework that was made available publicly in 2012(198). However, an additional recommendation "Do not list at the submitted price" was used for medicines that were showcasing a significant clinical benefit but were not deemed cost-effective. Prior to 2012, this category was falling into the "Do not list" recommendations(198). Since 2020, CADTH harmonised CDR and pCODR procedures using the same recommendations scale for both oncology and non-oncology medicines. Information on the description of recommendations and reimbursement conditions can be found in the Procedures for CADTH Reimbursement Reviews Report (293). In our study the three recommendations used currently by CADTH were used for our recommendations categorisation which include: 1) List; 2) List with restrictions (including clinical and economic conditions), and 3) Do not list.

A. Examples of language used by CADTH for clinical and economic restrictions and main reasons for recommendation

<u>Restrictions</u>

Example	
Active substance	Azacytidine
Brand name	Onureg
Indication	Maintenance therapy in adult patients with acute myeloid leukemia (AML) who achieved complete remission (CR) or complete response with incomplete blood recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation (HSCT).

Clinical Restrictions:

Onureg should only be covered to treat adult patients (at least 18 years of age) with newly diagnosed AML who have certain genetic changes that lead to greater risk of having unfavourable disease outcomes (i.e.: intermediate- or poor-risk cytogenetics) and who are ineligible for HSCT. **(Population restriction)**

Patients eligible for reimbursement of Onureg must have achieved first remission (defined as CR or CRi) following induction with or without consolidation chemotherapy, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3, and adequate organ function. **(Population restriction)**

Onureg should only be reimbursed if prescribed by clinicians with expertise managing patients with AML, familiarity with Onureg's toxicity profile exists. **(Specialist prescription/care)**

➔ **Classification:** Multiple clinical restrictions

Economic Restrictions:

Onureg should only be reimbursed if prescribed by clinicians with expertise managing patients with AML, familiarity with Onureg's toxicity profile exists, and its cost is reduced. **(Price reduction)**

➔ **Classification:** Price reduction

Main reasons for recommendation for Onureg:

"Clinical trial evidence demonstrated that, compared with placebo, Onureg prolongs overall and relapse-free survival and has a manageable toxicity profile".

"Based on public list prices, Onureg is not considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to best supportive care (BSC). A price reduction of at least 85% is needed to ensure Onureg is cost effective at this threshold. Structural issues within the pharmacoeconomic model introduced a bias in the results, meaning that a greater price reduction is likely needed"

➔ **Classification:**

Improvement in the clinical benefit: Yes

Optimal cost-effectiveness: No

Other examples of the language used in the main reasons for recommendation

(i) **Improvement in the clinical benefit**: *"The committee made this recommendation because it was satisfied that there is a net clinical benefit of the addition of the treatment in this patient population compared with placebo based on a statistically significant and clinically meaningful improvement in overall survival".*

(ii) **Optimal cost-effectiveness**: "*The committee concluded that based on the submitted economic analysis and the submitted price the treatment is cost-effective in patients compared with standard of care".*

(iii) **Achievement of both clinical and cost-effectiveness:** Mention of both previous examples.

(iv) **Failure to achieve both clinical and cost-effectiveness** : "*Although two double-blind, randomized controlled trials (RCTs) demonstrated that treatment was associated with statistically significant absolute improvements in percent predicted forced expiratory volume in one second (ppFEV1) compared with placebo, the magnitude of improvement was of uncertain clinical significance"…* and "Based on public list prices, the treatment is not considered cost-effective at a willingness-to-pay

threshold of $50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to best supportive care (BSC). A price reduction of at least 85% is needed to ensure that the treatment is cost effective at this threshold. Structural issues within the pharmacoeconomic model introduced a bias in the results, meaning that a greater price reduction is likely needed."*)* (13)

B. Examples of decisions by the Committee to Evaluate Drugs (CED) and the Executive Officer decisions of Ontario

Example	
Active substance	Idursulfase
Brand name	Elaprase
Indication	Treatment of Hunter syndrome (Mucopolysaccharidosis II, MPS II)

CED recommendation: *"The CED recommended that idursulfase (Elaprase) not be funded through the Ontario Public Drug Programs. Although preliminary data show that the medicine demonstrates biological activity, there is no evidence of meaningful benefits (such as improvements in survival, pain, physical function or quality of life). Moreover, the cost of treatment is extremely high."*

Executive Officer decision: *"Based on the review of Hunter Syndrome and idursulfase (Elaprase) through the Drugs for Rare Diseases (DRD) evaluation framework, the Executive Officer has decided to fund idursulfase (Elaprase) through Ontario Public Drug Programs for specific sub-groups of patients."*

9.6.3 Appendix 3

Annual medicine costs per patient extracted by CADTH for the sensitivity analysis

We were able to extract the annual medicine cost per patient as reported in the reimbursement reviews of CADTH for 70 medicine-indication pairs. When a range was given, we calculated the average annual medicine cost per patient (For example as reported by CADTH: *"annual cost with risdiplam is weight dependent up until patients are 2 years of age and weigh at least 20 kg. At a cost of $193.9725 per mg, the cost per daily administration for such patients is $970, for a total annual cost of* ***$354,000****, while the average daily cost and annual cost for patients who are between 2 months and 2 years of age are $256 and* ***$93,456****, respectively*"→ Average annual cost was the average between 354,000 and 93,456= ***$*****223,728)**. For five medicine-indication pairs, the treatment costs were confidential, thus, annual medicine costs were not recorded. Three medicine-indication pairs had a one-time cost, which was recorded as annual cost. For the remaining, 77 medicine-indication pairs, we calculated the annual medicine costs, using the list price and the dosing information as reported by CADTH. When dosing and costs were varying across patient populations (e.g.: age or weight), we used the average.

9.6.4 Appendix 4

CADTH's recommendations, pCPA negotiation outcomes and funding decisions in Ontario for orphan medicine-indication pairs

		All sample		Conditional marketing authorisation		Standard marketing authorisation		Priority Review		Non-priority review		Ultra-orphan		Orphan	
CADTH recommendations		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	L	3	1.94	1	4.00	2	1.54	1	1.43	2	2.35	1	1.56	2	2.20
	LwR	119	76.77	19	76.00	100	76.92	56	80.00	63	74.12	50	78.12	69	75.82
	DNL	33	21.29	5	20.00	28	21.54	13	18.57	20	23.53	13	20.31	20	21.98
				P=0.711; Fisher's exact=0.582				*P=0.675; Fisher's exact=0.714*				*P=0.926; Fisher's exact=0.933*			
pCPA negotiations	**Successful**	102	65.81	20	80.00	83	63.85	58	68.24	45	64.29	44	68.75	59	68.84
	Unsuccessful	19	12.26	3	12.00	15	11.54	15	17.65	3	4.29	6	9.38	12	13.19
	N/A	34	21.94	2	8.00	32	24.62	12	14.12	22	31.43	14	21.88	20	21.98
				P=0.177tab pCPAdescriptiveStats PriorityMA,chi2 column exact; Fisher's exact=0.182				*P=0.004; Fisher's exact=0.003*				*P=0.757; Fisher's exact=0.825*			
Funding in Ontario	**F**	112	72.26	21	84.00	91	70.00	54	77.14	58	68.24	48	75.00	64	70.33
	DNF	43	27.74	4	16.00	39	30.00	16	22.86	27	31.76	16	25.00	27	29.67
				P=0.152; Fisher's exact=0.115				*P=0.218; Fisher's exact=0.146*				*P=0.523; Fisher's exact=0.325*			
	Total	**155**	**100**	**25**	**100**	**130**	**100**	**70**	**100**	**85**	**100**	**64**	**100**	**91**	**100**

Abbreviations: L: Listed; LwR: Listed with restrictions; DNL: Do not list; F: Funded; DNF: Not Funded

CADTH's recommendations, pCPA negotiation outcomes and funding decisions in Ontario for orphan medicine-indication pairs (continue).

		Pediatric patients (<18 years old)		Non-pediatric patients		First-in-class		Non-first-in-class		Cancer indication		Non-cancer indication	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**	**n**	**%**
CADTH recommendations	**L**	0	0.00	3	2.61	0	0.00	3	3.19	3	4.23	0	0.00
	LwR	34	85.00	85	73.91	42	68.85	77	81.91	57	80.28	62	73.81
	DNL	6	15.00	27	23.48	19	31.15	14	14.89	11	15.49	22	26.19
		P=0.284; Fisher's exact=0.349				*P=0.025; Fisher's exact=0.020*				*P=0.025; Fisher's exact=0.020*			
pCPA negotiations	**Successful**	30	75.00	73	63.48	41	67.21	62	65.96	53	74.65	50	59.52
	Unsuccessful	1	2.50	17	14.78	6	9.84	12	12.77	8	11.27	10	11.90
	N/A	9	22.50	25	21.74	14	22.95	20	21.28	10	14.08	24	28.57
		P=0.108; Fisher's exact=0.099				*P=0.848; Fisher's exact=0.908*				*P=0.081; Fisher's exact=0.077*			
Funding in Ontario	**F**	32	80.00	80	69.57	45	73.77	67	71.28	53	74.65	59	70.24
	DNF	8	20.00	35	30.43	16	26.23	27	28.72	18	25.35	25	29.76
		P=0.204; Fisher's exact=0.143				*P=0.735; Fisher's exact=0.855*				*P=0.541; Fisher's exact=0.592*			
	Total	***40***	**100**	***115***	**100**	***61***	**100**	***94***	**100**	**71**	**100**	**84**	**100**

Abbreviations: L: Listed; LwR: Listed with restrictions; DNL: Do not list; F: Funded; DNF: Not Funded

9.6.5 Appendix 5

Funding in Ontario through specialised funds

Of the 112 funded medicine-indication pairs: 73 were funded through the Exceptional Access Program (65.18%) which targets patient access on a case-by-case basis (392,393) to medicines not included in the general formulary list or for which there are no publicly funded alternatives; 26 were available through the New Drug Funding Program (23.21%) which covers new and expensive injectable in-patient cancer medicines (146); one was under the High-Cost Therapy Funding Program (394); five were available through the Inherited Metabolic Diseases Program (4.46%). Three medicine indication pairs were available through both the Exceptional Access and the New Drug Funding Programs, and one medicine-indication pair was available through the Exceptional Access and the High-Cost Therapy Funding Programs. Finally, only two medicine-indication pairs were included in the general Ontario Drug Formulary while one of them was listed for limited use, which restricts medicine use only when a set of criteria or conditions have been met (395).

