Regulatory Policies vs HTA Practices and Their Impact on Access to Innovative Treatments

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DECLARATION

I certify that the thesis I have presented for examination for the 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 60,108 words, excluding the bibliography and appendixes.

STATEMENT OF CONJOINT WORK

All of the articles presented in Chapters 2-5 in this paper-based thesis have been published in peer-review academic journals. Some of the articles have been co-authored with Dr. Panos Kanavos (primary supervisory at the London School of Economics and Political Science), Mr. Daniel Michaeli (research assistant at the London School of Economics and Political Science), and Mr. Aurelio Miracolo (research associate at the London School of Economics and Political Science). I confirm that I contributed a minimum of 70% towards each of the co-authored articles.

The first article (Chapter 2) was co-authored by Dr. Panos Kanavos. It was published in *Health Policy*.

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Author contributions: I conceived the study, collected the data, analysed the data, interpreted findings, drafted the manuscript and am the guarantor. Panos Kanavos supervised the study, provided methodological guidance, assisted with interpretation of findings, and revised the manuscript prior to submission.

The second article (Chapter 3) was co-authored by Mr. Daniel Michaeli, Mr. Aurelio Miracolo, and Dr. Panos Kanavos. It was published in *BMC Health Services Research.*

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Author contributions: I conceived the study, collected the data, analysed the data, interpreted findings, drafted the manuscript and am the guarantor. Daniel Michaeli provided research assistance with data

collection and data analysis. Aurelio Miracolo provided research assistance with data collection. Panos Kanavos supervised the study, provided methodological guidance, assisted with interpretation of findings, and revised the manuscript prior to submission.

The third article (Chapter 4) was co-authored by Dr. Panos Kanavos. It was published in *Pharmacoeconomics Open*.

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The fourth article (Chapter 5) was single authored by myself. It was published in *Pharmacoeconomics*.

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OTHER RELEVANT WORK

During my thesis, I co-authored a number of other papers which did not contribute directly to my thesis but are relevant to the work presented:

- Mills M, Kanavos P. Do pharmaceutical budgets deliver financial sustainability in healthcare? Evidence from Europe. *Health Policy.* 2020 Mar 1;124(3):239-51.
- Gill JL, Mills MJ, Wharton GA, Kanavos PG. The future of oncology policy. J Cancer Policy. 2022 Dec;34:100352. doi: 10.1016/j.jcpo.2022.100352. Epub 2022 Aug 8. PMID: 35952940.
- Michaeli, D. T., Mills, M., & Kanavos, P. Value and price of multi-indication cancer drugs in the USA, Germany, France, England, Canada, Australia, and Scotland. Applied Health Economics and Health Policy. 2022 1-12.
- Michaeli, D. T., Mills, M., Michaeli, T., Miracolo, A., & Kanavos, P. Initial and supplementary indication approval of new targeted cancer drugs by the FDA, EMA, Health Canada, and TGA. Investigational New Drugs. 2022 1-12.
- Miracolo A, Sophiea M, Mills M, Kanavos P. Sin taxes and their effect on consumption, revenue generation and health improvement: a systematic literature review in Latin America. Health policy and planning. 2021 Jun;36(5):790-810.

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ABSTRACT

Introduction: Innovative therapies must overcome two key hurdles to be made available for routine use in a patient population. The first hurdle is regulatory approval, where the safety and efficacy of a therapy is evaluated to ensure it has a positive benefit-to-risk ratio. The second hurdle is health technology assessment (HTA), where a therapy is compared to the existing standard of care in terms of relative therapeutic benefit and, in many cases, cost-effectiveness to inform funding decisions. Objectives: This paper-based thesis explores the relationship between regulatory approval and HTA and its impact on patient access to innovative treatments. Specifically, this thesis examines two types of regulatory pathways which reduce clinical development time and expedite regulatory approval: 1) conditional marketing authorisation and 2) approval of medicines with multiple therapeutic indications.

Methods: Study 1 presents a rich descriptive analysis on the evidence gap between regulatory approval agencies and HTA agencies on conditionally approved medicines, along with an examination of the key clinical and economic issues raised by HTA agencies during assessment. Study 2 explores whether current pricing practices generate perverse incentives for the launch of medicines with multiple therapeutic indications through a mapping and analysis of regulatory approval and HTA approval sequence of multi-indication medicines. Study 3 presents the results of semi-structured interviews with current and former healthcare payers on policies relating to the assessment and pricing of multi-indication medicines. Finally, study 4 explores whether conditionally approved medicines face increased barriers at HTA level relative to products with standard regulatory approval, through an econometric analysis on the determinants of HTA decision-making.

Key Findings: Results from confirmatory trials for conditionally approved medicines are frequently not available at the time of HTA, requiring HTA agencies to make recommendations on the basis of single arm or early phase studies. Rejection rates for conditionally approved medicines vary significantly across settings. Rejected medicines have a higher frequency of unresolved issues in magnitude of

clinical benefit, study design and economic modelling. Relative to medicines with standard approval, conditionally approved medicines likely face increased barriers at HTA level, both in terms of probability of HTA approval and time to HTA approval. Current pricing practices likely generate perverse incentives to sequence the launch of multi-indication medicines. Pharmaceutical firms show a tendency to prioritise niche indications with high unmet need for their first indication and frequently withhold the launch of subsequent indications. Despite evidence of launch sequencing, most healthcare payers express concern that a formal indication-based pricing model would involve high administrative burden and expressed confidence that current systems would facilitate access to innovative therapies when an unmet need is genuinely addressed.

Policy Implications: HTA, pricing, and reimbursement systems likely limit the extent to which expedited regulatory pathways can accelerate patient access to conditionally approved and multi-indication medicines. Greater alignment on evidence requirements could be achieved through enhanced use of joint early dialogue or through implementation of conditional reimbursement policies such as England's Cancer Drugs Fund. If a formal indication-based pricing system is not feasible, then existing methods should be refined to better capture the incremental value of individual indications.

ABBREVIATIONS

ADEC – Advisory Drug Evaluation Committee (Australia)

AEMPS - The Spanish Agency of Medicines and Medical Devices

AIC - Akaike information criterion

AIFA – Italian Medicines Agency

AMNOG - Arzneimittelmarkt-Neuordnungsgesetz

AR – Adverse reaction

ARTG – Australian register of therapeutic goods

ASMR – Added medical service rendered

ATC – Anatomical therapeutic chemical

ATMP - Advanced therapy medical product (EMA)

ATU – Temporary authorisation for use (France)

BAG - Federal Office of Public Health (Switzerland)

BCVA - Best-corrected visual acuity

BOR - Best observed response

BPCA – Best pharmaceutical for children act

CAA – Commercial access agreement

CADTH – Canadian Agency for Drugs and Technologies in Health

CAP – Centralised authorisation procedure (EMA)

CBE – Center for Biologics Evaluation

CDER – Center for Drug Evaluation and Research (FDA)

CDF – Cancer Drugs Fund (England)

CEPS – Economic Committee of Healthcare Products (France)

CERB – Center for Evaluation of Radiopharmaceuticals and Biotherapeutics

CHMP – Committee for Medicinal Products for Human Use (EMA)

CI – Confidence interval

CMA – Conditional marketing authorisation

CR – Complete response rate

CTS – Scientific Committee (Italy)

CUP – Compassionate use programme

DNL – Do not list

DoH – Department of Health

DOR - duration of response

EAA – Early Access Authorisation (France)

EAMS – Early access to medicines scheme

EC – European Commission

EMA – European Medicines Agency

ERG – Evidence review group

ESMO – European Society for Medical Oncology

EU – European Union

EUnetHTA – European network for Health Technology Assessment

FAERS – FDA adverse events reporting system

FDA – U.S. Food and Drug Administration

FDC – Federal Drug Commission (Switzerland)

FVC – Forced vital capacity

G-BA – Federal Joint Committee (Germany)

GDP – Gross domestic product

HAS – Haute Authorité de Santé (France)

HPFB – Health Products and Food Branch (Canada)

HTA – Health technology assessment

IBP – Indication-based pricing

ICER – Incremental cost-effectiveness ratio

IND – Investigational new drug

INESSS - Institut National d'Excellence en Santé et en Services Sociaux

IQWiG - Institute for Quality and Efficiency in Health Care

L – List

LWC – List with conditions

MA – Marketing authorisation

MAA – Marketing authorisation application

MAEC – Marketing authorisation under exceptional circumstances

MAH – Marketing authorisation holders

MCBS – Magnitude of clinical benefit scale

MCDA – Multiple criteria decision analysis

MCyR - Major cytogenic response

MEB – Medicines Evaluation Board (Netherlands)

MHRA – Medicines and Healthcare Products Regulatory Agency

MMR – Major molecular response

MoH – Ministry of Health

MPA – Medical Products Agency (Sweden)

NDA – New Drug Application

NDS – New drug submission

NHS – National health service

NICE – National Institute of Health and Care Excellence (England)

NOC – Notice of compliance

NOC/C – Notice of compliance with conditions

OECD - Organisation for Economic Co-operation and Development

OR – Odds ratio

ORR – Overall response rate

OS – Overall survival

PA – Provisional approval

PAS – Patient access scheme

PASS – Post-authorisation safety studies

PBAC – Pharmaceutical Benefits Advisory Committee

PBM – Pharmaceutical benefit manager

pCODR – pan-Canadian Oncology Drug Review

PFS – Progression free survival

PIP – Paediatric investigation plans

PMPRB - Patented Medicines Pricing Review Board (Canada)

PR – Primary response

PREA – Paediatric research equity act

PRIME – Priority medicine

PSP – Paediatric study plans

PSUR – Periodic safety update reports

QALY – Quality adjusted life year

R&D – Research and development

RCC – Renal cell carcinoma

RCT – Randomised controlled trial

RFS – Remission free survival

RIZIV-INAMI – National Institute for Health and Disability (Belgium)

RMAT – Regenerative medicine advance therapy (FDA)

RMP – Risk management plan

SEGA - subependymal giant cell astrocytoma

SGK – Social Security Agency (Turkey)

SMC – Scottish Medicines Consortium (Scotland)

SMR – Medical service rendered

SNDS – Supplement to a new drug submission

SVJ – Social value judgment

TGA –Therapeutic Goods Administration (Australia)

TKI – Tyrosine kinase inhibitors

UK – United Kingdom

UNCAM – National health insurance funds (France)

US – United States

USA – United States of America

VA – Veteran Affairs (USA)

VPAS – Voluntary scheme for branded medicine pricing and access (England)

WHO – World Health Organisation

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INTRODUCTION

I. Access to Innovative Medicines

A growing body of literature has reported substantial heterogeneity across settings in patients' ability to obtain medicines [1-4]. Patient access to medicines within a healthcare system typically requires two events: a) a marketing authorisation (MA) decision and b) a coverage decision. MA may be granted by a supranational (e.g. European Medicines Agency (EMA)) or national (e.g. Health Canada) regulatory agency once a medicine has demonstrated an acceptable risk-benefit profile on the basis of efficacy and safety data obtained through clinical trials. Subsequently, HTA bodies on behalf of insurance organisations (e.g. HAS - France) will typically assess and appraise the medicine's relative clinical and/or economic effectiveness to determine if there is value in including it in the package of care reimbursed for the eligible population.

Differences in the availability of medicines across settings suggests the presence of a 'post-code lottery' for access to potentially beneficial treatments [1]. This is particularly concerning given a) the level of annual expenditure on medicines and b) the role medicines play in promoting patient health. On average pharmaceutical expenditure accounts for 18-19% of total healthcare expenditure and approximately 1.5% of GDP in Europe, implying a substantial opportunity cost associated with inefficient spending [5]. Quantitative studies examining determinants of population health have found pharmaceutical expenditure to be a significant determinant of heath [6-8]. Delays in access to medicines are not only associated with negative health consequences for patients, but can also lead to long-term increases in health care costs [9].

Variable availability of medicines is further compounded by the presence of alternative access pathways across settings. In order to accelerate the availability of new therapies, a number of regulatory agencies have implemented early access to medicines schemes (EAMS). Typically, these pathways aim to provide earlier access to medicines that (a) represent substantial innovations, (b) provide important therapeutic benefits and (c) address an urgent unmet need [10]. Within the EMA, the conditional marketing authorisation (CMA) pathway provides authorisation to medicines on the basis of early clinical evidence for medicines that fulfil an unmet medical need on the condition that data collection is completed post-authorisation. Other schemes accelerate access by shortening the review time for innovative medicines (e.g. EMA accelerated assessment, Health Canada priority review), authorising new or extended therapeutic uses of a previously authorised medicine (EMA type II variation) or providing enhanced and early scientific advice (e.g. EMA PRIME) [11]

While MA may be accelerated at regulatory level, it remains unclear if this translates to earlier patient access at health system level, as many HTA agencies and reimbursement authorities require robust evidence to fund new treatments. As a result, a growing tension has emerged between regulators promoting early access and HTA agencies that make decisions on comparative clinical benefit and value for money. Evidence suggests that the ability of EAMS to select medicines with high added clinical value may be limited [12, 13]. This is reflected at national level, where uptake of medicines that have proceeded through an EAMS appears to be highly variable [14].

In order to hedge against the increasing cost of new medicines, many countries employ global budgets that fix annual medicine spending on historical data, affordability criteria, or other macro criteria [15]. Based on a fixed budget, health systems must then make resource allocation decisions around which patients to cover, how much of the cost to cover, and which medicines to include in the benefits catalogue.

New medicines, while potentially beneficial for patients, are increasingly presenting challenges for health care systems from a financing perspective due to a) uncertainty about their level of added benefit, b) their high cost, and c) their increasing number. In particular, HTA agencies may be reluctant to recommend high-cost medicines that only provide minor clinical benefit. Examples of total costs per patient in the range of US$ 15,000 - $90,000 for cancer medicines with increases in median overall survival of less than 3 months are shown on Table I.1.

Table I - Examples of High-Cost New Cancer Medicines with Minor Clinical Benefit

Medicine	Indication	Total costs per patient (US$)	Estimated increase in survival
Cetuximab	Non-small cell lung carcinoma	80 352	1.2 months
Bevacizumab	Metastatic breast cancer	90 816	1.5 months
Erlotinib	Pancreatic cancer	15 752	10 days
Sorafenib	Renal cell carcinoma	34 373	2.7 months

Source: [16]

Further, in deciding on coverage of a new medicine, countries are often faced with a trade-off between equity and efficiency. The WHO originally recommended that where the incremental cost-effectiveness ratio (ICER) is less than a country's GDP per capita, the technology should be considered cost-effective. In practice, many countries do not use explicit cost-effectiveness thresholds (e.g. Norway or Sweden) or frequently deviate from semi-explicit thresholds (e.g. England) for certain disease areas [5, 17]. Specifically, medicines for rare diseases (prevalence below 5 in 10,000), are frequently funded at extremely high prices in order to offset the limited potential revenue from a small patient population. New orphan medicines are frequently priced between US$ 300,000 and US$ 400,000 per patient per year [18].

High-priced medicines are likely to continue to pose challenges given high numbers of medicines undergoing development and given trends in the approval of medicines. Figure 1 shows trends in medicines receiving authorisation from the EMA between 1996 and 2017.