9.6.6 Appendix 6

Results of the sensitivity analysis

Variables	p value	Odds ratio (OR)	95% Confidence interval (CI)	
			Lower	Upper
Successful pCPA pricing negotiation	0.001***	15.28	2.99	78.00
Positive HTA recommendation	0.03*	8.64	1.26	59.04
Conditional MA	0.04*	10.25	1.16	90.37
Priority Review MA	0.04*	3.90	1.10	13.80
Cancer indication	0.06	4.92	0.92	26.22
Paediatric indication	0.27	2.21	0.54	9.00
Ultra-rare indication	0.88	1.11	0.27	4.55
First-in-class	0.31	0.48	0.12	1.94
Safety recall and alerts	0.72	1.52	0.15	15.84
Cost-effectiveness ratio				
< CAD50,000/QALY	*Reference*			
CAD50,000-CAD175,000/QALY	0.05*	0.12	0.01	1.01
CAD175,000-CAD500,000/QALY	0.07	0.11	0.01	1.21
> CAD500,000/QALY	0.17	0.22	0.02	1.92
Not reported	0.12	0.09	0.00	1.91
With an HTA re-submission	0.12	0.19	0.02	1.57
MA year	0.73	0.89	0.46	1.72
HTA year	0.17	0.65	0.34	1.21
Alternative available	0.46	1.49	0.52	4.29
Annual medicine costs per patient				
First quartile (CAD4,032-CAD70,758)	*Reference*			
Second quartile (CAD70,758 -CAD132,788)	0.21	0.30	0.04	2.00
Third quartile (CAD132,789- CAD288,788)	0.93	1.08	0.20	5.70
Fourth quartile (CAD288,789- CAD2,910,500)	0.57	0.53	0.06	4.57

Notes:

*p ≤ 0.05;***p≤ 0.001

Pseudo R2 = 0.4681

Abbreviations: HTA: Health Technology Assessment; MA: Marketing Authorisation; QALY: Quality adjusted life years

9.6.7 Appendix 7

List of the medicine-indication pairs in our sample

Branded	Molecules name	Indication	ATC code
Calquence	acalabrutinib-1	With or without obinutuzumab, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) for whom a fludarabine-based regimen is inappropriate.	L01
Calquence	acalabrutinib-2	As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy	L01
Fabrazyme	agalsidase beta	In patients with confirmed diagnosis of Fabry disease	A16
Myozyme	alglucosidase alfa	For the treatment of Pompe disease (acid a-glucosidase deficiency).	A16
Volibris	ambrisentan	For the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening	C02
Firdapse	amifampridine phosphate	For the symptomatic treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) in adults.	N07
Trisenox	arsenic trioxide	In combination with all-trans-retinoic acid (ATRA [tretinoin]) for the induction of remission, and consolidation in adult patients with newly diagnosed, low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤10 x 103/µl), characterised by the presence of the t(15;17) translocation and/or the presence of the Pro Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.	L01
Strensiq	asfotase alfa	Enzyme replacement therapy in patients with a confirmed diagnosis of pediatric onset hypophosphatasia (HPP)	A16
Bavencio	avelumab	To treat metastatic Merkel cell carcinoma	L01
Onureg	azacitidine	Maintenance therapy in adult patients with acute myeloid leukemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment, and who are not eligible for hematopoietic stem cell transplantation (HSCT)	L01
Cayston	aztreonam	To improve respiratory symptoms in cystic fibrosis (CF) patients with Pseudomonas aeruginosa	J01
Blincyto	blinatumomab-1	For the treatment of all adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL), including those who have had one prior line of therapy (i.e.: adult patients who are refractory or patients who are in first or later relapse)	L01
Blincyto	blinatumomab-2	For the treatment of pediatric patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL)	L01
Blincyto	blinatumomab-3	Patients with Philadelphia chromosome-negative CD19 positive B-precursor acute lymphoblastic leukemia (ALL) in first or second hematologic complete remission with minimal residual disease (MRD) greater than or equal to 0.1%	L01
Bosulif	bosutinib	Treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive	L01

Branded	Molecules name	Indication	ATC code
		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.	
Adcetris	brentuximab vedotin-1	For the treatment of patients with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates	L01
Adcetris	brentuximab vedotin-2	Treatment of Hodgkin's Lymphoma at high risk of relapse or progression post-ASCT	L01
Adcetris	brentuximab vedotin-3	For the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or cluster of differentiation (CD)30-expressing mycosis fungoides (MF) who have had prior systemic therapy	L01
Adcetris	brentuximab vedotin-4	For the treatment of previously untreated adult patients with systemic anaplastic large cell lymphoma (sALCL), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) or angioimmunoblastic T-cell lymphoma (AITL), whose tumours express CD30, in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).	L01
Adcetris	brentuximab vedotin-5	For the treatment of adult patients with pcALCL or CD30-expressing MF who have had prior systemic therapy.	L01
Adcetris	brentuximab vedotin-6	For second-line treatment of sALCL patients - i.e., after failure of at least one prior multi-agent chemotherapy regimen	L01
Tecartus	brexucabtagene autoleucel	For the treatment of adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) who have received treatment with a Bruton's tyrosine kinase inhibitor (BTKi).	L01
Crysvita	burosumab	For the treatment of X-linked hypophosphatemia (XLH)	M05
Ilaris	canakinumab-1	For the treatment of CryopyrinAssociated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including • Familial Cold Autoinflammatory Syndrome (FCAS) • Muckle-Wells Syndrome (MWS)	L04
Ilaris	canakinumab-2	Treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 through 16 years.	L04
Cablivi	caplacizumab	For the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PE) and immunosuppressive therapy.	B01
Kyprolis	carfilzomib-1	In combination with dexamethasone alone in the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy	L01
Kyprolis	carfilzomib-2	In combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma following one prior treatment failure	L01
Oxervate	cenegermin	For the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults	S01
Brineura	cerliponase alfa	For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency	A16
Verkazia	cyclosporine	For the treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age through adolescence.	S01

Branded	Molecules name	Indication	ATC code
Procysbi	cysteamine	For treatment of nephropathic cystinosis	A16
Cystadrops	cysteamine hydrochloride	For the treatment of corneal cystine crystal deposits (CCCDs) in adults and children from 2 years of age with cystinosis.	S01
Darzalex	daratumumab-1	For the treatment of patients with multiple myeloma who 1) have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD); OR 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD	L01
Darzalex	daratumumab-2	In combination with bortezomib, melphalen, and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant	L01
Darzalex	daratumumab-3	in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.	L01
Darzalex	daratumumab-4	In combination with lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.	L01
Darzalex	daratumumab-5	In combination with bortezomib, cyclophosphamide, and dexamethasone, for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis.	L01
Vyxeos	daunorubicin-cytarabine	For the treatment of adults with newly diagnosed therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	L01
Inqovi	decitabine	For treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-AmericanBritish subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.	L01
Exjade	deferasirox	For the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older.	V03
Unituxin	dinutuximab beta	To treat pediatric patients with high-risk neuroblastoma	L01
Soliris	eculizumab-1	For the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis	L04
Soliris	eculizumab-2	In adult patients with generalized Myasthenia Gravis (gMG).	L04
Soliris	eculizumab-3	For the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.	L04
Radicava	edaravone	For the treatment of amyotrophic lateral sclerosis (ALS).	N07
Trikafta	elexacaftor - tezacaftor-ivacaftor-ivacaftor-1	For the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.	R07

Branded	Molecules name	Indication	ATC code
Trikafta	elexacaftor - tezacaftor-ivacaftor-ivacaftor-2	For the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene	R07
Cerdelga	eliglustat	For the long-term treatment of adult patients with the Type 1 form of Gaucher disease	A16
Vimizim	elosulfase alfa	For patients with mucopolysaccharidosis IVA	A16
Revolade	eltrombopag olamine	For adult chronic Immune thrombocytopenia to increase plate let counts in splenectomized patients who are refractory to first-line treatments (e.g.: corticost eroids, immunoglobulin). As second-line treatment for adult non-splenectomized patients where surgery is contraindicated.	B02
Afinitor	everolimus-1	Treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease	L01
Afinitor	everolimus-2	Treatment of adult patients with progressive, well-differentiated, non-functional, neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin, (excluding pancreatic) with unresectable, locally advanced or metastatic disease.	L01
Afinitor	everolimus-3	Treatment of adults with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery.	L04
Afinitor	everolimus-4	Treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection	L04
Inrebic	fedratinib	For the treatment of splenomegaly and/or disease-related symptoms in adult patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, including patients who have been previously exposed to ruxolitinib	L01
Naglazyme	galsulfase	For patients with Mucopolysaccharidosis VI (MPS VI)	A16
Mylotarg	gemtuzumab ozogamicin	In combination therapy with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia	L01
Xospata	gilteritinib	For the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by a validated test	L01
Givlaari	givosiran	For the treatment of acute hepatic porphyria (AHP) in adults	A16
Daurismo	glasdegib	In combination with low-dose cytarabine for the treatment of newly diagnosed and previously untreated acute myeloid leukemia in adult patients, who are age ≥ 75 years or who are not eligible to receive intensive induction chemotherapy	L01
Ravicti	glycerol phenylbutyrate	Use as a nitrogen-binding adjunctive therapy for chronic management of adult and pediatric patients at least 2 years of age with urea cycle disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone.	A16
Imbruvica	ibrutinib-1	To treat patients with mantle cell lymphoma (MCL), a rare and aggressive type of blood cancer.	L01

Branded	Molecules name	Indication	ATC code
Imbruvica	ibrutinib-2	For the treatment of patients with Waldenström's Macroglobulinemia who have received at least one prior therapy	L01
Imbruvica	ibrutinib-3	The treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.	L01
Imbruvica	ibrutinib-4	Treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.	L01
Firazyr	icatibant	For the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase inhibitor deficiency.	B06
Elaprase	idursulfase	For patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).	A16
Tegsedi	inotersen	For the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)	N07
Besponsa	inotuzumab ozogamicin	To treat adults with relapsed or refractory acute lymphoblastic leukemia	L01
Sarclisa	isatuximab-1	In combination with pomalidomide and dexamethasone, for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.	L01
Sarclisa	isatuximab-2	In combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.	L01
Cresemba	isavuconazole	To treat adults with invasive aspergillosis and invasive mucormycosis, rare but serious infections	J02
Kalydeco	ivacaftor-1	For the treatment of a rare form of cystic fibrosis (CF) in patients ages 6 years and older who have the specific G551D mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene.	R07
Kalydeco	ivacaftor-2	Treatment of cystic fibrosis (CF) in patients aged 6 years and older who have one of the following mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.	R07
Ninlaro	ixazomib	To treat people with multiple myeloma who have received at least one prior therapy	L01
Takhzyro	lanadelumab	To treat types I and II hereditary angioedema	B06
Aldurazyme	laronidase	For the treatment of mucopolysaccharidosis I	A16
Vitrakvi	larotrectinib	For the treatment of adult and pediatric patients with solid tumours that: have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options.	L01
Revlimid	lenalidomide-1	For the maintenance treatment of newly diagnosed multiple myeloma in patients after stem-cell transplantation	L04
Revlimid	lenalidomide-2	In combination with low-dose dexamethasone, for treatment of newly diagnosed multiple myeloma patients who are not candidates for stem cell transplantation	L04

Branded	Molecules name	Indication	ATC code
Lenvima	lenvatinib-1	To treat patients with progressive, differentiated thyroid cancer (DTC) whose disease progressed despite receiving radioactive iodine therapy (radioactive iodine refractory disease).	L01
Lenvima	lenvatinib-2	For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC)	L01
Prevymis	letermovir	Treatment of prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). Consideration should be given to official guidance on the appropriate use of antiviral agents.	J05
Onivyde	liposomal irinotecan	For use in combination with 5-fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas that has progressed following gemcitabine-based therapy	L01
Orkambi	lumacaftor-ivacaftor-1	Treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene	R07
Orkambi	lumacaftor-ivacaftor-2	Treatment of cystic fibrosis (CF) in patients aged 6-11 year old who are homozygous for the F508del mutation in the CFTR gene	R07
Reblozyl	luspatercept-1	For the treatment of adult patients with -thalassemia associated anemia who require red blood cell (RBC) transfusions.	B03
Reblozyl	luspatercept-2	For the treatment of adult patients with red blood cell (RBC) transfusion-dependent anemia associated with beta ()-thalassemia. the treatment of adult patients with transfusion-dependent anemia requiring at least two RBC units over 8 weeks resulting from very low- to intermediate-risk myelodysplastic syndromes (MDS) who have ring sideroblasts and who have failed or are not suitable for erythropoietin-based therapy.	B03
Lutathera	lutetium (177Lu) oxodotreotide	To treat a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropancreatic neuroendocrine tumors (GEP-NETs).	V10
Opsumit	macitentan	To treat adults with pulmonary arterial hypertension (PAH), a chronic, progressive and debilitating disease that can lead to death or the need for lung transplantation.	C02
Increlex	mecasermin	For the treatment of growth failure in children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency (SPIGFD).	H01
Rydapt	midostaurin-1	in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated acute myeloid leukemia (AML)	L01
Rydapt	midostaurin-2	For the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).	L01
Galafold	migalastat	To treat adults with Fabry disease.	A16
Zavesca	miglustat	for the treatment of mild to moderate Type I Gaucher disease in adults for whom enzyme replacement therapy is not a therapeutic option	A16
Ofev	nintedanib-1	For the treatment of idiopathic pulmonary fibrosis (IPF)	L01