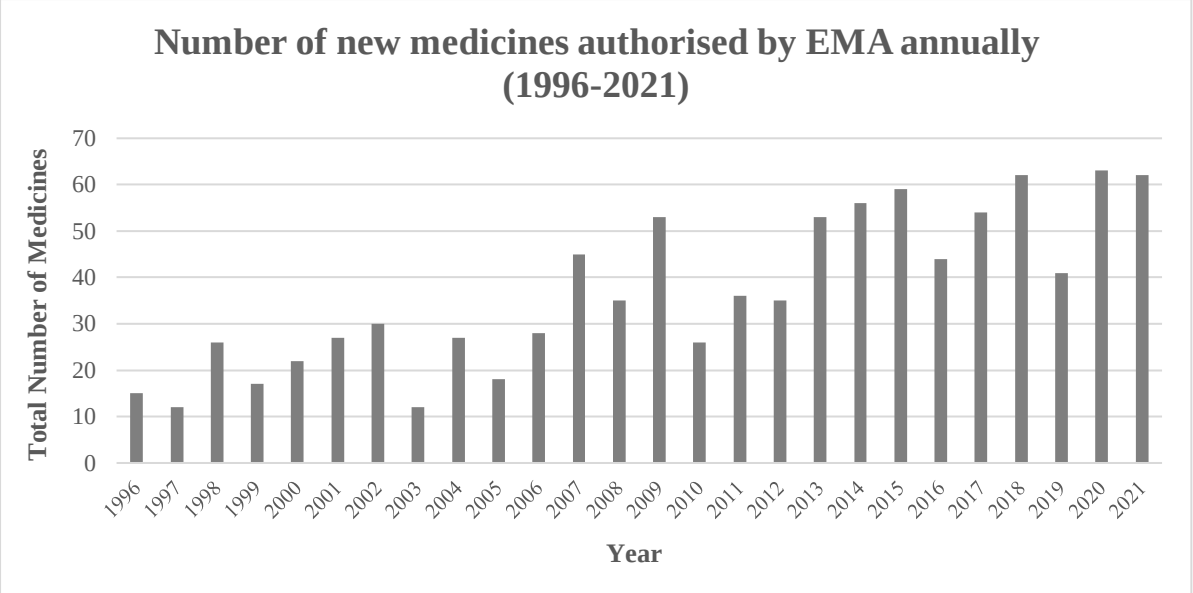


Figure I - Annual New Medicine Authorisations by EMA (1996-2021)

Source: Adapted from [19]

Given current trends in the pharmaceutical market, delays in access to medicines and differences in availability of medicines across settings are likely to become more prominent as countries attempt to allocate their medicine budgets to achieve value for money and to cover as wide a range of conditions and patients as possible. Health technology assessment is likely to become increasingly relevant in this context, as a key tool used by health systems to inform coverage decisions [20]. However, the methodologies employed, types of evidence considered, and the interpretation of evidence by HTA agencies vary considerably across settings [21].

The present thesis evaluates differences in regulatory practices vs HTA practices in order to assess their impact on access to innovative medicines. Specifically, this thesis focuses on two regulatory policies which aim to reduce clinical development time: a) conditional marketing authorisation; and b) marketing authorisation indication extensions.

II. Thesis Requirements

This thesis adheres to Department of Health Policy, London School of Economics and Political Science guidelines for a Thesis by Publishable Papers, which states that "(1) the papers concerned should actually have been published in high quality refereed journals, be submitted for publication to such a journal, or be of a quality to be published in such a journal; (2) the introduction to the thesis should link the papers; (3) the thesis should consist of at least 3 papers, an introduction, conclusion and any other linking chapters that might be appropriate; (4) the thesis should have a minimum of 50,000 words and a maximum of 100,000 words including figures and tables in the overall count; (5) the introduction and conclusion should have no specific word limit; (6) the large majority of the work for the papers concerned should have begun after the student's initial registration for MPhil/PhD; (7) at least one paper should be single authored, and any other papers should be primarily authored, by the student; and (8) if there are any co-authored papers, the thesis should be accompanied by specific detailed statements on the contribution of the co-authors.

III. Structure of the Thesis

Chapter 1 provides a literature review outlining the currently available literature examining determinants of availability of medicines and provides a review and comparison of different regulatory and HTA policy modalities. Chapter 1 also identifies outstanding gaps in the literature and research objectives.

Chapters 2 through 5 present the empirical results of each of the four papers that make up this thesis.

Chapter 6 summarises the key conclusions of each paper, discusses policy implications, outlines research limitations, and provides areas of future research.

A more detailed overview of the data sources and methods is provided in an Appendix chapter.

1. REVIEW OF LITERATURE ON ACCESS TO MEDICINES

1.1 Review of literature examining pharmaceutical firm entry and availability of medicines

Economic theory on institutional design suggests that both formal and informal institutions play a key role in determining the entry rate of new firms within a market [22, 23]. Formal institutions (e.g. regulatory barriers) are explicitly defined and set the 'rules of the game' while informal institutions (e.g. traditions, customs, social capital) are commonly known, but tend to be implicit [23]. While some studies report that high regulation generally deters entry of new firms [24, 25], others suggest that the interaction is likely more complex in the sense that both formal and informal institutions can have either positive or negative impacts on firm entry [22].[1]

In the context of the medicines market, published literature has contributed a great deal into understanding differences seen in the availability of medicines across settings, with a particular focus on the role of regulation, among other types of institutions, in new firm entry to market. In a review of anti-cancer medicines availability in Europe, Ades et al. explores the various institutions that are responsible for hurdles of patient access to medicines. Specifically, delays and differences in access to medicines can arise from all stages of a medicines life cycle including: a) during medicine development; b) during regulatory review; c) during HTA; d) during subsequent pricing and reimbursement; and e) during adoption of a reimbursed medicine into clinical practice [26].

[1] For instance, while lack of protection of property rights may deter firms from entering a market, this may be compensated by informal institutional mechanisms such as access to illegal credit or a lack of enforcement of labour regulations. For more information on the characteristics and role of institutions on new firm entry see Estrin and Prevezer 2010.

1.1.1 Medicine development

Medicine development is guided by requirements for marketing authorisation set by national or supranational regulatory agencies. Increasingly, evidence requirements from HTA agencies are also playing a role in medicine development [27]. In theory, early access pathways such as conditional marketing authorisation can reduce medicine development time by providing marketing authorisation on lower levels of evidence under the condition that additional evidence is generated. In a study of the EMA conditional approval and marketing authorisation under exceptional circumstances pathway, Boon et al. find that EMA conditional marketing authorisation is associated with a shorter clinical development period, while EMA authorisation under exceptional circumstances (typically granted in cases where large scale clinical trials are either unfeasible or unethical) is associated with longer clinical development periods [28]. However, another study finds that reductions in development time from conditional approval are offset by significantly longer review time at EMA level [14]. A recent study by Liberti et al. found that medicines entering combinations of early access pathways have median development times up to 690 days shorter than standard review medicines. These results indicate that clinical development time can also be accelerated through enhanced and early engagement with the regulatory agencies [29]. Some heterogeneity in time to access may also be explained by differences in clinical development time across settings. For instance, Hoekman et al. demonstrate that mean development time for cancer medicines proceeding through conditional marketing authorisation in the EMA is substantially longer than for cancer medicines proceeding through the comparable FDA accelerated approval pathway. Here, the difference is attributed to variability in evidence requirements between the two pathways [30]. Overall, differences across settings in the types of early access pathways present likely accounts for some of the heterogeneity observed in availability of medicines.

Clinical development can also be significantly reduced through medicine-repurposing (development of a previously approved medicine in a new therapeutic indication) relative to de-novo medicine development [31] . De-novo medicine development can take between 10-12 years, including the initial discovery phase, pre-clinical studies (pharmacokinetics and toxicology), and human clinical trials. Given existing evidence from initial discovery and pre-clinical studies, along with established manufacturing and supply chains, the time required to launch a new indication for an existing medicine is potentially much shorter (3-4 years) [32]. Differences across settings in regulatory incentives for medicine-repurposing may contribute to difference in diffusion of indication extensions.

1.1.2 Marketing authorisation

A number of studies have explored differences in regulatory review time across settings [14, 33-37]. Many regulatory agencies offer priority review or accelerated assessment pathways that shorten the length of time for a marketing authorisation, however both the frequency with which these are applied and the extent to which review time is reduced vary across settings [10]. For instance, in a qualitative comparison of Swissmedic, FDA and EMA approval pathways, the authors find that the Swissmedic accelerated review pathway is similar in time to the FDA priority review pathway but faster than the EMA accelerated assessment [34].

The regulation and administration of these schemes vary across settings. Within Europe, early access pathways such as conditional marketing authorisation is regulated at supranational level through the European Medicines Agency (EMA). Meanwhile, compassionate-use and named patient programmes, that provide access to medicines in emergency situations prior to marketing authorisation, are administered by national regulatory agencies such as the Medicines and Healthcare products Regulatory Agency (MHRA). Outside of Europe, both

streamlined marketing authorisation pathways and the use of medicines prior to marketing authorisation may be administered by different departments within the same agency. For instance, within Canada, the Special Access Pathway and NOC/C pathways are administered by different departments within Health Canada.

Procedural differences in approval pathways may account for some of the difference in review times across settings. In the EMA, following evaluation of a medicine by the Committee for Medicinal Drugs for Human use (CHMP), the review is paused for an undefined period of time while applicants answer questions raised by the committee [26]. In a review of TKIs approval in Europe and in the US, Shah, Roberts and Shah demonstrate that the active review time between EMA and FDA is similar, but that overall approval time in the EMA time was on average 184.2 days longer due to clock stops in the review [35].

Beyond regulation and administration, countries also differ in the types of medicines admitted onto early access pathways. For instance, a recent study of cancer medicine approval found that only 7% of recently approved medicines received CMA from the EMA, while 56% of medicines proceeded through the comparable accelerated approval pathway with the FDA [14]. Another recent study found similar results with the FDA priority review pathway and EMA accelerated assessment pathway, which both provide shortened review times in order to accelerate approval of medicines with a likely major benefit to public health. Despite similar aims, the FDA conducted a priority review for 55.0% of new molecular entities approved between 2007 and June 30, 2015 compared to the 15.0% of medicines that received accelerated assessment [13]. Differences in admittance to early access pathways have also been shown between Switzerland, Europe and FDA [34], and between Canada and the FDA [37]. Overall, this heterogeneity in the medicines entering early access schemes suggests there are underlying differences in the evidence requirements and eligibility criteria across settings.

1.1.3 HTA

The methodologies employed and criteria considered by individual HTA agencies vary considerably [21, 38]. Differences are present in the types of evidence considered, the interpretation of evidence and in the impact of interpretation on the final recommendation [39]. Broadly speaking a distinction can be made between health technology assessments that assess efficiency based on cost-effectiveness (e.g. England, Canada, Scotland & Sweden) and health technology assessment agencies that assess relative clinical effectiveness (E.g. Germany and France) [5, 40]. In terms of health economic evaluation, differences emerge in the acceptability of indirect costs, the use of explicit cost-effectiveness thresholds, and in the types of economic modelling (e.g. cost-utility, cost-effectiveness, or cost-minimisation) [41].

Meanwhile, other countries (e.g. Germany and France) have not traditionally considered efficiency through cost-effectiveness. France assesses a medicine's medical benefit (SMR) and a medicine's improvement in medical benefit (ASMR) to inform reimbursement and pricing decisions respectively. Only recently (since 2013), has France begun to evaluate cost-effectiveness, and only in medicines which show significant improvements in medical benefit (ASMR ratings of I, II, or III) [42]. In Germany, economic evaluation is not conducted for new medicines. In 2010, a new process called AMNOG was been implemented which requires that the clinical benefit of all new medicine be assessed by IQWiG, who then provides a report to the G-BA (Federal Joint Committee) where a final recommendation is made [43]. Beyond consideration of efficiency vs relative effectiveness, countries also show differences in the choice of comparator, acceptability of indirect comparisons, acceptability of cross-over data, type of statistical methods (Bayesian vs Frequentist) and patient outcome measurements [44-46]. Overall, there are substantial differences in the methodologies use in HTA, in the types of evidence accepted and in the interpretation of that evidence. As a result the HTA landscape

offers little predictability for market access from an industry standpoint, which can have a negative impact on investment decisions [47].

Recent studies have begun to explore the link between HTA methodology and coverage decisions [39, 48, 49]. Grepstad and Kanavos explore differences in appraisal methods across Denmark, Norway and Sweden, and highlight the role of economic evaluation in shaping coverage decisions [48]. Nicod and Kanavos explore the heterogeneity in HTA recommendations for medicine-indication pairs from a qualitative standpoint and propose a mixed methods framework for systematically comparing HTA recommendations. In a pilot of the framework, the authors found substantially variation in how HTA bodies interpreted similar evidence [39]. Beyond differences in interpretation of clinical and economic evidence, HTA bodies also differ in the way they consider additional 'social value judgments' [49-51]. In a systematic review of HTA recommendations across 8 EU countries, Angelis et al. explore the extent to which these value dimensions are either explicitly or implicitly considered in the HTA process. They report substantial differences in the extent to which burden of disease, therapeutic impact and safety, innovation level, socioeconomic impact, efficiency, technological placement in the therapeutic pathway, ethical considerations and equity [49].

A number of studies have shown significant variability in the both the time from marketing authorisation to HTA recommendation and on the duration of HTA evaluation [14, 47, 52]. Health technology assessment aims to bridge the gap between marketing authorisation and health policy decision-making by evaluating additional medicine characteristics related to the medical, social, ethical, and/or economic impacts of a technology [26]. Differences in HTA across settings may account for some of the heterogeneity in time to availability of medicines across settings, particularly in cases were a negative decision is given and a resubmission is required [26]. Other potentially relevant factors include the ability of HTA agencies to conduct evaluations in parallel with marketing authorisation (e.g. Canada and Australia) and the

availability of scientific advice to align submissions and development with HTA recommendations [10].

A key limitation in research on HTA relates to the ability to quantitatively analyse decision-making. The complexity of aggregating detailed clinical and economic inputs into a single decision, paired with differences in relevant endpoints across therapeutic areas and limitations in sample size create significant challenges to empirical analysis. Nevertheless, a small number of studies have analysed HTA decision-making through multivariate analysis (See **Table 1.1**). These studies have predominantly focused on exploring the impact of clinical evidence, cost-effectiveness, disease area, presence of therapeutic alternatives and disease severity on HTA decision-making and are limited to single country analysis.

Table 1.1 - Literature review of studies exploring determinants of HTA recommendations

Type of Analysis	Countries	Number and type of Medicines	Dependent variable	Explanatory variables	Key findings	Citation
Multinomial logistic regression	France	1453 assessed by the transparency commission in five therapeutic areas	Reimbursement recommendation	Efficacy, disease severity, therapetic alternatives, place in therapeutic strategy, public health value, therapeutic area	Efficacy and disease severity are significantly associated with reimbursement recommendation. Other variables had limited effect. Probability of obtaining recommendations varies according to therapeutic class	(Le Pen, Priol, and Lilliu 2003)
Multinomial logistic regression	England and Wales	All 73 medicines assessed by NICE prior to 31 December 2003	Reimbursement recommendation	Quantity of clinical evidence, quality of clinical evidence, decision date, cost-effectiveness, therapeutic alternatives, budget impact, technology type	Medicines with randomised trials are more likely to receive positive ratios while higher cost-effectiveness ratios are associated with negative recommendations. Increased number of systematic reviews and patient group submissions are associated with positive recommendations.	(Dakin, Devlin, and Odeyemi 2006)
Multinomial logistic regression	Australia	858 medicines assessed by PBAC between 1994 and 2004	Reimbursement recommendation	Cost-effectiveness, quality of clinical evidence, quantity of clinical evidence, disease severity, model design, costs, therapeutic alternatives	Clinical efficacy, cost-effectiveness , total costs, and disease severity were significantly associated with HTA recommendations	(Harris et al. 2008)
Binomial logistic regression	Australia	227 medicines assessed by PBAC between 2005 and 2008	Reimbursement recommendation	Therapeutic area, quality of clinical evidence, quality of economic evidence, restrictions on listing, economic model design, costs, therapeutic alternatives, type of application (e.g. new medicine vs new indication)	Type of application, type of economic model, and estimated cost to PBS are significantly associated with reimbursement recommendation.	(Chim et al. 2010)
Binomial logistic regression	Australia	245 medicines identified through systematic review of economic evaluations published between 1989 and 2005.	Reimbursement recommendation	Therapeutic area, disease characteristics, type of intervention, economic model design, clinical efficacy, cost-effectiveness	High cost-effectiveness ratios are associated with negative recommendations. Funding status of interventions, and community values are also significantly associated with funding decisions.	(Segal, Dalziel, and Mortimer 2010)

Source: The author from [53-57].

1.1.4 Pricing and reimbursement

Following health technology assessment, governments must decide on the pricing and reimbursement of a medicine. The role of HTA in informing pricing and reimbursement decisions varies across settings. Under the transparency directive 89/105/EEC, governments in Europe have 120 days to conduct price negotiations before a medicine is launched within a market [58]. The majority of governments control the initial prices of reimbursed medicines, either through price negotiation or some form of reference pricing. In theory, the UK and Germany allow companies to price their medicine freely. In practice, confidential discounts are frequently applied for medicines to meet cost-effectiveness threshold within the UK and prices are frequently reduced after one year on the market in Germany if it is deemed that a medicine does not have evidence of added therapeutic benefit. Extensive international price referencing throughout Europe may contribute to significant delays in access in small markets. Under a reference pricing system, companies have incentive to launch their medicine in free-pricing markets such as the UK and Germany in order to obtain a high initial price, prior to launching in other markets where price is likely to be deflated [59, 60]. Beyond price referencing, parallel trade can also significantly impact the launch of a new medicine. In an analysis of medicines launched in 25 countries in the 1990s, Danzon et al. find that the probability of launching a new medicine is significantly lower in EU countries that are significant parallel exporters [59].