Branded	Molecules name	Indication	ATC code
Ofev	nintedanib-2	For the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (also known as progressive fibrosing ILD)	L01
Zejula	niraparib-1	As maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy	L01
Zejula	niraparib-2	As monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	L01
Orfadin	nitisinone	For adjunctive therapy to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1	A16
Spinraza	nusinersen	To treat children and adults with spinal muscular atrophy (SMA)	M09
Ocaliva	obeticholic acid	For the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid in adults with an inadequate response to ursodeoxycholic acid or as monotherapy in adults unable to tolerate ursodeoxycholic acid.	A05
Gazyva	obinutuzumab-1	For use in combination with chlorambucil to treat patients with previously untreated chronic lymphocytic leukemia (CLL).	L01
Gazyva	obinutuzumab-2	For the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen	L01
Gazyva	obinutuzumab-3	In patients achieving at least a partial remission for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma	L01
Lynparza	olaparib-1	For the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy	L01
Lynparza	olaparib-2	As monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy	L01
Zolgensma	onasemnogene abeparvovec	For the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene	M09
Sensipar	parathyroid hormone	For the treatment of secondary hyperparathyroidism in patients with chronic kidney disease	H05
Signifor	pasireotide	To treat Cushing's disease patients who cannot be helped through surgery	H01
Onpattro	patisiran	To treat the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adult patients	N07
Somavert	pegvisomant	For the treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate	H01

Branded	Molecules name	Indication	ATC code
Pemazyre	pemigatinib	For the treatment of adults with previously treated, unresectable locally advanced or metastatic Cholangiocarcinoma with a FGFR2 fusion or other rearrangement.	L01
Esbriet	pirfenidone	For the treatment of idiopathic pulmonary fibrosis (IPF)	L04
Mozobil	plerixafor	In combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.	L03
Polivy	polatuzumab vedotin	In combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, who are not eligible for autologous stem cell transplant and have received at least one prior therapy.	L01
Pomalyst	pomalidomide	In combination with low-dose dexamethasone for patients with multiple myeloma for whom both bortezomib and lenalidomide have failed and who have received at least two prior treatment regimens and have demonstrated disease progression on the last regimen	L04
Iclusig	ponatinib-1	For the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML)	L01
Iclusig	ponatinib-2	For the treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.	L01
Folotyn	pralatrexate	For the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)	L01
Cyramza	ramucirumab	As a single agent or in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy	L01
Ultomiris	ravulizumab	For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).	L04
Adempas	riociguat-1	Chronic thromboembolic pulmonary hypertension (CTEPH):	C02
Adempas	riociguat-2	For the treatment of PAH (WHO Group 1) as monotherapy or in combination with ERAs in adult patients (≥ 18 years of age) with functional class II or III pulmonary hypertension	C02
Qinlock	ripretinib	For the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.	L01
Evrysdi	risdiplam	For the treatment of spinal muscular atrophy (SMA) in patients 2 months and older.	M09
Istodax	romidepsin	For the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy.	L01
Nplate	romiplostim-1	To increase the platelet levels in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): • who are non-splenectomized and have had an inadequate response or who are intolerant to corticosteroids and/or immunoglobulins	B02

Branded	Molecules name	Indication	ATC code
Nplate	romiplostim-2	To increase the platelet levels in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): • who are splenectomized and have had an inadequate response to splenectomy	B02
Banzel	rufinamide	for adjunctive therapy of seizures associated with Lennox-Gastaut syndrome in patients 4 years of age or older	N03
Jakavi	ruxolitinib-1	Treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.	L01
Jakavi	ruxolitinib-2	For the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis	L01
Kuvan	sapropterin dihydrochloride	in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU)	A16
Enspryng	satralizumab	As monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients who are anti-aquaporin 4 (AQP4) seropositive. ENSPRYNG is not intended for acute treatment of an NMOSD relapse.	L04
Kanuma	sebelipase alfa	To treat patients with a rare disease known as lysosomal acid lipase (LAL) deficiency	A16
Uptravi	selexipag	For long-term treatment of idiopathic pulmonary arterial hypertension (PAH), heritable HPAH, PAH associated with connective tissue disorders, and PAH associated with congenital heart disease, in adult patients with World Health Organization (WHO) functional class (FC) II to III to delay disease progression.	B01
Sylvant	siltuximab	To treat patients with multicentric Castleman's disease (MCD), a rare disorder similar to lymphoma (cancer of the lymph nodes)	L04
Xyrem	sodium oxybate	For the treatment of cataplexy associated with narcolepsy	N07
Nexavar	sorafenib-1	Treatment of locally advanced/metastatic renal cell (clear cell) carcinoma in patients who have failed prior cytokine therapy or are considered unsuitable for such therapy.	L01
Nexavar	sorafenib-2	Treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DCT) that is refractory to radioactive iodine treatment.	L01
Diacomit	stiripentol	In combination with clobazam and valproate as adjunctive therapy of refractory generalized tonicclonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome), whose seizures are not adequately controlled with clobazam and valproate alone	N03
Vyndaqel	tafamidis meglumine	Treatment of transthyretin amyloid cardiomyopathy in adult patients	N07
Elelyso	taliglucerase alfa	For long-term enzyme replacement therapy (ERT) for adults and children with type 1 Gaucher disease (GD) or for hematological manifestations in pediatric patients with type 3 GD.	A16
Revestive	teduglutide	To treat adults with short bowel syndrome (SBS) who need additional nutrition from intravenous feeding (parenteral nutrition).	A16
Xermelo	telotristat ethyl	To treat carcinoid syndrome diarrhea	A16

Branded	Molecules name	Indication	ATC code
Jinarc	tolvaptan	To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)	C03
Remodulin	treprostinil inhalation solution	For the long-term, subcutaneous treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) Class III and IV disease who do not respond adequately to conventional therapy.	B01
Dojolvi	triheptanoin	As a source of calories and fatty acids for the treatment of adult and pediatric patients with long-chain fatty acid oxidation disorders (LC-FAOD).	A16
VPRIV	velaglucerase alfa	for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with type 1 Gaucher disease	A16
Venclexta	venetoclax-1	As monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi)	L01
Venclexta	venetoclax-2	In combination with rituximab (V+R) is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy	L01
Venclexta	venetoclax-3	In combination with low dose cytarabine for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.	L01
Luxturna	voretigene neparvovec	For the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.	S01
Brukinsa	zanubrutinib	For the treatment of patients with Waldenström's macroglobulinemia (WM).	L01

10 Conclusions

'Healthcare is a right, not a privilege', as the chief of WHO has stated. And many nations stand by this idea by offering universal health coverage to their citizens. In countries with free healthcare, such as the EU member states, the UK and Canada, medicines are funded through the public purse, incurring no or a small cost to patients and their families. This way, access to medicines is not conditional on patients' socioeconomic profile or on whether a disease affects a smaller or a bigger part of the population. Notably, in the case of medicines treating rare diseases, which are exceptionally expensive, patients and their families might have to face catastrophic costs. However, access to medicines within markets remains conditional on local resources, the wealth, and the negotiating power of a nation, which can all indirectly impact patient access.

The provision of free healthcare coupled with increasing pharmaceutical expenditure, mainly driven by the introduction of new and innovative treatments as discussed in chapter 2, threatens the affordability and sustainability of healthcare systems. Despite the introduction of novel therapies, evidence on whether higher public spending is associated with better health outcomes for patients and society remains dubious. To tackle such issues, HTA is used by numerous countries as a pricing and reimbursement tool to help with the allocation of finite resources in a way that improves patients' health and quality of life but does not inversely affect the sustainability of the healthcare system. HTA provides funding recommendations to health insurance based on whether a health technology provides an added clinical benefit compared to existing treatments and is good value for money. Contrary to other pricing and reimbursement policies, HTA does not set bluntly a price for a medicine. It rather assesses its value in terms of its comparative clinical benefit and cost-effectiveness. At the same time, it considers additional dimensions of value such as innovation, the rarity of the disease and unmet need. This way, manufacturers are encouraged to invest in R&D and launch their products within markets. And healthcare systems can invest their limited resources in health technologies that are worth investing in. Ultimately, access to innovative medicines and medicines for rare diseases within markets can be optimised with the sophisticated use of HTA.

Despite the numerous benefits of HTA, limitations have been seen with its implementation. These pitfalls can have knock-on effects on access to medicines. Even though HTA has been widely used across high-income countries, evidence is scarce on the extent to which HTA recommendations are followed during funding decision-making. In addition, as HTA is a national competency, HTA assessment processes and the additional values that HTA takes into consideration, as explained in

section 3.3.2.2, differ across settings, leading to divergent recommendations for funding for the same medicines across markets. Beyond how health technologies are assessed during HTA, which has been extensively studied in the literature (summarised in section 3.4), there has been a gap in our knowledge on how differences in HTA's set-up within the healthcare system can influence the extent to which HTA recommendations are considered during funding decisions. In addition, there has been no framework on the operational features of HTA that allows comparisons across settings which might use HTA extensively or to some extent.

Looking at the literature and the findings of the thesis' first and second studies (chapter 6), we can conclude that HTA is multi-dimensional. Therefore, efforts to improve access to medicines at HTA level should holistically target this policy (i.e.: the way it is set up, its legal procedures, its evaluation processes and its relationship with funding) rather than focus only on individual parts of HTA. Different features of HTA might also target different dimensions of access, namely the availability of clinically- and cost-effective medicines within markets, the affordability of the healthcare systems and of the patients and timely access. Even though the literature has discussed what features of HTA were responsible for access variations and hurdles (summarised in section 3.4), it has mainly focused on individual parts of HTA or has looked at HTA recommendations across countries for the same medicines only. In addition, the current literature has not examined yet how HTA affects access using various access metrics. And recent evidence has not been validated by key stakeholders who are actively involved in policy- and decision-making. Therefore, validated evidence on which features of HTA must be prioritised and improved to facilitate access to medicines within markets is lacking.

Beyond the broader implementation of HTA, an interesting case study to explore is the value assessment of medicines treating rare diseases. Orphan medicines carry very high price tags and they are associated with high clinical uncertainty due to the small population size affected by the disease, as described in sections 2.3.1 and 3.5. Therefore, in HTA terms, these medicines are deemed as cost-ineffective to be funded through the public purse. To tackle issues around equity, some settings implement orphan regulations, which offer numerous incentives to manufacturers, and specialised frameworks for their assessment, which account for other dimensions of value beyond clinical- and cost-effectiveness (presented in section 3.5.2). Implementations of these regulations and processes in some settings might lead to access variations. While whether access to orphan medicines has been better with the presence of such regulations and processes has not been explored yet. Finally, the case of orphan medicines is a great example of exploring whether

HTA recommendations are translated into funding decisions, especially in systems where HTA recommendations are not legally binding, and the role of HTA is advisory only.

This PhD thesis focused on access to improved medicines within markets rather than patient access, which depends on many other system-related and macro- factors that are not easily quantified or detected. Unlike existing studies, this thesis recognised that HTA is just one stage of the access pathway. And access to innovative medicines within markets depends on the success of all the regulatory stages of the pathway, from MA to funding, as discussed in section 3.3. Therefore, in this thesis, the dynamics, and the relationship of HTA with different regulatory stages were explored. Finally, access to medicines was examined using a more refined definition of access as suggested by the results of the scoping review summarised in section 3.2. Therefore, the following metrics of access were used: (i) availability of clinically- and cost-effective medicines within markets, (ii) affordability of the healthcare system and (iii) timely access. This thesis provided evidence on how variations in the implementation of HTA, as a critical part of the access pathway, can influence access to new medicines and medicines treating rare diseases across markets.

10.1 Summary of key findings and contributions to the literature

Three main policy questions were identified in this thesis by looking at the pressing issues and the difficult decisions healthcare systems face upon the entry of innovative medicines and medicines treating rare diseases. These were the following:

I. *How does the implementation of HTA differ across settings and how these variations are reflected in access to medicines?*
II. *Considering finite budgets, should very expensive treatments, whose costs run in the millions of dollars and have potentially significant clinical benefits, be funded at public expense?*
III. *Should decision- and policymakers treat orphan medicines differently than non-orphan medicines to optimise their access within markets?*

To address these overarching policy questions, this thesis focused on the value assessment of medicines and, specifically, the implementation of HTA. The three main policy issues were subsequently broken down into the following four research questions:

1. *How do HTA systems differ in the way they are operationalised within healthcare settings, and what implications do these differences have on the consideration of HTA recommendations during funding decisions?*
2. *What features of HTA could facilitate access to innovative medicines, and what HTA features need improvement?*

3. *Does the presence of specialised processes for orphan medicines translate into more favourable HTA recommendations for these medicines?*
4. *Do HTA recommendations align with outcomes of pricing negotiations and funding decisions for medicines treating rare diseases?*

As a starting point for this thesis, the first study (chapter 6) provided a conceptual framework that allowed comparisons across settings which use HTA. Using this framework, I was able to map HTA systems across 32 countries and identify how differences in the way HTA is set up and operationalised within the healthcare system may explain differences in the extent HTA recommendations are considered during funding decision-making across settings. Unlike existing studies in the literature, this study provided evidence on HTA at a system level rather than focusing on differences in the evaluation processes employed by different HTA bodies. And it deep dived into two critical stages of the access pathway: HTA and funding. The second study (chapter 7) focused on features of HTA that might facilitate or impede access to new and better medicines in terms of clinical- and cost-effectiveness. The features of HTA were identified through a scoping review and the results of the first study of this thesis. The study holistically looked at HTA and included HTA features such as its set-up, procedures, evaluation processes and the relationship between HTA and funding. A panel of European stakeholders validated the scoping review findings using the Delphi technique. Through this exercise, I was able to identify what features of HTA could be ameliorated and how to optimise access to new medicines within markets. The third and fourth studies (chapters 8-9) focused on the unique case of medicines treating rare diseases. The third study was the first study in the literature that explored whether the presence of specialised processes for orphan medicines was associated with better access, meaning more favourable HTA recommendations and timely market access. HTA recommendations for funding for a large sample of orphan medicines were analysed and compared in one setting where these medicines are classed as "orphan" (Scotland) to another where they are considered "non-orphan" (Canada). Finally, the fourth study explored whether HTA recommendations for funding orphan medicines were followed during pricing negotiations, and translated into funding decisions in Ontario, Canada. In addition, it explored what other factors important to decision-makers might influence funding decisions for orphan medicines. In Canada, HTA has an advisory role and is conducted at the federal level, while funding decisions are a provincial competency (except Quebec). Even though few studies have looked at a similar question, this was the first study that focused only on orphan medicines, given that their funding through public funds could threaten the affordability and sustainability of the local healthcare system.

A summary of each study's relevant findings and conclusions, as seen in the main chapters of this thesis, are presented below. Based on the results of all four studies, areas for improvement to optimise access to medicines within markets while ensuring the sustainability of healthcare systems are discussed in section 10.2.

10.1.1 Paper 1

Research question: *How do HTA systems differ in the way they are operationalised within healthcare settings, and how does this contribute to the funding decision-making process?*

Literature contributions	*This paper studied HTA at a system level and designed a conceptual framework of the main HTA's operational components and salient features. It contributed to our deeper understanding of similarities and differences in HTA systems and the implications of these variations to the uptake of HTA recommendations during funding decisions.*

This study first developed a conceptual framework which identified the main operational pillars of HTA. These were: (i) governance of HTA, (ii) types of organisations performing HTA, (iii) role of HTA, (iv) scope and geographical coverage of HTA, (v) remit of HTA, (vi) model of HTA, (vii) assessment versus appraisal, (viii) stakeholder involvement in the HTA process, and (ix) HTA recommendations and funding decisions. Unlike existing frameworks, this conceptual framework provided a holistic overview of the different facets of HTA, which helped us examine how HTA processes differed across the study countries (i.e.: EU member states, the UK, Canada and Australia) and why, how HTA systems functioned within the healthcare system, and whether HTA recommendations were likely to be directly linked to funding decisions or not.

An unmet need was identified to make reimbursement and negotiation processes more transparent to better understand how policy- and decision-makers use HTA outputs during negotiations with manufacturers and to further investigate the extent to which HTA recommendations can influence funding.

Whilst similar patterns were observed for some of the operational components of HTA across the 32 study countries, differences in its implementation were seen. HTA infrastructure and activities reflected the structure of the healthcare systems they operated in, mirroring the administrative setting of a nation. While variations in the implementation of HTA were mainly related to how well HTA processes were developed and integrated into the decision-making within the healthcare system and the extent to which local health insurances considered evidence-based information

when deciding about the funding of technologies. For instance, HTA bodies operating at arm's length were present in more developed HTA systems compared to newly founded and less well-developed HTA systems. The observed differences could explain why HTA recommendations for the same medicines may differ, but more importantly, they signalled differences in the use of HTA recommendations in funding decisions. In addition, as most HTA recommendations were non-binding across the study countries, the extent to which these recommendations were followed during decision-making processes seemed to remain at the decision-makers' discretion.

In summary, this study found that most HTA bodies were independent of the government (73%), while the remaining were integrated within the local government. The role of HTA in the pricing and reimbursement of technologies varied across settings: half of the HTA bodies had an advisory role (52%) where HTA outcomes act only as recommendations that can be used as a supplementary tool or an additional criterion during negotiations. At the same time, only 28% of the HTA bodies had a regulatory role where they were directly responsible for the pricing and reimbursement of health technologies. A wide variation in the technologies which undergo HTA was observed across countries. However, most HTA bodies (76%) evaluated pharmaceuticals predominately or exclusively. The clinical and cost-effectiveness model was mainly employed across the study countries (73%). And it was used by all national insurance organisations that conduct HTA as an additional criterion during their decision-making process. Variations were also seen in the type of assessment followed, with 56% of HTA bodies performing appraisals, meaning that they were contextualising the evidence against local values and needs and were not solely collecting and synthesising evidence on the clinical and/or economic effectiveness of technologies. HTA bodies conducting appraisals were mainly national institutions. However, approximately 44% of the HTA bodies limited their evaluations to the assessment phase. Involvement of various stakeholders as members of HTA committees was present across almost all the HTA bodies (94%). However, the type of stakeholders involved in decision-making varied considerably across settings. Finally, in 81% of the HTA bodies, HTA outcomes were non-binding, and their consideration in reimbursement decisions and the negotiation process was unclear.

10.1.2 Paper 2

Research question: *What features of HTA could facilitate access to clinically- and cost-effective medicines, and what HTA features need improvement?*

Literature contributions	*This paper elicited the views of key European stakeholders to validate HTA features that existing studies in the literature has found to have an impact on access to medicines. The study further explored how a better understanding of these features can help improve HTA in a holistic way in order to facilitate access to better medicines.*

Even though studies in the literature have used the Delphi method for expert elicitation on value assessment systems, to my knowledge, there is only one study similar to ours in remit [33]. However, the second study of this thesis validates HTA features that existing studies have found to have an impact on access to medicines, and explored how a better understanding of these features through expert views can help improve HTA at national, regional and supranational levels.

Using the Delphi technique to elicit the group opinion of 19 European stakeholders with different expertise and perspectives, this study concluded that in order to optimise access to medicines through HTA, more clarity and transparency on the HTA process are needed. While better collaborations between regulatory institutions within and between countries are paramount to improve access to innovative medicines. These results are of great interest as agreement on more clarity and transparency in the HTA processes was reached from experts representing both countries with well-developed and less-developed HTA systems in Europe. This result underlines a common theme that is our lack of complete understanding on how HTA decisions are made and how do they inform reimbursement decision-making. Even in countries where the latter relationship seems straightforward, this does not seem to be the case, at least based on the findings of this study.

From the 13 HTA features and components (identified from a scoping review and the findings of paper 1), 11 had a positive impact on at least one dimension of access (i.e.: availability of medicines within markets, affordability of the healthcare system and of patients and timely access). Two HTA features reached consensus amongst participants on their positive impact on all three access dimensions. These were (i) '*scientific advice to manufacturers before the commencement of the formal HTA process and* (ii) '*clarity in evidence requirements used during value assessment'*.

Taking into consideration the limitations associated with the Delphi technique, strict rules were applied for the interpretation of the study results to make confident conclusions. Therefore, three features were identified that participants agreed assertively on their positive impact on the respective access dimensions. These were the following:

(i) '*Reliance on RWE'* on the availability of medicines;

(ii) *'Provision of scientific advice to manufacturers ahead of the commencement of formal HTA process'* on both availability of medicines and affordability of the healthcare system and patients, and;

(iii) '*Clarity of evidentiary requirements used during value assessment'* on timely patient access.

These findings identified a call for action: Currently, many well-established HTA bodies in Europe provide early scientific advice to manufacturers and have published guidelines for evidence requirements. However, access hurdles and delays to new medicines were still observed. Therefore, HTA bodies need to (i) emphasise the provision of early support to manufacturers before HTA initiation, (ii) provide more clarity on the evidence required for evaluation, and (iii) be more transparent and systematic in the way they deal with uncertainty if it arises.

Looking at the different access dimensions, Delphi participants believed that the included HTA features mostly had a positive impact on timely patient access to publicly funded medicines (10 out of the 13 features), followed by the availability of medicines within markets (8 out of the 13) and the affordability of patients and healthcare systems (6 out of the 13). This finding defied previous concerns that HTA processes can hinder timely access to medicines due to assessment delays and the presence of an additional regulatory step to medicines' availability within markets. In addition, even though HTA is considered to be predominantly a resource allocation tool, this study found that improved HTA processes and procedures will have a less clear impact on affordability of the healthcare system.

All features in the HTA evaluation process category reached consensus on their positive impact on at least two access dimensions. Therefore, standardising HTA evaluation processes and creating coherent and consistent scientific evidence collection, generation and interpretation across Europe could achieve better and more controlled access to medicines within countries.

However, it is important to note that results from this study should be interpreted with caution due to the inherited limitations of the Delphi method, such as low participation and high dropout rates. In our study, a small number of experts participated in both rounds, and responses were

predominantly received from research and policy makers, with no opinions from healthcare professionals and decision-makers captured.

10.1.3 Paper 3

Research question: *How HTA recommendations and time to issue of HTA outcomes differ in two setting where medicines for rare diseases are treated differently both at MA and HTA levels?*

Literature contributions	*This paper explored, in a sampled of orphan medicines, whether implementation of specialised processes for these medicines was associated with more favourable HTA recommendations and timelier issue of HTA recommendations in two healthcare systems that differ considerably on how they treat orphan medicines.*

Scotland, where orphan designation and specialised HTA processes for orphan medicines exist, showed only slightly better access to orphan medicines than Canada, where these processes are not implemented. For the purposes of this study, access to medicines was defined as positive/restricted HTA recommendations which are more likely to translate into funding in both settings (given the nature of the HTA system in both countries). However, when looking at timely access, Scotland had a slower time to access than Canada. Therefore, from the findings of this study, it was unclear whether the presence of orphan designation and HTA specialised processes for orphan medicines alone could have been associated with better access to orphan medicines. The study's findings further highlighted the need for holistic approaches at all levels of the access pathway, together with better collaboration across respective agencies and relevant stakeholders to optimise access to orphan medicines while ensuring the sustainability of the healthcare system.