The impact of pricing policy on medicines is particularly complex in the case of multi-indication medicines. New medicines are increasingly being developed and launched across multiple therapeutic indications, courtesy of regulatory pathways that permit extensions to authorised therapeutic indications. In theory, medicine-repurposing and approval through indication extension pathways is more efficient, both in terms of time and cost, than de novo development of medicines. However, most health systems are only able to accommodate a single price per molecule. There has been considerable debate in the peer-review literature

about the best method to finance multi-indication medicines [61-64]. Different possible approaches include a single price per molecule, a weighted pricing model, differential discounting and indication-based pricing [61]. While economists argue that providing separate prices for each use of a molecule is the optimal approach for maximising welfare, most countries opt for indirect methods such as weighted pricing or differential discounting due to regulatory barriers and administrative burden [62, 64].

Indication-based pricing (IBP), also known as indication-specific pricing or multi-indication pricing, is a form of price discrimination whereby each indication for a molecule is priced separately according to the incremental value it provides above the standard of care in that particular indication (**Figure 1.1**).

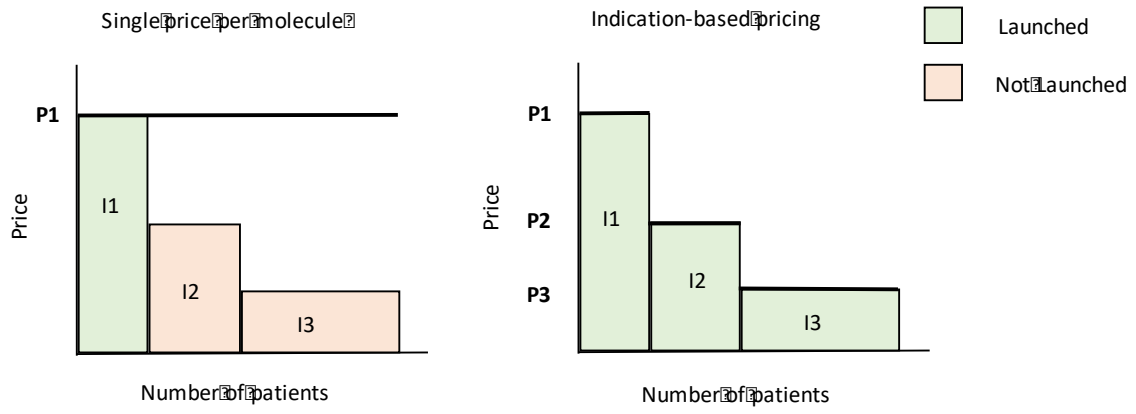


Figure 1.1 - The Impact of Indication-Based Pricing on Launch Decisions

A conceptual comparison of a single price per molecule system to an indication-based pricing system. Under a single-pricing system, price is anchored at P1 based on the first indication launched (I1). Indication 2 (I2) and indication 3 (I3) may not launch in order to avoid price erosion. Under an indication-based pricing model, price discrimination allows different prices to be set for each indication, P1, P2 and P3.

Source: The authors, adapted from [65]

Under a single-price-per-molecule system, the price is anchored at the first indication launched for a molecule and manufacturers may not launch indications with lower incremental value to avoid price erosion and a loss of producer surplus in the higher value indication. Under an

indication-based pricing model, price discrimination across indications ensures that the price is linked to the incremental value each indication provides relative to the standard of care. In theory, this removes incentives to withhold the launch in subsequent indications, which improve health (but not necessarily to the same extent as the first indication), increases the number of patients that have access to the medicine in question and maximises social welfare. Overall, differences across settings in pricing methods for multi-indication medicines may contribute to differences in availability and time-to-availability of medicines [66].

1.1.5 Adoption of reimbursed medicine into clinical practice

Following pricing and reimbursement decisions, additional delays can occur due to slow uptake of a medicine in clinical practice. Specifically, uptake is likely to be slower in cases where medicines are not reimbursed, in cases where there is significant co-payments for patients, and in cases where there is significant competition from other medicines in the indication [26].

A number of studies have undertaken empirical assessments of the determinants of time to availability of medicines from a quantitative standpoint (see **Table 1.2**). The majority of quantitative studies have focused on the impact of institutions (regulatory policies), market characteristics (competition) and firm characteristics (firm size) on time to availability. However, studies on the role of institutions thus far have focused predominantly on the impact of pricing regulation (specifically the impact of reference pricing), placing very little emphasis on HTA regulations and differences in the characteristics of HTA agencies across settings.

Table 1.2 - Literature review of studies assessing determinants of time to availability of medicines

Type of Analysis	Countries	Number and type of medicines	Dependent variable	Explanatory variables	Results	Citation
Cox proportional hazard model	25 countries	85 medicines launched between 1994 and 1998	Hazard rate of launch	Firm characteristics, expected price at launch, market characteristics, country effects	Small market size and lower expected prices are associated with longer time to availability.	(Danzon, Wang, and Wang 2005)
Linear regression	Sweden and Finland	242 medicines launched between 1995 and 2003	Time between marketing authorisation and reimbursement	Country of reimbursement, authorisation year, size of manufacturer, level of therapeutic value, and level of sales post-reimbursement	Low sales volume post-reimbursement is associated with longer time to availability and large company size is associated with shorter time to availability.	(Lundkvist, Jonsson and Rehnberg 2006)
Discrete-time survival analysis	28 countries	1482 medicines launched between 1980 and 2000	Hazard rate of launch	Firm characteristics, market competition, market characteristics	Markets that share borders or language with local manufacturer headquarters are associated with shorter time to availability	(Kyle 2006)
Discrete-time survival analysis	28 countries	1444 medicines launched between 1980 and 1999	Hazard rate of launch	Market competition, market characteristics (e.g. use of price controls), firm characteristics, medicine characteristics.	Use of price controls and legalisation of parallel trade are associated with delays in availability of medicines.	(Kyle 2007)
Fixed and random effects regression models	Japan	212 medicines launched between 2000 and 2009	Overall regulatory review time	Medicine attributes, firm characteristics, therapeutic area, early consultations, priority review, clinical evidence, and resubmissions	Priority review and early scientific advice are associated with shorter review time.	(Ishibashi et al. 2012)
Survival analysis, complementary log-log regression	20 countries	22,397 medicines launched between 1999 and 2008	Hazard rate of launch	Expected price at launch, market competition, market size, firm characteristics	Importance of therapeutic area, market size, and firm size are associated with shorter time to availability, while pricing regulations are associated with delays in availability.	(Costa-Font, McGuire and Varol 2015)
Survival analysis, complementary log-log regression	Sweden, Scotland, Belgium and Estonia	46 cancer medicines with EMA authorisation between 2000 and 2014	Hazard rate of launch	Type of marketing authorisation, ATC class, FDA early access programme, local manufacturer headquarters, expected price and volume per DDD, time to submission, clinical added value and safety (Drug bulletin Prescrire)	Shorter times from marketing authorisation to HTA submission, the presence of local manufacturers headquarters and the FDA earl access pathways are associated with a higher hazard of launch	(Ferrario 2018)
Survival analysis, proportional hazard model	76 countries	642 medicines between 1983-2002	Hazard rate of launch	Price regulation, patent regulation, market size, medicine quality, therapeutic area	Price controls significantly delay medicine diffusion while long patent duration significantly reduces launch lag.	Cockburn et al. 2016

Source: [59, 67-73]

Overall, determinants of availability of medicines are likely to depend on some combination of the following factors: a) differences in regulatory review time across settings, b) differences in frequency of early access pathway use across settings, c) differences in evidence requirements and interpretation of evidence for reimbursement across settings, d) launch delays from manufacturers due to reference pricing, and e) availability of previously authorised therapeutic indications.

1.2 Overview of regulatory and HTA systems

This section provides a review of regulatory structures and HTA systems that define the market access landscape across a selection of OECD markets. Specific focus is placed on the countries included in the empirical papers of this thesis in order to provide context to the resource allocation environment and firm entry conditions.

1.2.1 Standard marketing authorisation processes

Marketing authorisation (MA) or regulatory approval is undertaken to verify the quality, safety and efficacy profile of a medicinal product in order to establish whether its benefits outweigh its harms in the context of a proposed therapeutic use or indication. Marketing authorisation agencies across settings can vary in both their evidence requirements and review timelines. The FDA (USA), Health Canada, and the TGA (Australia) have comparatively lower median approval times than other settings [74]. **Table 1.3** provides a comparison of MA agency budget, fees, and timelines across settings.

Table 1.3 - Budgets, product approvals, timelines, and fees of various regulatory authorities for new pharmaceutical products

Regulatory authority	Budget for the fiscal years 2015/2016 (in US$ millions)*	Number of technical reviewers in 2016	Number of NDA submissions for new drugs in 2015/2016‡	Number of new therapeutic approvals in 2015/2016‡	Standard review timelines (days)	Median time for approval (days) in 2015	Fees per NDA in 2016 (in US$ thousands)*
European Medicines Agency (EMA)	340/342	~4,500§	61/68	39/27	210	422‖	316
US Food and Drug Administration (FDA)	1,194/1,230	~2,000	35/41	45/22	300	333‖	2,374
Pharmaceuticals and Medical Devices Agency (Japan)	246/241	~560	127/NA	42/48	365	311‖	274
Chinese Food and Drug Administration	199/250	~120¶	NA	72/31#	900	639	862
UK Medicines and Healthcare products Regulatory Agency (MHRA)	438/477	NA§	NA	146**/NA	210	230	120
Health Canada	84/108	~1,570	27/25	20/27	270	361	248
Swissmedic	115/108	~60	295	27/42	365	464	72
Central Drugs Standard Control Organization (India)	26/NA	~130	NA	17/22	270	523	1
Roszdravnadzor (Russia)	55/NA	NA	NA	NA	210	335	8
Health Sciences Authority (Singapore)	146/NA	~300	NA	61/72	295	409	62
Therapeutic Goods Administration (Australia)	104/NA	NA	43	27/NA	255‡‡	373	172
Brazilian Health Surveillance Agency	NA/NA	NA	NA	NA	730	834	69

NA, not available; NDA, new drug application. *Currency conversion rates are as of 22 May 2017. ‡Where possible, numbers are for NDAs for new therapeutics, such as new molecular entities approved by the US FDA's Center for Drug Evaluation and Research. Direct comparisons between regulatory authorities are not possible owing to differences in definitions; see Supplementary information S2 (box). §The EMA has a regulatory network with a pool of 4,500 scientific experts from member countries. MHRA experts are part of the EMA network. ‖Data from 2016. ¶Data from August 2015; by January 2017, this number had increased to ~300. #Excludes traditional Chinese medicines. **Data includes all decentralised (concerned member state and reference member state) product licenses. ‡‡Working days.

Source: [74]

Marketing authorisation typically involves three stages: 1) pre-submission, 2) evaluation, and 3) post-authorisation. See **Table 1.4** for a comparison of marketing authorisation pathways across Europe, USA, Canada, and Australia.

i) Pre-submission

A number of interactions between firms and regulatory agencies precede marketing authorisation applications. Pre-submission activities include scientific advice/protocol assistance, pre-submission meetings, applications for orphan designations and applications for paediatric investigation plans. The pre-submission phase plays a critical role in ensuring firms and regulatory agencies are aligned on the evidence requirements and submission requirements for a given therapeutic area, in order to avoid delays during the evaluation stage. Pre-submission advice can pertain to a range of aspects related to medicine development including quality aspects (e.g. chemical and biological testing necessary to demonstrate quality), non-clinical aspects (e.g. toxicology testing for safety), clinical aspects (e.g. appropriate endpoints, trial design, comparators, crossover) and pharmacovigilance plans [75-77].

ii) Evaluation

Marketing authorisation evaluation is conducted to ensure medicinal products have a positive benefit-to-risk ratio for the indicated patient population. Pharmaceutical firms are required to submit information on the intended patient population, the level of unmet need addressed by the new medicine, the quality of the medicine, evidence on manufacturing and research compliance, biological mechanisms of action, medicine distribution systems and elimination mechanisms within the body, clinical efficacy, and adverse events. Additionally, firms must submit risk managements plans and plans for follow-up studies post-authorisation to mitigate any identified risks or uncertainty in data. Within Europe (EMA), the assessment period for medicines is 210 days, although the timeline may be paused up to two times for clarification

or requests for additional analyses. The overall timeline for standard marketing authorisation assessment is approximately one year, although the assessment time may be reduced for medicines eligible for accelerate assessment pathways.

iii) Post-authorisation

Following authorisation, pharmaceutical firms must undertake a range of activities including pharmacovigilance, applications to vary marketing authorisation, and reporting on medicine defects or recalls. Pharmacovigilance involves monitoring the safety of a medicine used by patients on the market and can take the form of post-authorisation safety studies (PASS), periodic safety update reports (PSUR) and risk management plans [78]. Variations to marketing authorisation can range from minor administrative changes with little to no impact on quality, safety or efficacy to major changes which require review and approval by regulators [79]. Changes to the approved therapeutic indications are considered major variations and are discussed below.

Table 1.4 - Comparison of Marketing Authorisation Processes Across USA, Europe, Canada, and Australia

		USA	Europe	Canada	Australia
	Regulatory Agency	Food and Drug Administration	European Medicines Agency	Health Canada	Therapeutic Goods Administration
	MA Pathway	New Drug Application (NDA)	Centralised Authorisation Procedure (CAP)	New Drug Submission (NDS)	Category 1 Application
Pre-Authorisation	Scientific Advice & Pre-submission meetings	Firms submit an investigational new drug (IND) application based on results from initial testing which include plan for testing the drug on humans. The FDA conducts an IND review to provide feedback on evidence generation plan. At the end of phase 2, the FDA and firms meet to discuss design of large-scale phase III studies. A review meeting also takes place prior to submission of an NDA. Enhanced advice is provided for medicines with Fast-track, Breakthrough, or Regenerative medicine advance therapy (RMAT) designations.	Firms submit an eligibility request and notice of intent to submit a marketing authorisation application (MAA) up to 18 months before submission. Once rapporteurs from the CHMP are assigned, applicants can request pre-submission meetings to clarify potential regulatory or scientific issues relating to their medicine. Scientific advice can be obtained at any stage of the development process to ensure appropriate tests and studies are being conducted. Enhanced dialogue and advice are available through the priority medicines (PRIME) pathway.	Pre-submission meetings or pre-clinical trial application consultation meetings may be requested by sponsors prior to filing a submission. Pre-clinical trial consultation meetings are used to provide guidance on the acceptability of proposed trials. Pre-submission meetings can relate to: familiarizing Health Canada review staff with the submission prior to filing, identifying potential problems or issues and manage disputes early in the submission process; identifying studies the sponsor is relying on as adequate and well controlled in establishing the safety and efficacy of the drug; providing an opportunity to discuss potential eligibility of the submission for Priority Review or NOC/c consideration, and increasing the quality of information submitted.	Pre-submission meetings may take place at any stage prior to filing of a pre-submission planning form to discuss aspects of their proposed application with the TGA. Pre-submission meetings help to obtain a common understanding of the therapeutic good, what supporting documentation is needed to evaluate the application, what issues need to be resolved prior to submission, to plan for the submission, manage timeframes and resources, and discuss eligibility for Orphan or Priority review designations. Pre-submissions are not intended to include evaluation of data or advice on developing a data package.
	Orphan Designations	Orphan Drug Designation available for any disease or condition which: a) affects less than 200,000 persons in the US or b) affects more than 200,000 in the US and for which there is no reasonable expectation that the cost of developing and making available in the US a drug for such a disease or condition will be recovered from sales in the US of such drug. Medicines with Orphan designation received 7 years market exclusivity.	Orphan Designation available for medicines intended for the treatment, prevention or diagnosis of a disease that is life threatening or chronically debilitating. The prevalence of the condition within the EU must be less than 5 in 10,000 or the applicant must be unlikely to generate sufficient returns on investment by marketing the medicine within the EU. Medicines with orphan designation are eligible for reduced fees for protocol assistance and authorisation applications, receive 10 years of market exclusivity, and receive administrative and procedural assistance.	N/A	Orphan drug designations are available for the treatment, prevention or diagnosis of a life-threatening or seriously debilitating condition and one of the following applies: a) if used for treatment, the condition affects fewer than 5 in 10,000 individuals in Australia when the application is made; b) if used for prevention or diagnosis it would not likely be supplied to more than 5 in 10,000 individuals in Australia during each year; c) it is not likely to be financially viable for the sponsor to market the medicine in Australia unless each fee referred to in paragraph 45(12)(c) of the Regulations were waived in relation to the medicine. Medicines

					with orphan designation receive a waiver of fees for the signation application, new drug application and other fees as part of the registration of designated orphan drug.
	Cell and Gene Therapies	Regenerative Medicine Advance Therapy Designation (RMAT) applies to cell therapies, therapeutic tissue engineering products, human cell and tissue products, and any combination product using such therapies or products. Therapies must be intended to treat, modify reverse, or cure a serious or life-threatening condition. RMAT products receive early, more frequent and more intensive interactions with the FDA and are eligible for rolling review.	Advanced Therapy Medical Product (ATMP) designation available for gene therapies, somatic-cell therapies, and tissue-engineered medicines. ATMP products receive a rapporteur from the committee for advanced therapies in order to receive tailored evidence generation advice and are eligible for reduced fees.	Cell and gene therapies are regulated as biologics (Schedule D) drugs. Biologics are reviewed by the Centre for Biologics Evaluation (CBE) or the Centre for Evaluation of Radiopharmaceuticals and Bio therapeutics (CERB). No specific designations apply.	Cell and gene therapies are classified as "Advanced therapies" and are regulated under section 23 of the 'Therapeutic Goods Act 1989'. A dedicated authorisation branch reviews submissions for advanced therapies. Four classes of biologicals (Class 1,2,3 and 4) apply and are stratified by a risk-based approach. Dossier requirements depend on the level of classification.
	Paediatric Populations	Paediatric Research Equity Act (PREA) requires firms to conduct Paediatric Assessment on safety and effectiveness of new drugs/biologics in paediatric patients. Firms to discuss Paediatric Study Plans (PSP) with FDA at end of phase II and prior to initiation of phase III studies. Additional/optional financial incentives for conduct of paediatric studies available through Best Pharmaceutical for Children Act (BPCA). Requirements may be waived for diseases that don't exist in paediatric patients.	A separate process applies for the development and authorisation of paediatric medicines. Firms must submit paediatric investigation plans (PIPs) for review by the Paediatric Committee during early stages of clinical development. Free scientific advice is provided by the EMA for paediatric medicines. All PIP data must be included in marketing authorisation applications.	Drug development programs should usually include the paediatric patient population when a product is being developed for a disease or condition in adults and it is anticipated the product will be used in the paediatric population. Expert advice is provided by the Paediatric Expert Advisory Committee. A manufacturer of an innovative drug is allowed a period of 8 years of market exclusivity after issuance of a Notice of Compliance. An extended period of six months may be added when information regarding paediatric use is provided.	The TGA has adopted ICH/European guidelines concerning paediatric data generation. New chemical entities, new combinations, extensions of indications or major variations must include a paediatric development program form which outlines plans to obtain data through studies in children, when it is safe to do so. Data must also be submitted regarding paediatric plans in the USA and European Union.
Evaluation	Review Team	Center for Drug Evaluation and Research (CDER)	Committee for Medicinal Products for Human Use (CHMP)	Health Products and Food Branch (HPFB)	Advisory Drug Evaluation Committee (ADEC)
	Evidence Considered	NDAs must include: a) proposed text of labelling for the drug; b) pharmacologic class, scientific rationale, and intended use; c) foreign marketing history; d) chemistry, manufacturing and controls data; e) nonclinical pharmacology and toxicology data; f) human pharmacokinetic and bioavailability data; g) microbiology summary; h) clinical data; and f) a discussion of the	MAAs must include information on the intended patient population, the level of unmet need addressed by the medicine, the quality of the medicine, data on manufacturing and research compliance, the mechanism of action, the distribution and elimination mechanism within the body, the clinical benefits, the side effects, risk management plans, and plans for follow-up studies post authorisation.	New Drug Submissions (NDS) must include: a) a list of ingredients; b) a description of manufacturing methods and equipment; c) reports of tests made to establish the safety of the new drug; d) evidence of the clinical efficacy of the new drug; e) a copy of all clinical case reports where a subject died or suffered a serious or unexpected adverse reaction; f) a statement of all the representations to be made for the promotion of the new drug.	Application Dossiers must contain 5 modules: a) Module 1 consisting of administrative and prescribing information; b) Module 2 consisting of a summary of Modules3, 4 and 5; c) Module 3 consisting of evidence on product quality; Module 4 consisting of evidence on non-clinical aspects and module 5 consisting of clinical evidence. Submissions must also include risk management plans (RMPs).

		benefit/risk relationship and proposed post-marketing studies.			
	Review Time	10 months	210 days (not including clock stops)	300 days	255 days
	Dissemination	Drug Approval packages and label history outlining review outcome published via Drugs@FDA FDA-Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/	European Public Assessment reports published on EMA website: https://www.ema.europa.eu/en/medicines	Summary Basis of Decision documents are published on Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/summary-basis-decision.html	Assessment reports are available in the Australian Public Assessment Reports dataset: https://www.tga.gov.au/resources/auspar
Post-Authorisation	Pharmacovigilance	New molecular entities are subject to post-marketing safety surveillance as stipulated in the 21st Century Cures Act. Post-marketing surveillance strategies are defined on a product-specific basis using a risk-based approach.	Marketing authorisation holders face legal requirements for pharmacovigilance to monitor the safety of a product on the market through post-authorisation safety studies (PASS), periodic safety update reports (PSUR) and risk management plans.	Marketing Authorisation Holders (MAH) are subject to Mandatory Adverse Reaction (AR) Reporting and are required to provide annual summary reports on product safety. NDS include risk management plans (RMP) which must followed post-authorisation	All sponsors with medicines registered on the Australian Register of Therapeutic Goods must have an Australian pharmacovigilance contact person, submit any serious adverse reaction reports, notify the TGA of any significant safety issues, keep records pertaining to reporting and safety and answer any requests for additional information within specified timeframes.
	Variations	Four categories of changes: a) *major changes*[1] have substantial potential to effect the identity, strength, quality, purity, or potency of a drug, and require submission of a supplement and approval from FDA; b) *moderate changes effected in 30 days* have a moderate potential to have an effect on the identify, strength, quality, purity or potency of a drug and require a supplement to be filed 30 days prior to implementation of any changes, during which time the FDA can inform applicants if a prior approval supplement is needed; c) *moderate changes being effected* are moderate changes for which distribution can occur as soon as a supplement is received by the FDA; and d) *minor changes* have minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug, and must be described in an Annual report.	Three categories of variations to marketing authorisation: a) *Type IA variations* are considered to be minor variations with little to no impact on the quality, safety or efficacy of medicinal products and does not require prior approval before implementation; b) *Type IB variations* are also considered to be minor variations, but require MA holders to notify the regulatory authority before implementation; and c) *Type II variations* have potential impact on the quality, safety and efficacy of medicinal products and require submission of a type II variation application. Advance notice is required for intention to submit an extension of indication (6 months). Type II variations follow a 60-day timetable (90 days for extensions of indication)	Four categories of post-approval changes to an NOC: a) *Level 1 – Supplements* have the potential to increase exposure levels of the drug, either by expanding the population that is exposed or by increasing individual exposure; b) *Level II (90 day) Notifiable Changes*, have the potential to improve the management of risk/harm to the population and must be filed 90 days prior to implementation of any changes; c) *Level II (120 day) Notifiable changes*, include all additional changes requiring Health Canada prior approval which do not classify as a level I, II (90 day) or level III changes, and was implemented to differentiate amongst level II changes and provide priority in processing changes that involve risk/harm management; d) *Level III changes – Annual Notifications* refer to any change to the label that is not	Separate processes in place for variations that require evaluation of clinical and bio-equivalence data vs variations that do not require evaluation. Variations that do not require evaluation include corrections to an ARTG entry, notifications, with very low risk, where implementation would not affect the established quality safety and efficacy of a registered medicine, and additional changes to quality information or product information deemed low risk. Major variations are subject to the prescription medicines registration process and are likely to have an impact on the quality safety or efficacy of a product.

				expected to impact the safety, efficacy, and/or effective use of a drug.	
	Reporting	Firms are required to report any issues in quality or safety to the FDA Adverse Events Reporting System (FAERS) database as part of the FDA's post-marketing safety surveillance program.	Firms are required to submit periodic safety update reports (PSUR) in an online PSUR repository.	The MedEffect platform provides access to new safety information and adverse reaction reporting for both prescription and non-prescriptions medicines, biologics, natural health products, cell therapies and radiopharmaceuticals.	Firms are required to submit safety reports to the electronic data interchange platform E2B (R2).

1. FDA major changes include changes to manufacturing site; changes to manufacturing process; changes to specifications (i.e. tests, analytical procedures, acceptance criteria); changes to container closure system; changes to labelling (including extension of indication); and additional miscellaneous changes including change requiring complication of studies, addition or change to stability protocol; or extension of an expiration.
2. EMA type II variations include: variations related to the addition of a new therapeutic indication or to the modification of an existing one; variations related to the addition of a new contraindication; variations related to a change in posology; variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza; other type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern
3. Health Canada level 1 Supplements include new or expanded safety or efficacy claims (new indications), changes or withdrawals of existing indications, new formulations/routes of administration, changes to risk management measures, changes to brand name, results of confirmatory trials, submission for Data Protection Extensions, or other changes to label design.
4. TGA major variations include extension of indication, new formulation or route of administration, extension of provisional registration, transition of provisional to full registration and variations to product information requiring evaluation of clinical, nonclinical or bio-equivalence data.

(The author, adapted from [80-85])

1.2.2 Expedited & conditional regulatory pathways

Expedited regulatory pathways aim to promote timely access to innovative medicines that are used for the treatment, diagnosis or prevention of serious or life-threatening or chronically debilitating diseases and that are likely to address an unmet medical need. A number of indirect and direct regulatory mechanisms have emerged across settings to expedite the regulatory approval process. The most common mechanisms include: a) reducing the authorisation review time; b) conditional approval based on immature/early clinical data; c) approval based on prior registration in overseas authorities; d) enhanced regulatory support to avoid delays in approval; and e) iterative authorisation [10, 11]. **Figure 1.2** provides an overview of early regulatory pathways across Europe, Canada, the USA, and Australia.

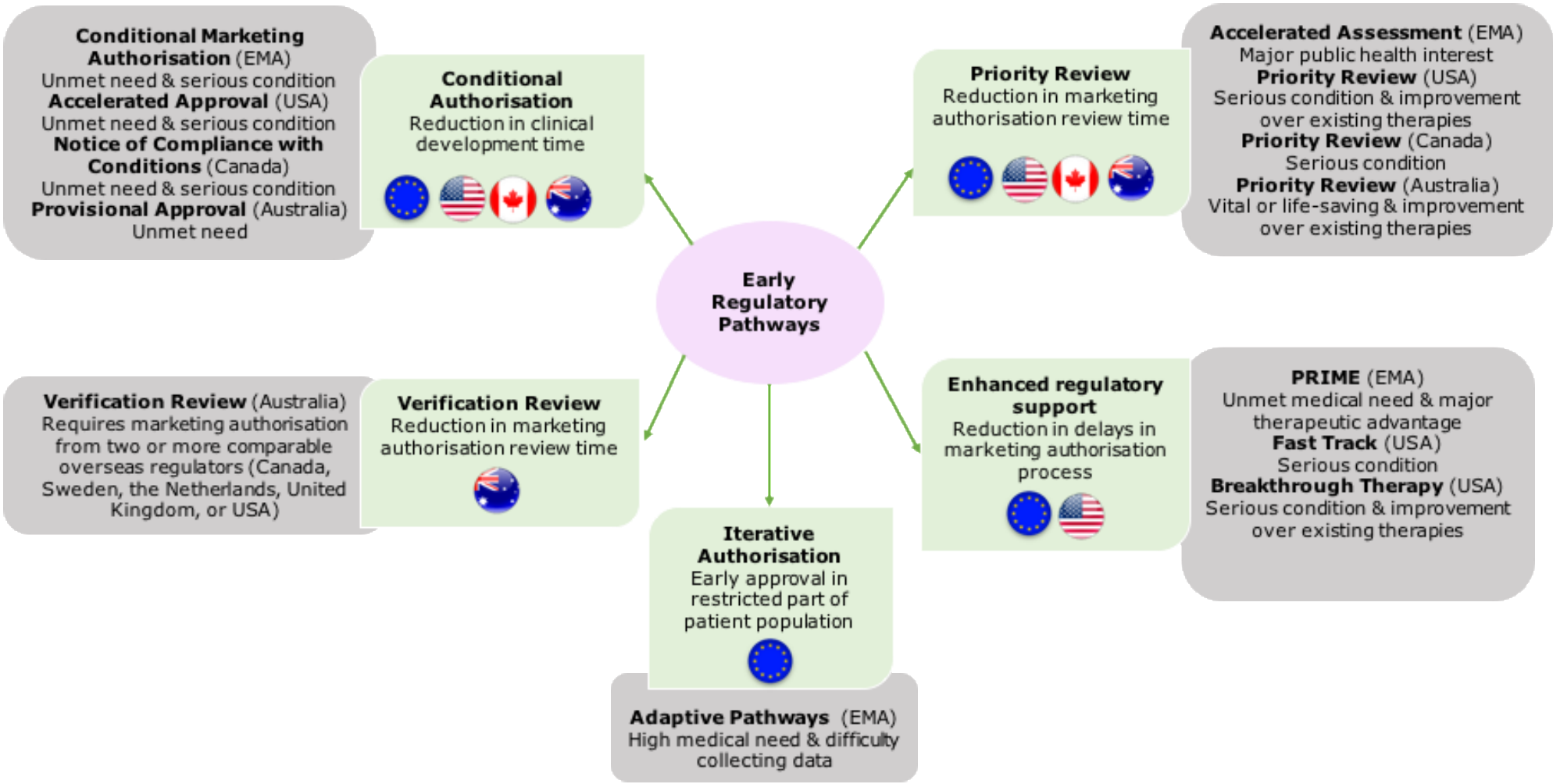
i) Priority Review

Priority review pathways, including the FDA, Health Canada and TGA priority review schemes and the EMA accelerated assessment scheme expedite access to medicines by reducing the review time for marketing authorisation [86-89]. Reductions in review time are achieved by prioritising review and committing additional resources towards assessment of submissions. Importantly, the evidence standards for approval (i.e. the demonstration of a positive benefit-risk ratio) remain the same as standard marketing authorisation pathways. The extent to which time is reduced and the eligibility criteria for entry varies across settings (See **Table 1.5**).

ii) Conditional Approval

Conditional approval pathways, including EMA conditional marketing authorisation (CMA), FDA accelerated approval, Health Canada Notice of compliance with conditions (NOC/C), and TGA provisional approval, expedite access to medicines by reducing clinical development time (EMA, FDA, Health Canada, TGA) .

Figure 1.2 - Early Regulatory Pathways in Europe, USA, Canada, and Australia



Sources: The author, adapted from [10, 11, 86-97].

Conditional approval reduces clinical development time by approving medicines on the basis of early or immature clinical evidence, on the condition that additional data is generated post-approval. In doing so, evidence generation activities are shifted from pre-authorisation to post-authorisation. Conditional approval is typically reserved for medicines that address a life-threatening or chronically debilitating disease in cases where there are no suitable therapeutic alternatives. Conditional approval is often granted on the basis of surrogate or intermediate clinical endpoints. The specific eligibility criteria, evidence generation activities, and terms of conditional approval vary slightly across settings A full comparison of conditional approval pathways is shown in **Table 1.5**. Within the EMA, conditional marketing authorisation may be granted if the CHMP finds that all of the following requirements are met:

1. the benefit-risk balance of the product is positive;
2. it is likely that the applicant will be able to provide comprehensive data;
3. unmet medical needs will be fulfilled;
4. the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data [91].