By analysing a sample of 116 orphan medicine-indication pairs with MA approval from 2001 to 2019 in Europe and Canada, I found that all medicine-indication pairs were commercially marketed in both settings, except for one instance in Scotland for which evidence was unclear. Thus, the presence of orphan designation at MA did not seem to impact the commercial availability of orphan medicines. Looking at HTA recommendations, Scotland had more positive funding recommendations than Canada. However, the proportion of positive HTA recommendations was low in both settings. In Scotland, orphan medicines had fewer negative HTA recommendations compared to Canada. And HTA recommendations for orphan medicines in Scotland were more likely to be accompanied by economic restrictions suggesting risk-sharing mechanisms in the form of MEAs. However, in Canada, HTA recommendations were often subject to both clinical and economic restrictions, limiting patient access to a greater extent to mitigate affordability concerns. The kappa analysis showed low levels of agreements on HTA recommendations and the main

reasons for final recommendations between the two countries, highlighting discrepancies in the way clinical benefit and cost-effectiveness were assessed in the two countries. And whether other value dimensions, such as unmet need and burden of disease, among others, impacted the final recommendation.

Better access to orphan medicines was observed in Scotland compared to Canada possibly due to the following reasons:

- Presence of specific processes to account for high clinical uncertainty associated with orphan medicines, such as the SMC modifiers and the PACE process;
- Larger number of dossier re-submissions to change previously negative HTA outcomes;
- Price negotiations through PAS during the HTA process.

Despite the lack of an orphan designation in Canada, more than half of the sample orphan medicine-indications pairs were granted MA through specialised pathways in comparison to Europe, where less than half of the sample received MA through specialised pathways. In both settings, medicines which received MA through specialised pathways were less likely to receive an unfavourable funding recommendation than medicines with standard MA.

Even though specialised assessment processes for orphan medicines were not available in Canada, the regulatory agency seemed to optimise access to orphan medicines by granting MA through specialised pathways. And CADTH subsequently did not halt access to these medicines through negative HTA recommendations.

Orphan medicines with MA through specialised pathways took more time to market access compared to medicines undergoing standard approval in both countries. In general, Canada had shorter timelines between receiving MA to a positive/restricted HTA recommendation than Scotland. Additional steps might explain this in the Scottish assessment process, such as the PACE and consideration of PAS during HTA. And the presence of parallel review in Canada, where MA and HTA assessments are conducted simultaneously.

10.1.4 Paper 4

Research question: *Do HTA recommendations align with funding decisions for medicines treating rare diseases?*

Literature contributions	*This paper provided empirical evidence on whether recommendations for funding of orphan medicines by CADTH are followed during national pricing negotiations and funding decision-making in Ontario, Canada. In addition, it explored whether other factors important to decision-makers have an impact on provincial funding decisions.*

This study showed that national efforts in Canada to harmonise access to orphan medicines across provinces are broadly successful. However, there is still a lot of room for improvement. Stronger collaborations and information exchange across stakeholders at all levels of the Canadian healthcare system are needed to make the HTA tool more relevant and applicable. While the implementation of a national strategy for orphan medicines in Canada could help alleviate access variations to orphan medicines across provinces.

As per this study's findings, there was only a fair agreement between HTA recommendations and funding decisions in Ontario for medicines treating rare diseases. The agreement remained fair even after April 2016, when the Ontario Ministry of Health stopped the routine assessment of medicines which have undergone review by CADTH as an effort to align HTA recommendations and funding decisions. However, in comparison to older studies, our percentage agreement was higher, signalling that efforts to improve alignment between HTA recommendations and funding decisions in Canada might have been successful to some extent.

Positive HTA recommendations were found to be a good predictor of funding in Ontario. However, a negative HTA recommendation did not necessarily result in no pan-Canadian pricing negotiations and no funding in Ontario. More than half (52%) of medicine-indication pairs with a negative HTA recommendation were available to patients in Ontario, predominately through specialised funds. Interestingly, most medicines with a negative HTA recommendation were deemed as neither clinically- nor cost-effective by CADTH, while some of them also had unsuccessful pricing negotiations by the pCPA. Therefore, a question arises as to how medicines that have not shown a significant therapeutic benefit and have not gone through successful pricing negotiations are still being offered to patients in Ontario.

Most orphan medicine-indication pairs received a positive funding recommendation subject to clinical and/or economic restrictions (77%). While 72% of the sample orphan medicine-indication

pairs were funded in Ontario and 28% were not. Positive HTA recommendations did not always translate to successful pricing negotiations by the pCPA or funding in Ontario. However, the percentage of medicines with positive HTA recommendations and unsuccessful pricing negotiations was very low.

The logistic regression model, which tested associations between different explanatory variables and funding status in Ontario, concluded that receiving funding in Ontario was significantly more likely to have occurred when there was a favourable HTA recommendation. However, successful pan-Canadian pricing negotiations were the strongest predictor of coverage in Ontario. Similarly, there was a positive association, but not statistically significant, between conditional MA, priority review, and a cancer indication with positive funding in Ontario. However, medicines which were first-in-class or had an ultra-orphan indication were, surprisingly, less likely to receive funding in Ontario.

10.2 Policy implications

In this sub-section, six main overarching policy topics are discussed as identified from the key findings and conclusions of the four thesis' studies. These are: (i) the relationship between HTA and funding; (ii) the multidimensional nature of HTA; (iii) HTA-specific areas for improvement for better access to medicines; (iv) the role of HTA in the medicines' access pathway; (v) implementation of specialised processes for orphan medicines, and (vi) ways to optimise access of orphan medicines within markets, focusing on their value assessment.

10.2.1 HTA and funding

Considering increases in medicine spending, the aim is not always to control costs but to find a way to optimise the population's health without overburdening the healthcare system's budget. Although once this seemed like a pipe dream, HTA has provided policymakers with a cost-optimisation tool that assesses the added value of new health technologies and moves away from strict pricing and reimbursement measures that set prices bluntly. It was first seen in the US in the 1970s, but in the early 2000s, we saw its widespread implementation in Australia, Canada and Europe (322).

Despite its use for almost 20 years, issues associated with this policy are still observed. And more interestingly, as per the results of the first and fourth studies, we cannot still comprehend completely the extent to which HTA recommendations are used during funding decision-making. This is mainly because negotiations between health insurance and manufacturers remain confidential. From the findings of this thesis, which deep dived into the dynamic relationship

between HTA and funding, a straightforward link was recorded only when HTA recommendations were favourable. However, the same did not apply when HTA recommendations were unfavourable. This phenomenon was not only seen in countries where HTA was implemented recently, but also in settings with well-established and well-developed HTA systems, as illustrated by the first study's results. One could, then, wonder why do local governments implement HTA when health technologies deemed not good value for money for the healthcare system are still funded (as seen in the fourth study)? And do healthcare systems make the most of HTA as a cost-optimisation tool rather than just adding yet another administratively complex stage in the access pathway? Even though protecting the sustainability and affordability of the healthcare system is one of HTA's main objectives, according to the results of the second study, key European stakeholders believed that the affordability of the healthcare system was the access dimension that was the least likely to be positively influenced by HTA.

Due to lack of transparency, the use of HTA recommendations in funding decision-making remains unclear, especially when HTA recommendations are negative. As per the findings of the fourth study of this thesis, there were occasions when medicines which were deemed neither clinically- nor cost-effective by the national HTA body, they were still funded by the local health care system. Therefore, a question remains as to why such medicines are still being offered to patients. In addition, the uptake of HTA recommendations differs across settings, making cross-border comparisons impossible.

There is a need for national policymakers to have a clear and explicit framework that outlines how HTA is linked with reimbursement decisions and to what extent. Possibly, unified frameworks in nations of close geographic proximity (i.e.: EU member states) or in regions within decentralised healthcare systems (i.e.: Canadian provinces) could be introduced to alleviate variations in access to medicines, at least to some extent. Even though these variations might not be eradicated fully, given that HTA recommendations differ due to local needs and budget discrepancies, a fair and impartial system will be in place. And funding decisions will not only be based on the socioeconomic profile and the negotiating power of a nation, or a region, as seems to be currently the case. In the fourth study of this thesis, Ontario, the largest province of Canada, offered orphan medicines with negative HTA recommendations to its population through specialised funds. Thus, access variations to orphan medicines seem to still exist across Canada, with poorer or smaller provinces possibly facing access hurdles and delays.

10.2.2 The multidimensional nature of HTA

Another common theme was observed: Whilst HTA is multidimensional and consists of several salient features and components that can determine how HTA informs funding decisions, researchers and policymakers seemed to target specific or individual parts of the HTA process when seeking ways to improve access to new medicines. Yet the findings of the first, second and fourth study showed that the way HTA systems were set up within healthcare systems and the way HTA was operationalised were equally important as the assessment processes employed. In addition, policymakers should not forget that HTA can constantly adapt to new types of evidence, innovative technologies, and redefined objectives of healthcare systems. HTA is a dynamic and transformative process which should be reviewed regularly to align with the healthcare system's goals. And it should only be reviewed holistically rather than target only single parts of the policy. Otherwise, the success, relatability, and readiness of HTA systems might not be granted.

10.2.3 Ways to improve HTA

Current efforts to harmonise HTA methodologies and processes across Europe through the EU HTA cooperation and the new EU HTA regulation can improve the availability of new medicines and accelerate access within markets, but only to some extent. Unfortunately, there is no one-size-fits-all solution for improving HTA systems and processes. Local policymakers should not rely solely on these efforts to alleviate access hurdles and delays since they cover only a small fraction of the HTA process. While HTA remains a national competency. Therefore, HTA bodies should always be prepared to generate local data to contextualise available evidence against certain values that are aligned with the country's healthcare system's objectives and needs.

As per the second study's findings, clear guidelines for evidentiary requirements used during value assessment should be in place and easily accessible. Clear guidelines on what evidence is accepted by the respective HTA body seem straightforward and could immediately increase transparency and trust in the HTA process. In addition, by providing early scientific advice to manufacturers, HTA bodies can open an early dialogue with manufacturers and provide guidance from the onset, resulting in much faster assessment timelines. Similarly, involving various stakeholders during the HTA process can allow for open communication amongst the directly affected and impacted stakeholder groups. And it is one of the features of HTA that makes the process unique, increases its relatability, and separates it from blunt pricing and reimbursement regulations. However, implications for timely access should be recognised when multiple stakeholders are being involved in the process and decision-making. Finally, HTA bodies, in consultation with the local governments, should thoroughly consider what values are essential to account for during

assessment and find ways to incorporate these values explicitly and routinely in the evaluation process. For instance, innovation should be rewarded during HTA to encourage manufacturers to invest in R&D. However, validated measures or scales should be used in a systematic manner to decide whether a new medicine is a therapeutic advancement and whether it provides therapeutic value compared to existing treatments. In addition, certain weights must be applied to each value dimension to reflect their respective importance to the final decision. Notably, the additional dimensions of value should be applied for every medicine undergoing assessment and not considered on an ad-hoc basis or only for specific medicines as this can introduce bias in the assessment process.

At the supranational level, efforts should prioritise areas that local HTA bodies and healthcare systems seem to struggle with or lack the knowledge, expertise and capacity. For instance, a universal framework for generating, using, and assessing RWE is still missing, despite the increased importance of RWE when clinical evidence is limited or incomplete. This was further illustrated by the second study's findings: As RWE seems to be uncharted waters for most national healthcare systems and HTA bodies and their use is not always accepted at HTA level or during funding negotiations, supranational efforts should prioritise the provision of a framework for the use of RWE. Ultimately, using observational data can improve access to new medicines at HTA level but can also provide an additional tool for payers for the implementation of MEAs.