It is important to note that conditional approval is distinct from marketing authorisation pathways such as the EMA marketing authorisation under exceptional circumstances or the FDA animal efficacy rule [98, 99]. These pathways provide approval of medicines based on lower evidence thresholds in cases where developers are unable to provide comprehensive clinical evidence due to practical or ethical reasons. Examples include conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances [99]. In these cases, strict monitoring and risk management conditions apply to authorisation, however there is no expectation that mature efficacy data will be collected. As such there is no shift of evidence generation from pre-launch to post-launch. Within conditional approval pathways, there is an expectation that additional data will be collected.

iii) Verification Review

Verification review expedites access to medicines by reducing review time for medicines with prior regulatory approval in trusted overseas regulatory authorities. Within Australia, verification review reduces the regulatory review period by up to 4 months. Applicants must have received prior authorisation from two of Canada (Health Canada), Europe (EMA), Sweden (MPA), the Netherlands (MEB), the United Kingdom (MHRA) and the USA (FDA). Compared to the overseas medicine, the medicine must: a) be identical in dosage, formulation, strength and levelling; b) be produced by the same manufacturer; c) be produced using an identical manufacturing process; and d) have no specific issues regarding applicability in the Australian clinical context. No equivalent schemes are currently present in Health Canada, EMA or FDA.

iv) Enhanced regulatory support

Beyond priority review, verification review or conditional approval, access to medicines can also indirectly be expedited through enhanced regulatory support. Regulatory support can play a key role in aligning evidence generation plans with regulatory evidence requirements. Within Europe (EMA) and the USA (FDA) medicines may be eligible for designations, including PRIME (EMA), Fast Track (FDA) and Breakthrough Therapy (FDA), that entitle them to enhanced regulatory support. Enhanced regulatory support typically entails more frequent contact and involvement of more senior officials. The PRIME pathway identifies priority medicines early in the development pathway in order to aid in development through regulatory and scientific support. In order to qualify, medicines must address an unmet medical need and offer a major therapeutic advantage over existing treatments based on early clinical data.

Successful medicines receive an early rapporteur appointment, more frequent scientific and regulatory support, and a dedicated contact person within the EMA.

The fast-track designation is granted to medicines intended for the treatment of serious or life-threatening disease with the potential to fill an unmet medical need. In addition to more frequent FDA engagement, fast track medicines are also eligible for rolling review, whereby parts of the marketing authorisation pathway can be submitted and reviewed sequentially as they are ready for submission.

The breakthrough designation is complimentary to the fast-track designation, and carriers the same benefits along with earlier FDA guidance, senior FDA involvement, and access to a cross-disciplinary review team. It is available for medicines that treat serious or life-threatening diseases and that show early clinical evidence of substantial improvement over existing therapies based on a clinically meaningful endpoint.

v) *Iterative Authorisation*

Within the EMA, iterative authorisation approaches were explored as part of the Adaptive Pathways pilot project which ran between March 2014 and August 2016, and subsequently though a follow-up pilot project in the context of parallel scientific advice with HTA bodies [90]. Iterative authorisation expedites access to medicine by first authorising a medicine for use in a restricted population, before providing wider approval. The adaptive pathway program was targeted towards treatments in areas of high unmet medical need, where traditional routes of data collection through large clinical trials would unnecessarily expose patients who are unlikely to benefit from a medicine [100]. The adaptive pathways program utilises real-life data to supplement clinical trial.

Table 1.5 - Comparison of expedited approval pathways between EU, US, Canada and Australia

TYPE	EMA (Europe)	FDA (US)	TGA (Australia)	Health Canada
Accelerated review	**Accelerated Assessment** ▪ Reduction in review time from 210 to 150 days ▪ Must be of major public health interest, particularly from point of view of therapeutic innovation.	**Priority Review** ▪ Reduction in review time from 10 to 6 months. ▪ Serious condition and demonstrates a significant improvement in safety or efficacy over existing therapies. ▪ Evidence thresholds the same as standard authorisation.	**Priority Review Pathway** ▪ Reduction in review time from 255 to 150 days ▪ Vital and life-saving prescription medicines for which a complete data dossier is available ▪ No available treatment or substantial therapeutic advantage over available therapies	**Priority Review** ▪ Reduction in review time from 300 to 180 days ▪ Serious, life-threatening or severely debilitating disease ▪ Benefit/risk evaluation consistent with standard review
Conditional Approval	**CMA** ▪ Unmet medical need with positive benefit risk ratio. ▪ Serious condition ▪ Granted based on likelihood of data collection post-approval ▪ Valid for one year, possible renewal ▪ Comprehensive data are generated post-authorisation	**Accelerated Approval** ▪ Serious or life-threatening disease ▪ Approval of a drug based on a surrogate endpoint or an intermediate clinical endpoint ▪ Sponsor must agree to undertake confirmatory clinical trials. ▪ Must demonstrate a preliminary effect on a surrogate endpoint or intermediate clinical endpoint that is likely to predict clinical benefit	**Provisional Approval (PA)** ▪ Addresses an unmet clinical need ▪ Clearly positive benefit/risk ratio. ▪ Based on surrogate endpoints ▪ PA given up to 2 years earlier than current framework. Duration is limited, with extensions of 1-2 years possible, maximum of 6 years ▪ Sponsor required to collect and submit confirmatory efficacy and safety data	**NOC/c** ▪ Serious, life-threatening or severely debilitating disease or conditions. ▪ Authorisation of a medicine under the condition that the sponsor undertake additional studies to verify clinical benefit. ▪ No alternative therapy available on Canadian market or significant improvement over existing therapies. ▪ Increased monitoring requirements
Other	**Adaptive Pathways** ▪ High medical need where data collection is difficult. ▪ Iterative development and approval of medicines building on CMA. ▪ Early involvement of patients and HTA bodies	**Fast-Track Designation** ▪ Offers more frequent engagement with FDA, along with rolling submissions/review of application as evidence becomes available. ▪ Serious/life-threatening diseases	**Verification Review** ▪ Reduces review time by up to 4 months based on marketing authorisation from two comparable overseas regulators: Canada, Sweden, the Netherlands, United Kingdom, USA. Evidence required that medicine is identical to overseas medicine	**N/A**
Other	**PRIME** ▪ Unmet medical need ▪ Preliminary data demonstrating unmet need and major therapeutic advantage ▪ EMA will provide early and enhanced support to optimise development, and speed up evaluation	**Breakthrough Therapy Designation** ▪ Fast-track benefits plus earlier FDA engagement (as early as phase I) and senior FDA involvement. ▪ Serious or life-threatening disease or condition ▪ Preliminary clinical evidence of substantial improvement over existing therapies on one or more clinically significant endpoints	**N/A**	**N/A**

Source: the author from [86-93, 97, 101]

1.2.3 Indication extensions

In 2019, over two-thirds of new oncology medicines were licensed for use in multiple therapeutic indications [102]. Medicine repurposing or development of medicines across multiple therapeutic indications carries a number of benefits relative to de-novo medicine development including reduced development costs and expedited access to treatments [103]. De novo medicine development can require over ten years from initial discovery and development (4-5 years), preclinical pharmacokinetic and toxicology studies (2-3 years), and human clinical trials (4-6 years). Medicine-repurposing can take place on a much faster time frame (1-3 years), given that pre-clinical studies and development work has already taken and a medicine already has established manufacturing and supply chains [32].

At regulatory level, the launch of a new indication for a previously approved medicine is classified as an indication extension. Regulatory practices for the assessment and approval of indication extensions vary across settings (see **Table 1.6**). Re-purposed medicines may receive regulatory approval benefits including reductions in review time, use of 'real-world' clinical data or pharmacovigilance data to establish safety, and extensions to market exclusivity. Within Europe, standard market protection for new active substances is 8 years of data exclusivity, followed by 2 years of market protection. New therapeutic indications which provide significant benefit over existing therapies receive an additional year of market protection. New therapeutic indications for a well-established substance may also be eligible for an additional year of data-exclusivity provided that significant pre-clinical or clinical studies were conducted for the new indication.

Table 1.6 - Comparison of regulatory processes for indication extensions

Country/Region	Europe	USA	Canada	Australia
Agency	EMA	FDA	Health Canada	TGA
Type of submission	Type II variation – Full dossier pathway[1]	Prior approval supplement	Level I – Supplement to a New Drug Submission (SNDS)	Category 1 application
Review time	90 days	4-10 months[2]	300 days	255 days
Orphan Designation	Separate orphan indication needed for new indication	Separate orphan indication needed for new indication	N/A	Separate orphan indication needed for new indication
Conditional Approval	Indication extensions are not typically eligible for conditional approval. If the original indication has conditional approval, the conditional approval may be altered. Alternatively, the new indication may need to be evaluated as a new drug submission	Accelerated approvals can apply to specific prior approval supplements	Notice of Compliance with conditions can apply to specific indications	Provisional approval can apply to specific indications.
Market Exclusivity	+1 year data exclusivity (if new clinical studies performed) +1 year market protection (if evidence of significant benefit shown)	+3 years exclusivity for brand-name drugs with indication extensions, provided new clinical studies in humans conducted	No extensions provided for new indications	No extensions provided for new indications

1 – Drugs that have been used for at least 10 years in the EU may apply for indication extensions through the well-established use pathway, which does not require applicants to provide (non)-clinical data in their dossier, instead referencing existing literature.

2 – Pre-approval supplements are eligible for priority review. Timelines vary according to priority review status and requirement for preapproval inspection of facilities in volved in manufacturing and drug testing. Priority review drugs where preapproval inspection is not required has a review time of 4 months. Standard prior approval supplements where preapproval inspection is required have a timeline of 10 months.

Source: (the author from [79, 104-108]

1.2.4 Compassionate use pathways

Compassionate use programmes (for a defined cohort of patients) or named patient programmes (for individual patients) are administered at national level and provide access to unauthorised medicines in emergency situations prior to marketing authorisation. Outside of clinical trial use, compassionate use programmes and named patient programmes represent the only other mechanisms for patients to legally access medicines prior to marketing authorisation [109]. The use of medicines within these pathways is highly regulated and is typically restricted to medicines used for life threatening or chronically debilitating diseases. Use of medicines through these pathways is restricted to patients that cannot access a medicine through clinical trials. The pathways are not intended for research purposes.

Within Europe, compassionate use programmes are subject to EC Regulation No 726/2004 which stipulates that: "For the purposes of this Article 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a **chronically or seriously debilitating disease or whose disease is considered to be life-threatening**, and who **cannot be treated satisfactorily by an authorised medicinal product**. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials" [110]. Beyond European legislation, many countries have employed their own national legislation to regulate and administer compassionate use and named-patient programmes. Compassionate use pathways vary across settings in terms of: a) how early in the development/approval pathway they can begin; b) how long they continue post-authorisation (e.g. some pathways bridge the gap between marketing authorisation and reimbursement); c) monitoring requirements; and d) funding (e.g. whether manufacturers are reimbursed or supply products free-of-charge). An overview of compassionate use pathways is provided in **Table 1.7**.

Table 1.7 - Overview of Compassionate Use Pathways Across Europe, Switzerland Canada, USA and Australia

COUNTRY	Access to medicines prior to MA?	Name of programme(s)	Available for named-patients?	Available for cohorts?	Serious condition?	Minimum level of evidence?	Funded (R) or Free of Charge (FOC)?	Report on adverse events?
England	✓	Early Access to Medicines Scheme (EAMS)	✓	✓	✓	Phase II completed	FOC	✓
Scotland	✓	Early Access to Medicines Scheme (EAMS)	✓	✓	✓	Phase II completed	FOC	✓
Belgium	✓	1) Compassionate Use Programme, 2) Medical Needs Programme, 3) Early Temporary Reimbursement	✓	✓	✓	Phase III started	R (Not guaranteed)	✓
The Netherlands	✓	Compassionate Use Programme and Named Patient Programme	✓	✓	✓	No information	No information	✓
Sweden	✓	License Procedure (and Compassionate Use Programme	✓	✓	No information	No information	FOC	✓
Germany	✓	AMHV Hardship Case Programme and Named patient programme	✓	✓	✓	Phase II completed	FOC	✓
France	✓	Authorisation Temporaire d'Utilisation (ATU)[1]	✓	✓	✓	Case-by-case	R	✓
Spain	✓	Temporary Use Authorisation	✓	✓	✓	Phase III started	R	✓
Italy	✓	Compassionate Use Programme	✓	✓	✗	No information	R	No information
Austria	✓	Compassionate Use Programme and Named Patient Programme	✓	✓	✓	Phase II completed	No information	✓
Denmark	✓	Compassionate Use Programme	✓	✓	✗	Case-by-case	No information	✓
US	✓	Expanded Access Programme	✓	✓	✓	Varies based on population size	R (Not guaranteed)	✓
Canada	✓	Special Access Pathway	✓	✓	✓	Case-by-case	R (Not guaranteed)	✓
Australia	✓	Special Access Scheme and Authorised Prescribers Scheme	✓	✓	✓/✗	Case-by-case	R (out-of-pocket)	✓

(Source: The author, adapted from [109, 111-122])

1 - The French Compassionate Use programme, first established in 1992, was simplified in July 2021 and is currently known as the Early Access Authorisation (EAA).

1.2.5 Health technology assessment systems

Health technology assessment is defined as "the systematic evaluation of properties, effects and/or impacts of health technologies and interventions. It covers both the direct, intended consequences of technologies and their interventions and their indirect, unintended consequences" [123]. The primary purpose of HTA is to inform resource allocation decision-making at national, regional, or local levels of a health care system relating to funding of new technologies, appropriate use of health technologies and in some cases the disinvestment in technologies that are no longer effective. This subsection provides a brief overview of the salient features of HTA and comparison of HTA systems across Europe, Canada, and Australia (See **Table 1.8**).

i. HTA governance, transparency, and best practices

Over the past two decades HTA has become increasingly important in promoting evidence-based medicine and rational use of health technologies, primarily in developed countries, but increasingly in middle-income and emerging markets as well. Growing fiscal pressures and concerns about efficiency in the healthcare sector have spurred the need to further develop methodologically robust policies promote high quality and effective healthcare in a sustainable way. The diffusion of HTA has largely been accelerated by a WHO resolution at the 67th World Health Assembly, calling on member states to develop and implement national HTA processes in support of universal health coverage [124].

While HTA processes vary in scope, type and number of technologies assessed, and in methodology, we can identify a number of best practices in the governance and application of HTA (see Box 1) [125]. It is critical that any HTA systems, have clearly defined goals and scope. An HTA system's role and structure should be clearly legislated, regardless of whether the outcome of an HTA decision is binding or advisory. Further, it is essential that the process

remains objective and transparent to a) provide legitimacy to the process and b) provide clear signals to industry on the value and evidence requirements of new health technologies. To this end, HTA decisions should be made publicly available, contain sufficient detail to provide reproducibility, and be communicated appropriately to relevant decision-makers.

From a methodological standpoint, there must be clear guidance on how value is considered and how stakeholder input is incorporated into the process. HTA agencies should consider a wide range of evidence and outcomes relating to the impact of a new health technology. In doing-so it is critical that HTA agencies evaluate the strength of evidence, levels of uncertainty, and generalisability of evidence to their local decision-making context. Finally, it is critical that the HTA process takes place in a timely manner to avoid unnecessary delays in patient access to potentially beneficial treatments.

Box 1 - HTA Best Practices

1. *HTA goals and scope should be explicitly defined*
2. *HTA should be unbiased and transparent*
3. *HTA should include all relevant technologies*
4. *A clear system for setting priorities for HTA should be in place*
5. *HTA should incorporate appropriate methods for assessing costs*
6. *HTA should consider a wide range of evidence and outcomes*
7. *HTAs should consider a full societal perspective*
8. *HTA should explicitly characterise uncertainty surrounding estimates*
9. *HTAs should consider and address issues of generalisability and transferability*
10. *All key stakeholder groups should be actively engaged in the HTA process*
11. *HTAs should actively seek and collect all available data*
12. *Implementation of HTA recommendations needs to be monitored*
13. *HTA should be conducted in a timely manner*
14. *HTA recommendations should be communicated appropriately to different decision-makers*
15. *The link between HTA recommendations and decision-making processes needs to be transparent and clearly defined*

Source: [125]

ii. HTA models – comparative clinical benefit assessment vs cost-effectiveness

HTA models are defined according to the type of assessment performed on health technologies. Two prevailing models of HTA are used across Europe, Canada, and Australia to inform decision-making on the pricing and reimbursement of new pharmaceuticals: a) comparative clinical benefit assessment; and b) cost-effectiveness.

HTA systems which evaluate comparative clinical benefit seek to understand whether a technology is less effective, just as effective, or more effective than the current standard of care for a defined patient population. Comparative clinical benefit assessment is used by Haute Autorité de santé (HAS) in France and The Institute for Quality and Efficiency in Healthcare and the Federal Joint Committee (G-BA) in Germany to inform pricing and reimbursement processes [126, 127]. Within France, the HAS provides two rankings, the medical benefit rendered (SMR) and the improvement in medical benefit rendered (ASMR), based on the clinical evidence submitted by manufacturers. The SMR rating provides an indication of the total medical benefit a medicine provides, irrespective of the existing treatments available, and determines the level of reimbursement within France. There are four possible SMR ratings, based on the level of evidence submitted: i) important (65% reimbursement), ii) moderate (30% reimbursement), iii) mild (15% reimbursement), iv) insufficient (not reimbursed). The ASMR rating provides an indication of the perceived improvement in clinical benefit over the existing standard of care and is used to inform pricing negotiations. There are five possible ASMR ratings: i) major (eligible for premium pricing), ii) important (eligible for premium pricing), ii) moderate (eligible for premium pricing), iv) minor (parity pricing), or v) none (discount pricing). Upon submission, firms are required to designate if they are applying for a rating of moderate or higher and, if so, must submit an economic evaluation that is considered separately as part of pricing negotiations.

Within Germany, IQWiG provides one ranking on the level of added benefit. There are six added benefit ratings in IQWiG: i) major (eligible for price negotiation), ii) significant (eligible for price negotiation), iii) minor (eligible for price negotiation), iv) non-quantifiable (eligible for price negotiation), v) no added benefit (price parity), and vi) lesser benefit (not reimbursed). In addition to the added benefit rating, IQWiG also provides a rating on level of proof (proof, indication of proof, or hint of proof), based on the strength of evidence submitted and alignment with IQWiG guidelines. Newly authorised medicines are able launch in Germany immediately following marketing authorisation and receive free pricing for one year. During this year, IQWiG assessed the new medicine and provides a recommendation to the G-BA who determines the final benefit rating and conducts pricing negotiations.

HTA systems which evaluate cost-effectiveness seek to understand whether a technology provides no-value-for-money, poor value-for-money, or good value-for-money relative to the current standard of care. Cost-effectiveness is considered by HTA agencies in England (NICE), Scotland (SMC), Canada (CADTH and INESSS) and Australia (PBAC) to inform funding decisions on new medicines. Cost-effectiveness is typically evaluated through the incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{\Delta costs}{\Delta effectiveness} = \frac{Cost_{int} - Cost_{comp}}{Eff_{int} - Eff_{comp}}$$

Effects are typically measured in terms of quality adjusted life year (QALY), while costs reflect a summation of direct and potentially indirect costs associated with treatment. HTA agencies may adopt different perspectives which determine the types of health outcomes and costs considered in an evaluation. At the narrowest level, consideration of costs and effects will be limited to the payor/health system perspective. However, some agencies will adopt a societal perspective, and consider indirect effects beyond the boundaries of a healthcare system (e.g. productivity loss).

The maximum acceptable ICER varies between countries, reflecting differences in the willingness to pay for health gains. In some cases (e.g. England) a clearly defined threshold is applied, above-which technologies are not-recommended for funding.

Beyond clinical effectiveness, and cost-effectiveness, HTA agencies are also increasingly considering additional dimensions of value to modify or adjust their decision making. These additional dimensions of value are known as social value judgments (SVJs) and can relate to a number of different dimensions such as disease severity, unmet need, innovative mechanisms of action, impact on family or carers, and administration advantage (among others). In some cases, such as the end-of-life criteria in England, SVJs are considered explicitly and directly shift decision-making processes. However in the majority of cases, consideration of SVJs is implicit and conducted in a non-systematic, non-transparent, and ad hoc manner [128].

Table 1.8 - Comparison of HTA systems across Europe, Canada and Australia

Country	England	Scotland	France	Germany	Australia	Canada	Canada (Quebec)
Agency	NICE	SMC	HAS	G-BA	PBAC	CADTH	INESSS
Agency website	https://www.nice.org.uk/	https://www.scottishmedicines.org.uk/	https://www.has-sante.fr/jcms/r_1455134/en/about-has	https://www.g-ba.de/english/	https://www.pbs.gov.au/pbs/industry/listing/participants/pbac	https://www.cadth.ca/	https://www.inesss.qc.ca/
Medicines selection	MoH	By submission	All authorised medicines	All authorised medicines	By submission	By submission	By submission
Publicly available decision reports (language)	Yes (English)	Yes (English)	Yes (French)	Yes (German)	Yes (English)	Yes (English)	Yes (French)
Clinical evaluation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Economic evaluation	Yes	Yes	No[1]	No	Yes	Yes	Yes[2]
Type of decision	Binding[3]	Binding[4]	Advisory[5]	Advisory	Advisory	Advisory[6]	Advisory[7]
Target review time	12 months	6 months	3 months	3 months	5 months	6 months	6 months
Parallel review available	Yes	No	No	No	Yes	Yes	Yes

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; EC- European Commission; G-BA – Federal Joint Committee, HAS – Haute Autorité de Santé; IQWiG - INESSS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium.

Source: The author, based on a review of HTA websites across France, England, Scotland, and Canada [129-135]

[1] Cost-effectiveness is not considered as a key criterion during HTA evaluation by the HAS. Medicines claiming an ASMR (Improvement in medical service rendered) of III or higher must submit an economic dossier which may be used to inform price negotiations following completion of HTA.

[2] Economic evaluation is only appraised by INESSS if the agency determines there is clinically meaningful benefit.
[3] Positively recommended medicines must be made available to patients by the NHS within 3 months of the decision.
[4] SMC informs NHS boards of positively recommended medicines four weeks before publishing a decision in order to provide preparation time for introduction of a new medicine in health boards.
[5] The Ministry of Health makes final decisions on reimbursement of a new medicine, according to recommendations from the Transparency committee with HAS and pricing negotiations with the Economic Committee of Healthcare Products (CEPS).
[6] Pricing and reimbursement decisions are made at provincial level. Provinces in Canada (excluding Quebec) use CADTH recommendations to inform decision-making.
[7] The Ministry of Health and Social Services in Quebec makes final pricing and reimbursement decisions based on recommendations from INESSS.

1.3 Gaps in the literature examining availability of medicines

There are several gaps in the current body of literature exploring pharmaceutical firm entry and availability of medicines. A growing tension has emerged between regulators promoting early access to medicines and HTA bodies that struggle with uncertainty and low levels of evidence. As a result, it remains unclear if the early access pathways implemented by regulatory agencies actually go on to accelerate patient access. Given HTA evidence requirements, it is possible that while medicines may receive accelerated authorisation, they may face delays at the HTA level, limiting the value of such pathways. Overall, work is needed to identify differences in the way countries value concepts such as 'serious conditions' and 'unmet medical-need', to investigate the gap between marketing authorisation authorities and pricing and reimbursement authorities, and finally to determine the value, if any, of early access to medicines pathways in providing accelerated or early access to innovative medicines.

In terms of HTA, it is clear that the criteria considered vary widely across settings, however it remains unclear to what extent specific criteria drive recommendations. In some settings, traditional and explicit economic criteria and health outcomes may drive decision-making. In other settings, less explicit criteria such as social value judgments may have a substantial impact on recommendations. Differences may be present in criteria considered across therapeutic areas, across countries and even across regions within a country. One possibility, although yet to be demonstrated in literature, is that the traditional criteria considered is relatively similar across settings and that the difference in medicine availability are predominantly a result of less explicit local priorities and social value judgments.

A second noteworthy trend in medicine development relates to medicine-repurposing or the development of medicines with multiple therapeutic indications. Given regulatory incentives and reduction in development time, oncology medicines are increasingly being launched across

a range of therapeutic indications. While some theoretical work has been done to argue the conventional pricing methods are insufficient for multi-indication medicines, there is a paucity of empirical data examining the launch and availability of medicines with multiple therapeutic indications. More work is needed to establish whether current pricing and reimbursement policies create adverse incentives for manufacturers and to explore the feasibility of adopting a more formalised price discrimination system.

The gaps in literature provide a number of interesting research questions on firm entry in the pharmaceutical market under two conditions: 1) the conditional approval of medicines and 2) medicines with multiple therapeutic indications.

To what extent do conditional approval pathways accelerate firm entry in the pharmaceutical market, given HTA evidence requirements for reimbursement?

To what extent do differences in criteria applied, interpretation of evidence and use of social value judgments help explain the heterogeneity seen across settings in availability of medicines?

To what extent and on what basis do firms sequence the development and launch of multi-indication medicines?

These questions will be explored through a paper-based thesis. The next section provides a summary of the objectives of the four papers that address these research questions. The first paper presents rich descriptive analysis on the evidence gap between regulatory agencies and HTA agencies on conditionally approved medicines, along with an assessment of the key uncertainties raised and additional dimensions of value considered by HTA agencies. The second paper provides a mapping and analysis of regulatory approval and HTA approval sequence of multi-indication medicines, along with a comparison of the characteristics of original indications and follow-on indications at medicine level. The third paper presents the

results of semi-structured interviews with former decision-makers and pharmaceutical policy experts on policies related to the pricing of multi-indication medicines. The final paper presents an econometric analysis on the determinants of HTA decision-making, with a specific focus on conditionally approved medicines.

1.4 Research objectives

1.4.1 Paper I – How Do HTA Agencies Perceive Conditional Approval of Medicines? Evidence from England, Scotland, France and Canada

Paper I presents a cohort analysis of innovative pharmaceuticals that have received conditional approval in Europe or in Canada, two settings where HTA plays a key role in informing or determining reimbursement status. This paper has two objectives:

1) To examine the evidence gap between marketing authorisation agencies and HTA agencies for conditionally approved medicines in England, Scotland France and Canada; and
2) To determine how HTA agencies in these four countries interpret and appraise clinical and economic evidence submitted for conditionally approved medicines.

In doing so, this paper provides an empirical contribution to our understanding of how HTA agencies respond to high levels of uncertainty in evidence and the extent to which unmet need or disease severity can compensate for limitations in evidence.

1.4.2 Paper II – Launch Sequencing of Pharmaceuticals with Multiple Therapeutic Indications: Evidence from Seven Countries

Paper II provides a cohort analysis of 31 innovative pharmaceuticals with multiple therapeutic indications across England, Scotland, France, Germany, the USA, Canada and Australia. This paper has two objectives:

1) To map the marketing authorisation and HTA coverage recommendation sequence of multi-indication oncology medicines with the view to understanding patterns in indication launch and whether these hold across different health care systems; and

2) To compare and contrast the first indication launched for a medicine with subsequent indications in terms of clinical trial characteristics, regulatory approval timelines, coverage decisions and HTA coverage recommendation timelines in order to understand how manufacturers prioritise the development of indications.

This paper adopts an international and comparative perspective that contributes to our understanding of how differences in regulatory settings and pricing policies affect firm entry strategies.

1.4.3 Paper III – Healthcare System Perspectives on the Assessment and Pricing of Oncology Multi-Indication Products: Evidence from nine OECD countries

Paper III presents insights from current and former health system pharmaceutical policy experts across nine OECD countries on policy developments in multi-indication medicines. This paper has three objectives:

1) To review current practices (over the period of the past 5 years) of price-setting and paying for medicines with multiple distinct indications with emphasis on oncology;
2) To assess the impact of said pricing practices on firm entry and the launch of multi-indication medicines; and
3) To identify issues around the practicality of indication-based pricing (IBP) implementation relating to political willingness, legal/regulatory structures, administration, and/or data infrastructure.

In doing so, this paper contributes to our understanding of how different settings are currently approaching the pricing of multi-indication medicines, of the impact these policies have on the availability of medicines, and on the feasibility of adopting a more formal indication-based pricing or price discrimination policy.

1.4.4 Paper IV – HTA Barriers for Conditional Approval Drugs

Paper IV presents an econometric analysis of HTA outcomes, with a specific focus on conditional approval medicines. This paper has two objectives:

1) To compare and contrast the health technology assessment of medicines that have received conditional marketing authorisation relative to those that have received standard marketing authorisation.
2) To examine whether differences in the characteristics of conditional approval medicines and standard approval medicines lead to a higher probability of HTA rejection or delays in HTA approval.

In doing so, this study contributes to our understanding of whether conditionally approved medicines face any barriers, over and above medicines that have received standard marketing authorisation, and enhances our understanding of the determinants of HTA outcomes across settings.

2. HOW DO HTA AGENCIES PERCEIVE CONDITIONAL APPROVAL OF MEDICINES? EVIDENCE FROM ENGLAND, SCOTLAND, FRANCE AND CANADA[2]

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Abstract

There is a growing disconnect between regulatory agencies that are promoting expedited approval to medicines based on early phase clinical evidence and health technology assessment (HTA) agencies that require robust clinical evidence to inform coverage decisions. This paper provides an assessment of the evidence gap between regulatory and HTA agencies on medicines receiving conditional marketing authorisation (CMA) and examines how HTA agencies in France, England, Scotland, and Canada interpret and appraise evidence for these medicines. A mixed methods research design was used to identify the types and frequency of parameters raised in the context of HTA decision-making for all conditional approvals in Europe and Canada between 2010 and 2017. Significant heterogeneity was found across the HTA agencies in England, Scotland, France, and Canada in the assessment of medicines receiving CMA, with the highest likelihood of rejection present in Quebec (50%) and Scotland (25%). Rejected medicines were more likely to have unresolved uncertainties related to the magnitude of clinical benefit, study design, and issues in economic modelling. More systematic use of joint early dialogue and conditional reimbursement pathways would help clarify evidence requirements and avoid delays in patient access to innovative medicines.

Keywords

Health technology assessment; Conditional marketing authorisation; Notice of compliance with conditions; Conditional approval of medicines

2.1 Background

Conditional approval pathways aim to promote faster entry to market for innovative medicines that treat serious or life-threatening diseases and address unmet medical needs. They do so by reducing the clinical development time of innovative medicines and shifting some evidence generation activities from pre- to post-marketing authorisation [11]. While conditional approval pathways, such as the U.S. Food and Drug Administration's (FDA) Accelerated Approval (AA), the European Medicines Agency's (EMA) Conditional Marketing Authorisation (CMA) and the Health Canada's Notice of Compliance with Conditions (NOC/C) are well established [28, 29, 96, 136], they can produce considerable challenges for health technology assessment (HTA) and resource allocation decisions, given that only immature and/or early phase clinical data is typically available at the time of regulatory submission [30].

Existing literature on conditional approval pathways raises several points of potential concern in the trade-off between strength of evidence and speed of access to technologies that address an unmet need in serious and life-threatening diseases. Randomised controlled trials (RCTs), the gold standard for evaluating safety and efficacy of medicines, typically only represent a minority of the evidence available for conditionally approved medicines with approval instead granted on the basis of small and, increasingly non-randomised, studies [137]. Conditionally approved medicines granted FDA approval are also more likely to experience post-market safety events than standard approval medicines [138]. Further, confirmatory trials for conditionally approved medicines, required according to the conditions of authorisation, frequently either have study designs which do yield significant improvements in the quality of evidence or are not completed [139].

Importantly, it remains unclear if conditional approval pathways achieve their primary aim to promote faster patient access to medicines due to requirements at HTA level [14, 140, 141]. When comparing across countries, significant heterogeneity exists in both the types of coverage recommendation and the timelines between EMA approval and reimbursement for cancer medicines approved through the CMA pathway in Germany, France, England, Scotland and Italy [14]. Overall, conditionally approved medicines tend to have poor success at HTA level within Europe [142], suggesting a disconnect between regulatory and HTA agencies relating to their value [14, 140-142].

Delays in access to medicines that address an unmet need may be partially alleviated by the presence of other types of expedited regulatory pathways (e.g. FDA priority review), which aim to expedite approval through alternative mechanisms (see Appendix - **Table 2.4** for a detailed overview and comparison of expedited regulatory pathways), or through compassionate use programmes (CUPs) such as France's Early Access Authorisation (EAA), formerly known as Temporary Authorisation for Use (ATU), and England's Early Access to Medicines Scheme (EAMS) [109, 143]. CUPs, distinct from conditional approval pathways, provide access to unauthorised medicines on compassionate grounds to patients with chronically debilitating or life threatening diseases, which cannot be treated satisfactorily by an authorised medicinal product. While CUPs may act as a stop gap for medicines that address an unmet need by accelerating access to new technologies, they should not be mistaken for MA providing access to an entire patient population. CUPs tend to be restricted to individual patients or narrowly defined patient populations and requirements to offer medicines free-of-charge (e.g. England EAMS) often further limit uptake into these schemes [109]. Although some patients may be eligible to receive conditionally approved medicines prior to reimbursement through clinical trial enrolment or on compassionate grounds, routine access of these medicines through reimbursement procedures remains an issue.