10.2.4 Best practice example of an HTA body

Looking at this thesis findings and based on my extensive research on HTA systems across developed countries, identifying an HTA system that could be considered as a best-practice example is not at all straightforward. However, looking at HTA in a holistic way, as I have extensively advocated throughout my work, NICE in England might be a good example other countries with less developed systems could use as a reference point. It is important to highlight though that by no means I deem NICE as the perfect HTA body. As with all best-practice examples, certain caveats and limitations associated with them should always be taken into consideration.

As shown in the first and second study, an independent HTA body at the government's arm-length as NICE is, may ensure greater transparency and confidence in terms of minimisation of bias during decision-making. Assessment of the available evidence is also conducted by a completely independent academic review group, the External Assessment Group. Subsequently, the NICE committee is deciding on whether a medicine is clinically- and cost-effective by considering both

the manufacturer's submission and the report produced by the External Assessment Group. To my knowledge, NICE is the only HTA body that makes all the relevant information publicly available, such as the evidence dossier submitted by the manufacturer and the committee papers. However, it is important to note that documentation of previous submissions is not available in the NICE website as it is for instance in HAS, the French HTA body.

In the second study of this thesis another HTA feature that was identified to have a clear positive impact on improving market and patient access to innovative medicines was the provision of clear guidance on the evidentiary requirements. Among many well-established HTA systems, NICE provides clear guidance to manufacturers through their methods guides. NICE's methods guides are also updated often after the implementation of new processes in order to adapt to the fast-paced and innovative pharmaceutical space. Moreover, NICE is one of the very few HTA bodies (another example is HAS in France that has a separate guidance on the assessment of RWE) that has published a framework for RWE. This framework targets manufacturers and researchers who are developing such evidence to inform NICE guidance. And its aim is to *"identify when real-world data can be used to reduce uncertainties and describe best practices for planning, conducting and reporting RWE to improve the quality and transparency of evidence*" (396). Therefore, NICE ensures a bit more clarity on how new types of evidence, beyond the gold standard RCTs, can be used in the context of HTA submissions, especially when long-term data are lacking, or in cases where other types of evidence cannot be generated, such as in the case of ultra-orphan medicines.

To improve timely patient access and ensure capacity to evaluate highly innovative medicines, the new proportionate approach to technology appraisals was recently adopted by NICE targeting medicines in the same disease area. This way, NICE ensures that HTA assessments are speeded up by up to 20 weeks for these medicines (397). Other accelerated approaches are seen in other HTA bodies. For instance, in France, the early access authorisation grants access to highly innovative medicines(398).

NICE provides the options to manufacturers to opt in for early scientific advice, and as shown in the second study of this thesis, provision of early scientific advice to manufacturers ahead of commencement of formal HTA process by HTA bodies can improve availability of clinically- and cost- effective medicines within markets and gatekeep the affordability of the healthcare system and of the patients. Therefore, the option of an early dialogue can help optimise both market and patient access to new and innovative medicines.

NICE is also an HTA body that seems to keep abreast with new and highly innovative medicines through acceptance of both non-randomised studies, such as single arm trials, especially in the case of HSTP, or new types of studies such as basket and/or umbrella trials in the case of new oncology treatments such as tumour-agnostic therapies. Nevertheless, this does not seem to be the case for other well-established HTA bodies such as G-BA in Germany which is more rigid and inflexible in terms of evidentiary requirements and acceptance.

As a common theme identified in this thesis, there is only a clear link between positive HTA recommendations and funding in England. For instance, the English NHS has to make available medicines approved by NICE within a period of three months (339). However, it is still unclear whether medicines with negative NICE recommendations are funded by the NHS. Nevertheless, NICE as the Scottish SMC are two HTA bodies that consider MEAs as a part of HTA. Therefore, funding recommendations are based on already negotiated discounted prices and/or agreements for additional evidence generation in cases where there is lack of (long-term) data, making the relationship between HTA recommendations and funding decision a bit more linear. In addition, NICE publishes the basis of commercial arrangements between the NHS and the manufacturer contributing to increased transparency and better understanding on how managed entry agreements are set up.

As mentioned above, even though NICE has many HTA features that could positively impact access to medicines, it has also been extensively criticised for its failings such as its inability to provide guidance on complex topics, heavy reliance on its quantitative methods, potential conflict of interest introduced by involvement of manufacturers during assessment, and ambiguity on how decisions are reached, among many others (153,399–403).

10.2.5 HTA and access to medicines

As illustrated from the results of all the thesis studies, although HTA is an essential instrument to streamline and monitor access to new medicines across settings, any action to achieve better and faster access should be complemented by other appropriate and effective regulatory policies and procedures, which are equally important. Targeted efforts and interventions at HTA alone will not necessarily translate to better access without adjustments in other areas of the access pathway. For instance, the fourth study of this thesis showed that medicines with a specialised MA or medicines with positive outcomes during pricing negotiations were positively associated with local funding.

In addition, even though this pricing mechanism has not been studied in this thesis, it is important to note that in many EU countries and in Canada, pricing of and/or reimbursement decisions for

new medicines are not only based on HTA recommendations. They are also informed or set by looking at a price benchmark calculated by the prices across a basket of reference countries, the so-called ERP (80,404,405). Therefore, ERP is another contributing factor as to why access to innovative medicines varies across countries. Such differences are due to the way ERP systems are designed, the reference prices used, and the way these prices inform pricing and reimbursement decisions. Specifically, variations across countries implementing ERP are observed due to inconsistent implementation of ERP's salient features including the basket countries used as a reference, the number of basket countries, the methods used to calculate reference prices and the frequency of price revisions, among others (406,407). Studies looking at the costs or prices of orphan medicines are limited, and they have shown that list prices of orphan medicines across countries using ERP, are broadly similar (404,405). Nevertheless, in a study that looked at prices of orphan medicines in twelve EU countries informing their prices through ERP, showed that when adjusting the costs using affordability parameters such as the countries' GDP and the country's ability to pay, the annual costs of orphan medicines were consistently higher in countries with lower GDP (404). Therefore, less wealthy countries have to considerably strain their limited budgets to provide patient access to these medicines. In addition, wealthier countries, which are usually used as basket countries, have a much higher negotiating power than less wealthy ones. Consequently, these countries may be granted higher price discounts (404). It has also been documented that as list prices rather than transactional prices are considered during ERP, less wealthy countries may end up referencing artificially higher prices.(8,404,408). It has also been noted that manufacturers are reluctant to launch their new medicines in countries which use ERP predominately to inform pharmaceutical prices, as these countries are more likely to have lower prices which might be used as reference in bigger markets (404,408,409). Therefore, launch delays have been observed in lower-income countries or countries solely relying on ERP when setting pharmaceutical prices (404,407,408). All these in addition to other international spillover effects of ERP, such as price convergence towards lowers prices across markets, are further factors that might results in a lack of incentives to manufacturers to invest in R&D of highly innovative medicines (407,409). This further reiterates that targeted efforts only at one stage of the access pathway, such as HTA, might not be enough to improve access to innovative and potentially life-saving treatments. Therefore, synergies and collaborations across all the stages of the access pathway are urgently needed. Otherwise, efforts at one stage of the pathway are likely to be unsuccessful.

Some collaborations across the stages of the access pathway are currently observed. However, they seem to be loosely enforced. For instance, in the third study, orphan medicines with a MA through specialised pathways had longer market access timelines than medicines that underwent standard MA in both study countries. This was the case also in Canada, despite the implementation of the parallel review process which allowed assessments for MA and HTA to occur simultaneously. This example showed that regulatory agencies were trying to expedite access to medicines of high unmet need. However, HTA processes for these medicines seemed to take much longer, potentially due to limited clinical evidence and high uncertainty. To tackle such issues and safeguard healthcare systems from the entry of technologies with modest efficacy and low added therapeutic value, timely information exchange is crucial between regulatory agencies and HTA bodies. Possibly, some harmonisation of the definitions and criteria used to decide whether a medicine is considered, for instance, as one that targets an unmet need, is needed. Moreover, similar clinical evidentiary requirements for MA and HTA might be beneficial to avoid potential discrepancies in the decision of the two agencies. At the same time, other collaborating initiatives could be further introduced. For example, the Scottish HTA body (SMC) has implemented an interim acceptance where medicines with a conditional MA receive a conditional HTA positive recommendation until more evidence is generated. However, this example highlights again the importance of RWE generation and its use in decision-making.

Finally, it is essential to mention that other healthcare system-related factors, such as the healthcare system's readiness, appropriate prescribing practices and care provisions at the national/regional level, are also equally important when looking at ways to optimise access to new medicines within markets. Therefore, efforts to improve access to new medicines within markets should holistically target all the stages of the access pathway which are all crucial in ensuing patient access.

10.2.6 Implementation of specialised processes for orphan medicines

As discussed extensively in this thesis, orphan medicines are a very interesting case study to explore when examining access to new medicines within markets and the dynamics across the different regulatory stages of the access pathway. High R&D costs and low sales, potentially not resulting in a return on investments, coupled with several incentives offered to manufacturers in some healthcare systems, are some of the key drivers of orphan medicines' high price tags. However, their transactional prices might also remain high: To not compromise equity and ensure that disproportionally affected patients are treated equally to other patient populations suffering from more common diseases, health insurances usually have to accept the high requested prices by manufacturers.

Further debate exists on whether orphan medicines should be treated differently than non-orphan medicines. For instance, whether specialised frameworks that introduce higher levels of flexibility in value assessments, or orphan regulations, which offer various incentives to manufacturers, should be implemented to ensure better access to these medicines. The thesis third study explored whether specialised processes for orphan medicines were associated with better and faster market access. While the fourth study explored whether having a national strategy for these medicines can help minimising access variations in a decentralised healthcare system.

However, according to the findings of this thesis, it is unclear whether specialised processes for orphan medicines should be implemented to improve access within markets. Arguments in favour and against their implementation exist, and policymakers should carefully consider the best strategy based on their healthcare system's objectives and values. While they should be prepared to make necessary trade-offs.

On the one hand, processes and policies targeting orphan medicines might emphasise affordability issues: Even though these processes may be considered critical in encouraging manufacturers to invest in R&D, they may have contributed to their very high prices (65,215). The policy environment for rare diseases in some countries has given leeway to manufacturers of orphan medicines to make a considerable profit, as they can exercise monopolistic power to request and retain high price tags while testing the flexibility of healthcare systems in accepting higher costs per QALY. For instance, as per the results of the third study, despite the positive impact of the Scottish PACE process, concerns were raised amongst key Scottish stakeholders as to whether it might have reduced manufacturers' incentives to lower prices and further weaken the negotiating position of the Scottish NHS (137,229,358). Affordability concerns were not limited only to the price of orphan medicines. Policies for rare diseases have also been criticised for taking up finite resources of healthcare systems that could have been redirected to non-orphan medicines treating more common conditions that affect a higher proportion of the general population (60,80,215,227,357). For instance, various specialised funds are present in the Canadian province of Ontario. These funds do not target solely medicines for rare diseases but also target cancer medicines or other high-cost therapies. However, as illustrated in the fourth study, most orphan medicines with negative HTA recommendations were made available through these funds, potentially leaving fewer monetary resources available for the reimbursement of other eligible non-orphan medicines.

On the other hand, dedicated assessment processes for orphan medicines can ensure that the patient's voice is considered during the assessment process (229), which was not seen in the case of Canada, where patient involvement is only seen in very few instances on an ad-hoc basis. Additionally, specialised assessment processes may increase HTA bodies' readiness to handle submissions with high uncertainty due to limited clinical evidence (23). This was illustrated in the third study by the Scottish HTA recommendations: Positive HTA recommendations in Scotland were mainly limited to economic restrictions (predominately funding mechanisms). However, HTA recommendations by CADTH were applying both clinical and economic restrictions to control the use of orphan medicines to a greater extent aiming to safeguard the sustainability and affordability of the healthcare system as much as possible. Finally, especially in the case of decentralised systems, such as that of Canada, where HTA is performed at federal level and funding decisions are a provincial competency (except Quebec), having national specialised assessment frameworks for orphan medicines might alleviate access variations and safeguard the sustainability of local healthcare systems. This way local governments will rely on the national process for the assessment of orphan medicines, which will apply higher flexibility in their assessments to respect their unique nature. And local funding will be further controlled to avoid availability of orphan medicines which show poor clinical and cost-effectiveness.

Therefore, there are strong arguments in favour and against of treating orphan medicines differently than non-orphan medicines. In the sub-section 10.2.7, I suggest ways to improve access to orphan medicines considering all the aforementioned arguments outlined in this sub-section.

10.2.7 Ways to improve access to orphan medicines

There are different ways that can be pursued to find the right balance between accounting for the sustainability of healthcare systems, a public health desire to drive prices of orphan medicines down and continuing to incentivise manufacturers to develop these medicines.

First, introducing competitive pricing negotiations as part of the value assessment process could be considered to aid in mitigating cost-effectiveness concerns during HTA. This way, HTA bodies can make final funding recommendations considering the already discounted prices of orphan medicines suggested by manufacturers from the onset. Therefore, access will be accelerated, and the relationship between HTA and funding will be more transparent. In Scotland, discounted prices or risk-sharing agreements proposed by the manufacturers were considered through PAS during the assessment process. However, such a strategy would not be as straightforward to implement in decentralised settings. In Canada, HTA recommendations are made at a federal level

(except Quebec) using a notional WTP threshold. Funding decisions are consequently made at the provincial level, considering the local budgets and risk-sharing mechanisms available as well as the outcomes of pan-Canadian pricing negotiations. Therefore, in decentralised systems, where local budgets exist, a possible solution could be to perform a comparative clinical benefit assessment of orphan medicines at the national level, while cost-effectiveness and budget impact analyses could be performed within regions. This way, potential duplication of efforts can be avoided, and the relatability of national HTA recommendations with regional funding can be strengthened. Another possible solution could be to have a fixed and strict range of a WTP threshold, which will serve as a top price ceiling, at the national level applied only for specific medicines such as orphan medicines. This way, manufacturers will be encouraged to discount prices before submitting their dossier to the HTA body.

Second, to avoid exploitation of available incentives by manufacturers and safeguard the sustainability of the healthcare system, HTA bodies and health insurance can introduce conditional positive recommendations and conditional funding, respectively, to orphan medicines for a specific timeline subject to some pre-agreed criteria such as generation of additional evidence. Such an example is seen in Scotland with the interim acceptance of SMC. By introducing similar initiatives, the equity principle will not be compromised, and patients will have timely access to orphan medicines. In addition, the local health insurance will not have to commit to the long-term funding of medicines that might not show substantial clinical benefit in the long run. A best practice example is seen in Australia, where orphan medicines with a negative HTA recommendation due to lack of cost-effectiveness but considered to be clinically effective, are subject to funding through the Life Saving Drugs Program. This program is a specialised fund targeting medicines for life-threatening and rare diseases. Unlike other specialised funds (as seen from the results of the fourth study), this program ensures access only to orphan medicines that are clinically effective.

Third, the use of MCDA tools could also be considered during HTA to account for the unique nature of orphan medicines, diverging views of key stakeholders, other value criteria along with clinical benefit and cost-effectiveness, and the quality of the submitted evidence (53,54,218). In addition, new value assessment systems could inform both pricing and funding of orphan medicines based on pre-defined evaluation criteria, including, amongst others, the level of research undertaken by the developer including manufacturing complexity, and follow-up measures required by regulatory and/or other authorities (60).

Fourth, as it has been increasingly observed over the last years, HTA bodies are adopting specialised processes for medicines treating ultra-rare diseases (i.e.: those affecting less than 1 in 50,000 people) with no available comparators or orphan medicines with no therapeutic alternative within the market, instead of applying different criteria for all the orphan medicines, which might have other available treatments in the same disease area within the market. Such examples are the HSTP implemented by NICE, the ICER's modified Value Assessment Framework for ultra-orphan medicines in the US, and both the Life Saving Drugs Program and the rule of rescue applied by PBAC in Australia (23,341). Most of these specialised processes recognise the potential challenges of generating evidence for ultra-orphan medicines or orphan medicines with no therapeutic alternatives while allowing for a higher WTP threshold recognising the burden of R&D costs by the manufacturers (410,411). While in Lithuania, Slovakia and Belgium, manufacturers of ultra-orphan medicines do not require to submit economic evidence to prove their cost-effectiveness (23). Unlike the implementation of specialised processes for all orphan medicines seen in other countries, such as in Germany, adoption of these processes is not anticipated to have a considerable burden to local budgets due to the very small portion of the population that will need access to these treatments. While incentives to invest in R&D for rare and very rare diseases in order to tackle areas of high unmet need still remain. Therefore, by limiting exceptions to ultra-rare medicines or orphan medicines with no therapeutic alternatives, rather than all orphan medicines, could potentially tackle previous concerns of healthcare systems about the exploitation of incentives by manufacturers, especially, when other alternative treatments are present within a market. However, it is important to note that based on the results of chapter 9 in this thesis, no positive association was observed between ultra-orphan status and favourable funding decisions in Ontario, Canada, showcasing that some payers might not treat differently treatments that target rare diseases versus those that target ultra-rare ones. Similarly, presence of other treatment alternatives in the same disease area within my sample of orphan medicines did not impact funding.

Finally, as discussed in section 10.2.5, better collaborations across respective institutions responsible for all the stages of the access pathway are needed for better and timely access to orphan medicines. And targeted efforts at different stages of the access pathway should be aligned to achieve their aims jointly. For instance, as illustrated in the third and fourth studies, access to orphan medicines in Canada was not halted even in the absence of specialised processes and of a national plan for orphan medicines. On the contrary, more than half of these medicines were granted MA through specialised pathways at the regulatory level; consequently, these medicines

(with a specialised MA) were more likely to receive favourable funding recommendations by CADTH, and at the provincial level, they were receiving funding through specialised funds.

Collaborations can also take place on a smaller scale: For instance, requirements for additional data collection should be aligned between MA and HTA bodies to reduce further complexity, as seen in Scotland. And the use of performance-based MEAs relying on RWE can be explored in some cases to optimise access to orphan medicines due to usually uncertain clinical evidence (24,54). The latter again highlights the importance of having an established framework for using RWE during HTA and funding decisions.

Yet, all these suggestions are not the panacea to access challenges observed in the case of orphan medicines. The introduction and use of programmes such as the ones mentioned above and other regulatory and value assessment policies targeting orphan medicines should be thoroughly assessed before their introduction and implementation. If specialised processes for orphan medicines are implemented within a setting, they should be accompanied by strict and transparent guidelines regarding the safety, clinical effectiveness, pricing of eligible medicines, and appropriate mechanisms to prevent potentially catastrophic costs to the healthcare system. However, it is also important to highlight that the complete absence of specialised processes for orphan medicines across the access pathway might impede availability and access to treatments that might not fit perfectly the strict HTA criteria, while it could result in higher unmet needs for patients suffering from rare diseases.

10.3 Key limitations

Limitations related to the specific research conducted in each of the four studies are discussed in the relevant main chapters of the thesis (please refer to chapters 6-9). In this section, I outline overarching limitations across the whole thesis that should be considered when reading my conclusions.

10.3.1 Access definition and metrics

This thesis focused on access to medicines within markets rather than studying patient access. Patient access may depend on many other system and macro-related factors, which are often challenging to quantify and standardise across different settings. In addition, especially in the case of new and innovative medicines and orphan medicines, patient access may be further granted either on a case-by-case basis or through dedicated funds (79,80). It can also be granted through compassionate use programmes available in some settings for medicines that the respective regulatory authority has not yet approved. However, this thesis did not capture access to new

medicines on a case-by-case basis or through compassionate use schemes. Access to medicines was explored only for medicines that have been granted a MA and have proven clinically effective and safe to use prior to HTA or in parallel to the HTA process.

This thesis did not capture the availability of medicines through private health insurance or OOP payments of patients. Funding of new and orphan medicines using public resources was only explored, given that the study countries provide universal health coverage to patients. Thus, a large proportion of the population can access medicines via the public system.

All the thesis studies examined access to medicines within markets by deep diving into HTA systems and the relationship of HTA with other regulatory stages of the access pathway. However, this thesis did not individually assess the performance of different regulatory stages of the access pathway, such as MA processes or implementation and uptake of MEAs. It provided evidence, when possible, on the dynamic relationship of HTA with other regulatory processes and studies, specifically the performance of HTA systems across the study settings.

Finally, the time to access analysis in the third paper and the metric used throughout the thesis for timely access did not capture any further delays that might have occurred after the publication of the HTA decision due to subsequent pricing and reimbursement negotiations.

10.3.2 Data sources and sample

Publicly available sources were used for the data collection in all the studies of this thesis. Reliance on secondary sources might mean that some nuanced information might not have been captured. However, publicly available reports on the operationalisation features of HTA and on HTA recommendations for funding were widely available through the websites of the respective HTA bodies. In addition, this evidence and data were deemed sufficient and comprehensive for examining the research questions of each of the thesis studies.

As the first and second studies of this thesis relied on primary data collection, potential bias might have been introduced to the findings. Relevant limitations associated with primary data collection include small sample size caused by low participation and high dropout rates, limited or lack of representation of some stakeholder groups and limited geographical representation. To tackle such issues, both studies relied on secondary data collection, while primary data collection was used to validate relevant findings. Thus, results from both studies can still be considered informative.

An iterative process was employed to code and classify the extracted information from publicly available sources. Therefore, a risk of bias due to subjectivity might have been introduced in the

categorisation of data. However, for both the first and second studies, primary data collection, through an expert consultation round and a Delphi panel, respectively, were collected to validate secondary data collection. And in the fourth and third studies, the categorisation of HTA outcomes and main reasons for recommendation have been previously used in similar studies (13,129,131,132).

A critical limitation of the thesis is that funding negotiation processes between health insurance and manufacturers occur behind closed doors. This way, it is impossible to understand fully whether HTA recommendations are informing funding decisions and to what extent. Or disentangle the main drivers of the funding decision-making process. To tackle such issues, I explored access to medicines in a holistic way, looking at different stages of the regulatory pathway, but also, I conducted research on settings where the use of HTA in funding decisions was, at least, clear to some extent (i.e.: when there is a positive HTA recommendation for funding). Therefore, one can assume that these medicines were more likely to be funded using public funds.

In the third and fourth studies, given that Canada has no orphan designation and definitions of rare diseases differ across settings (203), the sample of medicine-indication pairs might not be as accurate and inclusive as possible. However, using both the FDA and the EMA list of medicines, I tried to include a comprehensive and representative sample of orphan medicines to the best of my abilities. Lastly, the methodology employed for the sample identification was used to ensure that a broader range of products was included from the outset. However, all possible sampling strategies will have had an impact on the number and products included in the sample.

10.3.3 External validity

Concerns regarding the generalisability of the thesis findings arise mainly from the second and third studies. In the first study, the framework designed can be applied to all settings that use HTA explicitly regardless of how well-developed and established HTA processes are. However, it would be challenging to use this framework in settings where HTA is used implicitly and on an ad-hoc basis. Even though the second study focused mainly on the European perspective about what HTA features can improve access and what features need improvement, findings can be applied to other developed settings.

Contrary to the first two studies, the findings of the third and fourth studies cannot be extrapolated to other healthcare and HTA systems that are not similar to that of Scotland and Canada. Even these two countries differ in country size, population, and GDP, as well as their WTP threshold

per QALY and where funding decisions are made (i.e.: at national or regional level), among other factors which can directly and indirectly impact access to orphan medicines.