HTA agencies have frequently issued negative recommendations for conditionally approved medicines, however the salient features driving these decisions are unknown [142]. The potential disconnect between regulatory and HTA agencies is of particular significance in Europe, where the CMA pathway was implemented in 2006 and in Canada, where the NOC/C was implemented in 2002 [96, 136]. In both settings, HTA plays a fundamental role in resource allocation decisions [26, 144].

While some differences are present between the CMA and NOC/C pathway, both are similar in their eligibility criteria and their capacity to reduce clinical development time relative to medicines that receive standard marketing authorisation. Importantly, pre-mature or early phase clinical evidence is only accepted provided the medicine still demonstrates a positive benefit-risk ratio, one of the fundamental characteristics of all regulatory approval pathways. A full comparison of the CMA and NOC/C pathways is provided in **Table 2.1**.

In both Canada and in several settings across Europe, the impact of conditional regulatory approval on health technology assessment remains unclear. This study has two objectives: first, to examine the evidence gap between regulatory and HTA agencies for conditionally approved medicines in England, Scotland, France, and Canada; and second, to determine how HTA agencies in these four countries interpret and appraise clinical and economic evidence submitted for conditionally approved medicines. In doing so, this study provides an important empirical assessment of the critical issues that CMA generates at HTA level and enhances our understanding of the alignment (or lack thereof) that needs to happen between regulatory and HTA on innovative medicines.

Table 2.1 - Comparison of EMA conditional marketing authorisation pathway and Health Canada notice of compliance with conditions pathway

Agency	EMA	Health Canada
Expedited Approval Pathway	Conditional Marketing Authorisation	Notice of Compliance with Conditions
Eligibility Criteria	1. Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases; 2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC; or 3. medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.	Promising new drug therapies intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions for which a) there is no alternative therapy available on the Canadian market or, b) where the new product represents a significant improvement in the benefit/risk profile over existing products.
Evidence Requirements	For a product to be granted a conditional marketing authorisation it must fulfil all of the criteria set out in Article 4(1) of the same Regulation: (a) the risk–benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive; (b) it is likely that the applicant will be in a position to provide the comprehensive clinical data; (c) unmet medical needs will be fulfilled; (d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required A conditional marketing authorisation may be granted, where comprehensive pre-clinical or pharmaceutical data have not been supplied.	Potential of a therapy can be demonstrated with: (a) Trials with surrogate markers that require validation (b) Phase II trials that would require confirmation with Phase III trials consistent with the normal course of development of a therapeutic entity; (c) Phase III trials where a single small to moderately sized trial would require confirmation of either the efficacy or safety of the agent under question. Furthermore, there are multiple ways whereby clinical evidence may be established including literature review, expert opinions, panels or pharmacokinetic/ pharmacodynamic studies.
Limitations	Restricted to first indication approved for a molecule	N/A
Duration	One year	Case-by-case

Source: The authors adapted from [96, 136]

2.2 Methods

2.2.1 Analytical framework

HTA agencies vary not only in the types of evidence they consider, but also in their interpretation of such evidence. Upon completion of an assessment, many HTA agencies publish detailed assessment reports which outline the evidence submitted (clinical as well as economic, the latter if applicable), the agencies' interpretation of the evidence, and the results of the assessment to add legitimacy and transparency to the decision-making process. Beyond clinical and economic evidence, HTA agencies also discuss other contextual considerations (e.g. relating to disease severity, unmet need, or ethical considerations, among others), known as social value judgments (SVJs).

Large volumes of unstructured data present in HTA reports and complex decision-making processes based on multiple implicit and explicit criteria present limitations towards quantitative analysis of HTA outcomes. We adopt a sequential mixed-methods research design, as outlined in the analytical framework developed by Nicod and Kanavos [39], in order to mitigate these limitations and capture the widest possible range of criteria which may influence HTA outcomes. First, HTA reports are qualitatively analysed to capture: (a) the quality of evidence being submitted to HTA agencies; (b) how HTA agencies interpret this evidence; (c) the influence this evidence has on the final decision; and (d) additional social value judgments considered beyond clinical and economic evidence. Second, categorised and coded data is analysed quantitatively. When implemented across a large sample of medicines and their respective indications, the framework enables a meta-analysis of HTA decision-making and identification of key parameters considered in the HTA process.

2.2.2 Sample selection

The European Medicines Agency (EMA) and Health Canada's medicines approval databases were screened to identify all medicine-indication pairs that have received Conditional Marketing Authorisation (CMA) or Notice of Compliance with Conditions (NOC/C), respectively, between January 1st, 2010 and December 31st, 2017. The study period was selected in order to: (a) provide sufficient time for HTA evaluations to have been completed following marketing authorisation; (b) provide sufficient sample size for analysis; and (c) limit the impact of regulatory and HTA reforms on results. Medicines which have received Marketing Authorisation Under Exceptional Circumstances (MAEC), which is part of EMA's regulatory approval processes pro, where excluded from the study (See appendix for details on the MAEC pathway). A medicine-indication pair is defined as a molecule and the specific indication where the molecule's use is authorised.

The scope of this study is restricted to England, Scotland, France, and Canada. Country selection is based on the presence of an accelerated access regulatory pathway, public availability of marketing authorisation reports, public availability of HTA reports, and language (English and French). Three HTA agencies from Europe were included in the study, notably, the National Institute for Health and Care Excellence (NICE) [145], the Haute Autorité de Santé (HAS) [127], and the Scottish Medicines Consortium (SMC) [146], and two HTA agencies from Canada, notably the Canadian Agency for Drugs and Technology in Health (CADTH)/pan-Canadian Oncology Drug Review (pCODR) [134], and the Institut National d'Excellence en Santé et Services Sociaux (INESSS) [147]. European HTA agencies were screened to identify HTA reports for CMA medicine-indication pairs and Canadian HTA agencies were screened to identify HTA reports for NOC/C medicine-indication pairs. CMA and NOC/C medicine-indication pairs that had not been evaluated by at least one HTA agency were excluded from the study.

2.2.3 Data collection and coding

In order to enable (a) an assessment of the evidence gap between MA and HTA and (b) an evaluation of how HTA agencies interpret and appraise evidence of conditionally approved medicines, a number of parameters were extracted from publicly available MA reports and publicly available HTA reports (**Table 2.2**). Evidence was extracted into a database created in Microsoft Excel for coding and analysis. The parameters extracted from MA reports were: (1) the molecule name, (2) the brand name, (3) the exact wording of indication, (4) the therapeutic area, (5) the MA date, (6) the study name (trial identifier code) and study design of the pivotal clinical trial (trial phase, trial blinding, trial randomisation, and type of comparators) and (7) the conditions applied to the marketing authorisation. The parameters extracted from HTA reports were: (8) HTA outcome (List (L), List with conditions (LWC), Do not List (DNL)), (9) the number of resubmissions following a rejection if applicable, (10) the study name (trial identifier code) and study design of the main trial submitted (trial phase, trial blinding, trial randomisation, and type of comparators), (11) the assessment of clinical evidence in terms of the clinical uncertainties raised regarding the magnitude of clinical benefit, lack of clinical evidence, study design, choice of comparator, generalisability of trial population, and applicability local clinical practice, (12) the assessment of economic evidence in terms of uncertainties raised regarding modelling, the type of model, the choice of comparator, the estimation of costs and utilities, the cost-effectiveness ratio, and the sensitivity analysis performed, and (13) the consideration of additional elements of value including disease rarity, disease severity, unmet need, innovative mechanism of action, short life expectancy, administration advantages, and special demographics.

Table 2.2 - List of Variables Deployed in Analysis

Variable	Type	Variable Abbreviation	Definition/Explanation
Marketing Authorisation Reports			
Therapeutic Area	Categorical	ATC	The therapeutic area according to the Anatomical Therapeutic Chemical (ATC) classification system
Study Design of Pivotal Trial[1]	Categorical	PIVOTAL	1 = Observational study, 2= Phase I Study, 3 = Single armed phase II study, 4= Controlled phase II study, 5= Placebo controlled randomised phase III study, 6 = Actively controlled randomised phase III study
Marketing Authorisation Conditions[2]	Categorical	CONDITIONS	1 = Submission of follow-up data from ongoing studies, 2 = Completion of confirmatory phase II trial, 3 = Completion of confirmatory phase III trial
Health Technology Assessment Reports			
HTA Outcome[3]	Categorical	HTAOUTCOME	1 = List (L), 2 = List with conditions (LWC), 3 = List with conditions through a resubmission following an initial rejection (LWC after resubmission), 4 = Do not list (DNL), 5 = Do not list through a resubmission following an initial rejection (DNL after resubmission), 6. = No HTA submission.
Study Design of Main Trial for HTA	Categorical	HTATRIAL	1 = Observational study, 2= Phase I Study, 3 = Single armed phase II study, 4= Controlled phase II study, 5= Placebo controlled randomised phase III study, 6 = Actively controlled randomised phase III study
Clinical Uncertainties Raised in HTA			
Size of clinical benefit[5]	Continuous	CLINBEN	Number of uncertainties raised around the size of clinical benefit extrapolated from the evidence submitted
Generalisability[6]	Continuous	GENERAL	Number of uncertainties raised related to generalisability to the country's population
Study Design[7]	Continuous	DESIGN	Number of uncertainties raised related to clinical trial study design
Indirect Comparison[8]	Continuous	INDIRECT	Number of uncertainties raised related to suitability of indirect comparisons
Clinical evidence[9]	Continuous	CLINEV	Number of uncertainties raised related to the availability of clinical evidence
Clinical Practice[10]	Continuous	CLINPRAC	Number of uncertainties raised related to generalisability to the country's local clinical practice
Comparator Used[11]	Continuous	COMP	Number of uncertainties raised related to the compactor in the clinical trial
Economic Uncertainties Raised in HTA			
Modelling[12]	Continuous	MODELLING	Number of uncertainties raised related to the economic model structure and assumptions
Model Type[13]	Continuous	MODELTYPE	Number of uncertainties raised related to the appropriateness of the type of model employed
Comparator[14]	Continuous	COMPECON	Number of uncertainties raised related to the compactor employed in the economic model
Cost[15]	Continuous	COST	Number of uncertainties raised related to the cost estimates used in the economic model
Utilities[16]	Continuous	UTILITIES	Number of uncertainties raised related to the utilities estimates used in the economic model
Cost-effectiveness[17]	Continuous	COSTEFFECT	Number of uncertainties raised related to the cost-effectiveness estimate in the model
Sensitivity analysis[18]	Continuous	MODEL	Number of uncertainties raised related to the sensitivity analysis performed.
Social Value Judgments Identified in HTA			
Severity	Binary	SEVERITY	1= Severity of the disease explicitly recognised by HTA agency; 0 = Severity not recognised.

Administration route/frequency	Binary	ADMINAD	1= Route and the frequency of administration of the treatment explicitly recognised by HTA agency as offering advantage; 0 = Not recognised as offering advantage.
Unmet need	Binary	UNEED	1= Unmet need for the new treatment (e.g. few or no alternatives exist, need for additional treatments, high burden of disease) explicitly recognised by HTA agency; 0 = Unmet need not recognised.
Innovation	Binary	INNOVATION	1= Novel mechanism of action and overall innovativeness of the treatment explicitly recognised by HTA agency; 0 = Not recognised.
Rarity	Binary	RARITY	1 = Small patient population or disease rarity explicitly recognised by HTA agency, 0 = Not recognised
Short Life Expectancy	Binary	EXPECTANCY	1 = Short duration of life expectancy explicitly recognised by HTA agency; 0 = Not recognised
Special Demographics	Binary	DEMOGRAPHICS	1 = Special demographics of patient population in terms of age, sex, race or socioeconomic status explicitly recognised by HTA agency; 0 = Not recognised

Source: The author, adapted from mixed methods framework developed by Nicod and Kanavos [39]

Notes: 1 The study design of the pivotal trial used to support conditional regulatory approval. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled)

2 The specific post-marketing obligations imposed by regulatory agencies in order to fulfil the conditions of marketing authorisation. Conditions are classified according to the type of evidence generation requested (submission of follow-up data or completion of additional clinical trials)

3 HTA outcomes are classified as List (L), List with conditions (LWC), List with conditions through a resubmission following an initial rejection (LWC after resubmission), Do not list (DNL), Do not list through a resubmission following an initial rejection (DNL after resubmission), or No HTA submission. In France, the HAS assigns a rating based on the absolute clinical benefit (SMR) and relative clinical benefit (ASMR). SMR ratings include Insufficient, Low, Moderate, and Important and determines the reimbursement rate for a product (not reimbursed, 15%, 30% and 65% respectively). The ASMR rating ranges from V (non-existent added benefit) to I (Major added benefit) and determines a products price. In order to qualify for a price premium an ASMR rating of I or II is needed. HTA outcomes for France are classified according to SMR and ASMR ratings (DNL – SMR insufficient, L – SMR Important and ASMR I or II, or LWC- all other combinations)

4 The study design of the main trial used to support HTA assessment. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled)

5 Concerns raised around the magnitude of clinical benefit (e.g. is too little or confounded by other factors that are not related to the clinical design) may comprise but are not limited to: (1) Modest or low clinical benefit from trial; (2) The response of the pharmaceutical varied from study to study; (3) The response of the pharmaceutical is effective only in a sub-population; (4) The response of the pharmaceutical is not statistically significant compared with the comparator.

6 Concerns raised around the **generalisability of the population** used in the clinical evidence to the country of the HTA body may comprise but are not limited to: (1) the trial population is not generalisable to the country population due to ethnicity/ baseline characteristics and prevalence; (2) The trial population is not included/underrepresented the population of the indication under review; (3) Only a subgroup of the trial is considered suitable for the indication.

7 Concerns raised across the design of the trials (blinding, phase and clinical or surrogate endpoints, length, sample size, outcome measure, low patient numbers, study duration). It may comprise but it's not limited to: 1) Limitation in trial design leading to confounding in the clinical benefit (e.g. cross-over) 2) Study blinding unsuitable 3) Sample size (too small) 4) Use of surrogate endpoints vs clinical endpoints.

8 Concerns raised around the type of indirect comparison, adjustment methods, or studies included in indirect comparison. It may comprise but it's not limited to: 1) indirect comparison not well designed 2) population across different studies non comparable 3) Statistical analysis performed not suitable (e.g. butcher vs Bayesian model)

9 Concerns raised around lack of comparative clinical evidence, lack of evidence on a subgroup, or lack of long-term clinical evidence. It may comprise but it's not limited to: 1) Lack of comparative clinical data 2) Unsuitable data 3) Lack of long-term evidence 4) Lack of safety data

10 Concerns raised around **generalisability of the clinical practice** of the clinical trials submitted by the manufacturer (e.g. administration route or pre- and concomitant medication or a different use of the resource of the health system) may comprise but are not limited to: (1) differences in the pathway in the clinical practice of the country; (2) differences in the administration and dose in comparison with the standard of care; (3) When the treatment criteria (e.g. baseline of the patients for starting the treatment) differed between the study and clinical practice; (4) A pharmaceutical may have limited use in the study country (e.g. PBAC clinical pathways).

11 Comprises all the concerns raised across the comparator(s) such as use of placebo or the use of a comparator different from the one preferred by the HTA bodies or used routinely in the clinical practice. Comparator used in clinical trial was inappropriate. It may comprise but it's not limited to: 1) comparator not marketed in the country 2) comparator not suitable because not used in the clinical practice 3) comparator is not the standard of care in the country 4) Placebo-controlled trial

12 Concerns around the modelling used (e.g. in Markov/ partitioned survival model), or the extrapolation technique used for the clinical data may comprise but is not limited to: (1) the modelling used is not suitable; (2) the use of curves is not appropriate; (3) extrapolations method is not appropriate; (4) misrepresentation of the population under review or of some specific subgroup; (5) any computational errors.

13 Concerns around the use of a certain model (cost-minimisation or cost-utility etc) in that may not be suitable for the analysis.

14 Concerns around the appropriate comparator used within an economic model. It may comprise but it's not limited to: 1) comparator used in the economic model is not marketed in the country 2) comparator used in the economic model is not suitable because not used in the clinical practice 3) comparator used in the economic model is not the standard of care in the country.