Both the third and fourth studies, which focused on access to medicines for rare diseases, lacked a control group of non-orphan medicines. Therefore, in the third study, I could not determine whether more favourable HTA recommendations in Scotland were seen due to the presence of specialised pathways only and not due to other system-related factors or differences in the way medicines were assessed in both Scotland and Canada. In the fourth study, the lack of a control group did not allow to test whether the medicines for rare diseases might have influenced the associations between positive HTA recommendations and funding in Ontario. However, previous studies that have looked at the same question but not on orphan medicines showed similar results. Lastly, in the fourth study, access to orphan medicines was studied only in one province, and no comparisons with other provinces were made. Therefore, the finding that access to orphan medicines in Canada depends on each province's wealth and negotiating power cannot be conclusive without further research on the funding status of the same medicines in other provinces.

Finally, it is important to note that this thesis did not aim to prove causality in any of the included studies. Access variations to medicines can be attributed to a variety of factors: some are associated with broader-level features such as (i) the general country characteristics, including gross domestic product (GDP) per capita and the epidemiological profile; and (ii) the country's healthcare system characteristics, including healthcare expenditure, organisation of the healthcare system and clinical practices. Others are associated with more specific features such as (iii) the pharmaceutical market characteristics, including regulatory frameworks and the policies medicines undergo to become available and publicly funded in a given market. However, factors contributing to these variations are not only limited only to the aforementioned ones. In addition, the relatively small sample size of orphan medicines in my studies would have not allowed for multivariate analysis. Therefore, this thesis places a greater emphasis on descriptive and qualitative analyses aiming to get a better understanding of the multifaceted nature of HTA and its role in the market access pathway.

10.4 Ideas for future research

This thesis examined three overarching policy issues through four specific research questions addressed in chapters 6-9. However, several other areas for future research can be identified to explore further the broader policy issues and implications.

First, primary data collection through interviews of key stakeholders will be needed to gain a better insight into the funding negotiation processes and the extent to which HTA is used during pricing and reimbursement decision-making across the study countries. More specifically, semi-structured interviews with policymakers and health insurance officials can help us better comprehend the use of HTA as a cost-optimisation tool, given that negotiations are taking place behind closed doors and information on MEAs is usually kept in confidence. Key stakeholders from various settings where HTA systems differ could provide a deeper and broader understanding of the implementation of HTA in decision-making, its extent, and how HTA systems differ across countries.

Second, a Delphi panel including non-European stakeholders could help us further explore how HTA processes, procedures, and systems can be optimised from an international perspective to alleviate access variations caused by HTA. Even though current efforts to harmonise HTA processes at the European level are very helpful, we should consider that procedures and processes employed by other key HTA bodies, such as the Canadian and the Australian ones, are equally important to study when looking for ways to improve HTA procedures and processes. In addition, strengthening international collaborations could help in avoiding launch delays and launch sequencing strategies by manufacturers in settings where HTA processes are unclear and non-transparent. While it can contribute to information exchange which will increase the readiness of HTA bodies.

Third, to better understand the drivers of HTA outcomes and why these may differ across countries, we should explore in greater detail the HTA process of the sampled medicines in terms of assessment and appraisal of clinical and economic evidence. For instance, in the case of orphan medicines, beyond the implementation of specialised assessment processes, other determinants involved in the assessment process of these medicines may have influenced the final HTA outcome in the study countries. These include but are not limited to the type of clinical evidence submitted, the size of the clinical benefit, the performance of patient-reported outcomes, the economic model employed, the comparators used and the time horizon of the economic analysis. The way that HTA bodies deal with potential uncertainties raised, regarding the submitted evidence when benchmarked against scientific and social value judgments, is also important to explore when examining HTA outcomes across HTA bodies. Therefore, to account for all the drivers of HTA recommendations for funding across different HTA bodies, we should examine in greater detail the assessment and appraisal of each medicine-indication pair and subsequently compare these data across settings.

Fourth, to determine whether the presence of specialised assessment frameworks for orphan medicines is the main driver for better access to these treatments, a comparative analysis between a sample of orphan medicines and non-orphan medicines, as a control group, could be performed in a setting where specialised assessment processes for orphan medicines are implemented, such as Scotland, France, Germany or Australia. This way, we would be able to explore whether more favourable HTA recommendations are seen for orphan medicines compared to non-orphan ones. However, a study like this will entail a very thorough sample identification process of non-orphan medicines as we should make sure that non-orphan medicines are not subject to other flexible criteria as it would have been in the case of oncology medicines or other medicines treating life-threatening conditions. In addition, as an extension of the fourth study, having a comparative sample of non-orphan medicines could help us understand whether, in Ontario, negative HTA recommendations are not generally translated to no funding or whether this is the case only for medicines treating rare diseases.

Fifth, as suggested in sub-section 10.2.6, MCDA tools could also be used during HTA processes, especially in the case of orphan medicines, to account for diverging views of key stakeholders, other value criteria along with clinical benefit and cost-effectiveness as well as the quality of the submitted evidence (53,54,218). Through, MCDA tools different weights can be assigned to value dimensions to account for the healthcare system's objectives and values. In addition, potentially new value assessment systems could be developed to inform both pricing and funding of orphan medicines based on pre-defined evaluation criteria, including, amongst others, the rarity and severity of disease, the level of research undertaken by the developer including manufacturing complexity and follow-up measures required by regulatory or other authorities (60). Using the suggested system could provide a more transparent and collaborative approach amongst key stakeholders. It could give the opportunity to healthcare payers to decide on medicines funding based on a mix of societal preferences, the objectives of the healthcare system and the available resources (60). Alternatively, a value-based pricing policy based on HTA recommendations could be explored for the pricing of orphan medicines to link prices with their added clinical benefit and cost-effectiveness (53).

Sixth, price comparisons could be performed to explore whether orphan regulations that offer various incentives to manufacturers, including market exclusivity, result in higher prices in settings where such regulations are implemented. Provisional to the accessibility of such data, price comparisons of orphan medicines in European countries, the US and Australia could be conducted. In Europe and the US, manufacturers are granted a period of marketing exclusivity.

However, in Australia, despite the presence of an orphan regulation, manufacturers do not have monopoly in the market. Similarly, price comparisons could be performed in countries where orphan regulations exist compared to Canada, where a national strategy for orphan regulations has not been implemented yet. A limitation of such a study though would be the availability of only list prices rather than transactional prices which are confidential. Nonetheless, we would be able to initially explore whether the availability of incentives for manufacturers drives high prices of orphan medicines.

Finally, further research could be performed for time to access analyses to understand precisely how long it takes for a medicine to reach a specific market. For instance, from the time manufacturers have submitted a request for MA to the time the medicine has been listed in the local formularies.

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Appendices

10.5 Appendix 1

Example of country-specific document sent to the Belgian expert as a part of the expert consultation round of Paper 1

Country	HTA Agency/ Institution undertaking HTA activities (National/Regional)	Type of organisation	Governance of HTA	Role of HTA	Model of HTA	Type of assessment	HTA and funding decisions	Technologies assessed
Belgium	Kenniscentrum voor de gezondheidszorg · Centre fédéral d'expertise des soins de santé /Belgian Health Care Knowledge Centre (KCE)	Research institution	Arm's length	Advisory and coordination	Clinical and cost-effectiveness	Assessment	Non-binding	Pharmaceuticals, medical devices and other technologies
	Institut National d'Assurance Maladie-Invalidité/ National Institute for Health and Disability Insurance (INAMI)	National insurance organisation	Arm's length	Regulatory	Clinical and cost-effectiveness as a criterion	Appraisal	Non-binding	Pharmaceuticals, medical devices and other technologies
	Other (e.g.: Assessment at county council level). Please specify:							
	How the above organisations are connected to the use of HTA and reimbursement decisions? Please describe in the next cell							

Notes: *Type of organisation options: Research Institution; HTA-Research Institution= when the research institution has a department dedicated for HTA activities; National insurance organisation; National/Regional healthcare organisation= national or regional organisations, which might be independent or under the supervision of Ministry of Health focusing on public health ; National/Regional HTA Authority =when HTA is the main activity of the body; Governmental organisation =when it is part of the Ministry of Health; Drug Regulator= regulatory body for approval of medicines and/or medical devices with a clear separate HTA function.*

Governance of HTA: Integrated to the national and/or regional government= we considered the Ministries of Health, which undertake HTA activities directly themselves, as well as HTA committees, boards, councils and directorates, which perform assessments and function within the Ministry; Independent= the research institutions, HTA agencies, regulatory bodies with additional HTA activities beyond licencing and other governmental bodies, which might be subordinate to the Ministry of Health but still perform HTA activities in full independence.

Role of HTA options: Advisory= reimbursement or pricing recommendations to national or regional government, a ministerial department or a self-governing body; Coordination= independent research on HTA and are responsible for coordinating HTAs and/or developing clinical guidance by mainly collecting, producing and disseminating assessment research results; Regulatory= when the HTA function is incorporated into the regulatory agency

Model of HTA options: *Clinical and cost-effectiveness model= uses economic evidence in addition to comparative clinical benefit to assess health technologies; Comparative clinical benefit assessment model= model relies on ranking new interventions based on comparative efficacy or clinical benefit; Value based model= takes explicitly into consideration additional dimensions of value beyond effects and/or costs, such as disease severity, burden of disease, treatment innovativeness and equity considerations*

Type of assessment options*: Assessment= the collection and synthesis of clinical and economic evidence used to provide information to decision-makers to support funding decisions on new health technologies; Appraisal=the act of contextualizing evidence and formulating coverage recommendations and resource implications by interpreting the evidence and taking into consideration other socioeconomic factors such as severity of disease, unmet need and level of innovation.*

HTA and funding decisions options*: Binding; Non-binding*

Technologies assessed options: *Pharmaceuticals; Medical devices; Other technologies= Screening programmes, vaccination campaigns, evaluation of surgical and non-surgical interventional procedures, stem cell therapies, innovative cancer vaccines, gene therapies and other forms of personalized medicines and screening programmes*

10.6 Appendix 2

List of value dimensions as appeared to the Delphi participants in round 1

Value framework aspects	**Impact on availability** *(Availability in a market, but pre-reimbursement)*	**Impact on time to patient access** *(Availability to patients, post-reimbursement)*	**Impact on affordability** *(Prices in line with purchasing ability of systems and patients)*
Health technology assessment (HTA)			
Presence of an independent HTA body			
Scientific advice (feedback and advice on upcoming applications) provided to manufacturers ahead of commencement of formal HTA process by HTA bodies			
Use of horizon scanning			
Introduction of parallel review process to streamline MA and HTA			
Clarity of evidentiary requirements for value assessment in HTA (e.g.: clear instructions published by the HTA body on the evidence to be submitted by manufacturers; evidentiary requirements based on a validated or publicly available framework)			
Reliance on real-world evidence in HTA in case of limited, incomplete, immature, or early phase clinical evidence			
Stakeholder involvement during the HTA process			
Harmonization of rules for HTA methodologies, evidentiary requirements, and procedures across HTA bodies and systems at supranational level			
Coordination of HTA rules, methods and processes across national and regional level, if both co-exist			
Explicit recognition of additional dimensions of benefit beyond clinical and/or economic evidence considered during the evaluation of health technologies (example dimensions include unmet medical need, impact on carers and family, impact on society, etc.)			
Established procedures on how uncertainties resulting from submitted evidence are managed and resolved within an agreed-upon timeframe. (e.g.: request of additional evidence, sensitivity analysis, dossier re-submission)			

Value framework aspects	**Impact on availability** *(Availability in a market, but pre-reimbursement)*	**Impact on time to patient access** *(Availability to patients, post-reimbursement)*	**Impact on affordability** *(Prices in line with purchasing ability of systems and patients)*
Legally binding HTA recommendations to be implemented in the shortest possible timeframe during reimbursement negotiations			
No reliance on "HTA referencing" (requirement for positive HTA recommendations from other countries to commence or conclude the HTA process or reliance on HTA recommendations from other countries to inform decision-making)			
Agreed-upon timelines for the completion of HTA process			
Please insert other aspects during HTA processes that, in your opinion, can have an impact on either availability, time to patient access or affordability of medicines:			