15 Concerns around the **cost data** used to build the model leading to over- or under-estimation of the ICER may comprise but is not limited to: (1) some costs included in the model are too low or too high; (2) the model does not include specific cost that would lead to an over-estimation or under-estimation of the cost-effectiveness such as administration cost or wastage.

16 Concerns around the **utility data** used to build the model leading to over- or under-estimation of the ICER may comprise but are not limited to: (1) the utility values used in the model are not suitable leading to over-estimation or under-estimation of the ICER; (2) the utility source is not suitable/ or the measured was not appropriate.

17 Concerns around the magnitude of ICER to high or too much uncertainty in ICER estimate. It may comprise but it's not limited to: 1) cost-effectiveness over the threshold 2) ICER too high even after testing with sensitivity analysis or re-evaluation carried out by manufacturer/HTA body/ external reviewers

18 Sensitivity analysis performed to demonstrate robustness of model inappropriate or missing. It may comprise but it's not limited to: any issues around the sensitivity analysis performed by the manufacturer or by the HTA body experts. The sensitivity analysis produced cost-effectiveness ratios outside of acceptable levels The sensitivity analysis did test the deterministic sensitivity of a key variable or assumption.

2.2.4 Data analysis

Data analysis followed a sequential mixed-methods approach for decision analysis. First, text from HTA agency reports were qualitatively analysed in order to identify and code parameters. Uncertainties were double-coded based on the type of uncertainty and whether or not the uncertainty was addressed by any means in the context of the decision (e.g. with regards to the following text: "The committee was aware of the Evidence Review Group's (ERG) concerns that the trial included only a small number of patients from the UK. The Committee accepted advice from clinical specialists that the data were relevant to clinical practice in England and Wales." would be coded as "uncertainty in generalisability of trial population – overcome"). Second, descriptive quantitative analysis was performed in order to identify the frequency with which a particular coded parameter was raised in context of an HTA decision. Descriptive statistics are presented for the aggregate sample, followed by descriptive analysis of HTA outcomes, clinical evidence, clinical uncertainties, economic uncertainties and SVJs at country and agency level.

2.3 Results

2.3.1 Sample overview

Between 2010 and 2017, 25 medicine-indication pairs received CMA from the EMA and 59 medicine-indication pairs received NOC/C from Health Canada. Within Europe, 21 CMA medicine-indication pairs had at least one HTA evaluation by the HAS, SMC or NICE, 3 medicine-indication pairs were excluded due to withdrawal of marketing authorisation, and one medicine-indication pair was excluded due to lack of HTA evaluation. Within Canada, 20 of the NOC/Cs were granted to generic products and were excluded from the sample. Of the

remaining 39 medicine-indication pairs, 28 had at least one HTA evaluation by either CADTH/PCODR (Ontario) or INESSS (Quebec), 7 were excluded due to lack of HTA evaluation, 2 were excluded due to withdrawal of the marketing authorisation, and 2 were excluded due to an absence of marketing authorisation reports. In total, 49 medicine-indication pairs were included in the sample, 21 from the EMA and 28 from Health Canada (See Appendix - **Table 2.5** and **Figure 2.5** for complete list of the medicine-indication pairs and a breakdown of medicines by therapeutic area).

The majority of conditional authorisations in both Europe and Canada were for oncology products, classified according to the Anatomical Therapeutic Chemical (ATC) classification system as antineoplastic and immunomodulating agents, corresponding to 86% of Health Canada NOC/C approvals and 71% of EMA CMA approvals. In Canada the remaining approvals were for alimentary track and metabolism products (Kanuma for LAL deficiency, Ocaliva for primary biliary cholangitis, and Strensiq for hypophosphatasis) and for anti-infectives for systemic use (Daklinza for the treatment of chronic hepatitis C). In Europe the remaining approvals were for sensory organs (Holoclar for chemical or physical eye burns), anti-infectives for systemic use (Deltyba and Sirturo for tuberculosis), nervous system disorders (Fampyra for Multiple Scelerosis), systemic hormonal preparations (Translarna for Duchene Muscular Dystrophy), and musculo-skeletal system (Natpar for chronic hypo-parathyroidism). Concordance between EMA and Health Canada on conditional approvals was low. Only 43% (n = 9) of EMA CMA medicine-indication pairs had an NOC/C for the same indication (Adcetris for 2 indications, Blincyto, Bosulif, Darzalex, Tagrisso, Votrient, Xalkori, and Zykadia).

2.3.2 Descriptive statistics

Descriptive analysis of the aggregate sample according to HTA outcome yielded a number of statistically significant differences (See **Table 2.3**). In the aggregate sample, HTA outcomes were found to vary significantly when comparing across HTA agencies ($p = 0.038$), according to consideration of disease rarity ($p = 0.008$), according to presence of clinical uncertainties in study design ($p = 0.0005$), and according to presence of economic uncertainties related to cost-effectiveness ($p = 0.021$).

No significant differences in HTA outcomes were identified based on oncology vs non-oncology products, prior rejection and trial phase. Further, no significant difference was found in average time between MA and HTA across HTA outcomes or according to year of evaluation.

2.3.3 Analysis of HTA outcomes at agency level

HTA outcomes for CMA and NOC/C medicine-indication pairs vary considerably across settings. Positive listing recommendations (L, LWC or LWC after resubmission) range from 95% (HAS) to 43% (SMC) of outcomes, and account for 78%, 67% and 46% of outcomes in CADTH, NICE and INESSS respectively (See Appendix - **Figure 2.6**).

Table 2.3 - Descriptive Statistics

	HTA/funding outcome			
Outcome type (DNL/LWC/L)	Do Not List (DNL)	List With Criteria (LWC)	List (L)	Total
N (% of total)	30 (29%)	72 (71%)	0 (0%)	N= 102 (100%)
Country (Agency)				
		*χ^2 = 10.1737 (p=**0.038**)*		
Canada (CADTH)	6 (20%)	22 (31%)	0 (0%)	28 (27%)
Canada (INESS)	13 (43%)	13 (18%)	0 (0%)	26 (25%)
Scotland (SMC)	3 (10%)	9 (13%)	0 (0%)	12 (12%)
France (HAS)	7 (23%)	14 (19%)	0 (0%)	21 (21%)
England (NICE)	1 (3%)	14 (19%	0 (0%)	15 (15%)
Therapeutic area				
		χ^2 = 0.6209 (p=0.431)		
Non-oncology[1]	7 (23%)	12 (17%)	0 (0%)	19 (19%)
Oncology	23 (77%)	60 (83%)	0 (0%)	83 (81%)
Prior rejection by HTA				
		χ^2 = 0.3998 (p=0.527)		
No	25 (83%)	56 (78%)	0 (0%)	81 (79%)
Yes	5 (17%)	16 (22%)	0 (0%)	21 (21%)
Trial phase				
		χ^2 = 3.2583 (p=0.353)		
Phase 1	0 (0%)	1 (3%)	0 (0%)	1 (1%)
Phase II	15 (50%)	35 (49%)	0 (0%)	50 (49%)
Phase III	14 (47%)	35 (39%)	0 (0%)	49 (48%)
Other (Observational)	0 (0%)	2 (3%)	0 (0%)	2 (2%)
Social value judgments				
Severity				
		χ^2 = 2.0668 (p=0.151)		
Not considered	4 (13%)	19 (26%)	0 (0%)	23 (23%)
Considered	26 (87%)	53 (74%)	0 (0%)	79 (77%)
Unmet need				
		χ^2 = 0.0731 (p=0.787)		
Not considered	3 (10%)	6 (8%)	0 (0%)	9 (9%)
Considered	27 (90%)	66 (92%)	0 (0%)	93 (91%)
Administrative advantage				
		χ^2 = 0.1158 p=(0.734)		
Not considered	19 (63%)	43 (60%)	0 (0%)	62 (61%)
Considered	11 (37%)	29 (40%)	0 (0%)	40 (39%)
Innovation				
		χ^2 = 3.4358 (p=0.064)		

Not considered	21 (70%)	36 (50%)	0 (0%)	57 (56%)
Considered	9 (30%)	36 (50%)	0 (0%)	45 (44%)
		Rarity		
		χ^2 = 7.0247 (p=**0.008**)		
Not considered	26 (87%)	43 (60%)	0 (0%)	69 (68%)
Considered	4 (13%)	29 (40%)	0 (0%)	33 (32%)
		Short Life Expectancy		
		χ^2 = 0.0000 (p=1.000)*		
Not considered	20 (67%)	48 (67%)	0 (0%)	68 (67%)
Considered	10 (33%)	24 (33%)	0 (0%)	34 (33%)
		Special Demographics		
		χ^2 = 0.0000 (p=1.000)*		
Not considered	25 (83%)	60 (83%)	0 (0%)	85 (83%)
Considered	5 (17%)	12 (17%)	0 (0%)	17 (17%)
		Clinical uncertainties		
		Clinical benefit		
		t= -1.2346 (p=0.2199)		
Observations	30	72	0	102
Mean (SD)	2.5 (1.63)	2.1 (1.29)	-	2.2 (1.4)
		Generalisability		
		t=-1.3526 (p=0.1792)		
Observations	30	72	0	102
Mean (SD)	0.7 (0.60)	0.5 (0.71)	-	0.56 (0.68)
		Study Design		
		t=-3.5819 ***(p=0.0005)***		
Observations	30	72	0	102
Mean (SD)	3.2 (2.81)	1.65 (1.53)	-	2.11 (2.1)
		Indirect Comparison		
		t= 0.2724 (p=0.7859)		
Observations	30	72	0	102
Mean (SD)	0.33 (0.66)	0.375 (0.72)	-	0.36 (0.70)
		Clinical Evidence		
		t=-0.5378 (p=0.5919)		
Observations	30	72	0	102
Mean (SD)	1.13 (1.17)	1.01 (0.96)	-	1.04 (1.02)
		Clinical Practice		
		t=1.8204 (p=0.0717)		
Observations	30	72	0	102
Mean (SD)	0.46 (0.63)	0.76 (0.80)	-	0.68 (0.76)
		Comparator		
		t=-1.27 (p=0.2073)		
Observations	30	72	0	102
Mean (SD)	0.33 (0.55)	0.21 (0.41)	-	0.25 (0.45)
		Economic uncertainties[2]		
		Modelling		
		t=1.3756 (p=0.1720)		
Observations	30	72	0	102
Mean (SD)	1.20 (1.21)	1.68 (1.74)	-	1.54 (1.61)
		Model Type		
		t=0.4695. (p=0.6397)		
Observations	30	72	0	102
Mean (SD)	0.03 (0.18)	0.06. (0.23)	-	0.05 (0.22)

		Comparator *t=0.8002 (p=0.4255)*		
Observations	30	72	0	102
Mean (SD)	0.10 (0.31)	0.17 (0.41)	-	0.15 (0.38)
		Cost *t=-0.2728 (p=0.7856)*		
Observations	30	72	0	102
Mean (SD)	0.53 (0.97)	0.49 (0.71)	-	0.50 (0.79)
		Utilities *t=0.5992 (p=0.5504)*		
Observations	30	72	0	102
Mean (SD)	0.30 (0.65)	0.375 (0.54)	-	0.35 (0.57)
		Cost-Effectiveness *t=2.3407* ***(p=0.0212)***		
Observations	30	72	0	102
Mean (SD)	0.63 (0.67)	1.15 (1.13)	-	1.0 (1.0)
		Sensitivity Analysis *t=-0.1498 (p=0.8812)*		
Observations	30	72	0	102
Mean (SD)	0.03 (0.18)	0.03 (0.17)	-	0.03 (0.17)
		Days from MA to HTA/funding decision[3] *t= -1.5622 (p=0.1214)*		
Observations	30	72	0	102
Mean (SD)	600 (435)	453 (399)	-	496 (435)
		HTA/funding decision year $\chi^2 = 2.1803$ *(p=0.975)*		
2011	0 (0%)	2 (3%)	0 (0%)	2 (2%)
2012	0 (0%)	1 (1%)	0 (0%)	1 (1%)
2013	2 (7%)	8 (11%)	0 (0%)	10 (10%)
2014	3 (10%)	6 (8%)	0 (0%)	9 (9%)
2015	4 (13%)	11 (15%)	0 (0%)	15 (15%)
2016	8 (27%	16 (22%)	0 (0%)	24 (24%)
2017	8 (27%)	16 (22%	0 (0%)	24 (24%)
2018	4 (13%	10 (14%)	0 (0%)	14 (14%)
2019	1 (3%)	2 (3%)	0 (0%)	3 (3%)

Note: [1] Non-oncology drugs include alimentary track and metabolism products, anti-infective products, nervous system products, systemic hormonal preparations and products for sensory organs.
[2] France (HAS) does not conduct routine economic evaluations as part of their assessment process to determine SMR and ASMR rankings. Economic uncertainties are only recorded for CADTH, INESSS, NICE and SMC.
[3] Canadian HTA agencies (CADTH and INESSS) have the ability to undertake parallel review, whereby HTA takes place concurrently with marketing authorisation review.
* Equal distribution across HTA outcome categories

Sources: The authors.

All positive listing recommendations for the sample included either clinical (prescribing or population restrictions) or economic conditions (commercial access agreement or discount to improve cost-effectiveness). INESSS has the highest frequency of negative listing decisions (46%), followed by CADTH (21%), SMC (14%), NICE (5%) and HAS (5%). HTA submissions were not present for 9 medicine-indication pairs in SMC, 6 medicine-indication pairs in NICE, and 2 medicine-indication pairs in INESSS. Approximately 15−20% of medicine-indication-pairs were subject to resubmissions, following an initial rejection. The majority of resubmissions (90%) resulted in a positive listing recommendation. Two medicine-indication pairs, Imbruvica for the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL), and Votrient for the first-line treatment of advanced renal-cell carcinoma (RCC), were rejected following a resubmission by INESSS and HAS respectively.

Concordance across HTA agencies in outcomes was low. Within Europe, only 8 medicine-indication pairs (38%) had positive listing recommendations across all three HTA agencies (Adcetris, Blincyto, Bosulif, Darzalex, Tagrisso, Zykadia, Bavencio, and Xalkori). Of these medicine-indication pairs, four required at least one resubmission in either NICE, SMC, or HAS (Adcetris, Bosulif, Darzalex, and Xalkori). All medicine-indication-pairs in Europe obtained at least one positive HTA recommendation. Within Canada, 13 medicine-indication pairs (46%) had positive listing recommendations in both CADTH and INESSS and 4 medicine-indication pairs (14%) were rejected by both agencies (Darzalex, Alecensaro, Arzerra and Imbruvica). The remaining 11 medicine-indication pairs (40%) received diverging recommendations by CADTH and INESSS (32%) or were only evaluated by one agency (8%).

2.3.4 Clinical evidence–marketing authorisation vs HTA

NOC/C approvals by Health Canada were more frequently based on non-randomised clinical evidence than CMA approvals by EMA (72% vs 57% respectively). However, the most common pivotal trial design was single arm phase II trials in both the EMA (47%) and in Health

Canada (57%). Only 6 medicine-indication pairs (29%) relied on phase III trial data for EMA CMA approval and only 4 medicine-indication pairs (14%) for Health Canada NOC/C approvals (See **Figure 2.1**). In two instances, EMA CMA was granted on the basis of a phase I trial (Zykadia for ALK positive non-small cell lung cancer) and an observational study (Holoclar for the treatment of chemical or physical eye burns). In Canada, NOC/C approval was granted once on the basis of an observational study (Soliris for atypical hemolytic uremic syndrome) and three times on the basis of phase I trial data (Zykadia for ALK positive non-small cell lung cancer, Keytruda for metastatic non-small cell lung cancer and Keytruda for metastatic melanoma).

Three types of conditions were imposed by Health Canada and EMA for NOC/C and CMA approvals: (a) submission of follow-up data from pivotal clinical trials, (b) completion of a confirmatory phase II trial, or c) completion of a confirmatory phase III trial. Within Canada, 72% of NOC/C approvals required submission of follow-up data from pivotal clinical trials, 68% of approvals required completion of a confirmatory phase III trial, 21% of approvals required completion of a confirmatory phase II trial. Within Europe, 71% of CMA approvals required completion of confirmatory phase III trial, 19% required completion of a phase II trial, and 14% required submission of follow-up data from the pivotal clinical trial.

Relative to regulatory approval, HTA submissions were more frequently based on RCT designs. RCTs were the primary source of evidence in 62% of HAS submissions, 58% of INESSS submissions, 57% of CADTH submissions, 50% of SMC submissions, and 47% of NICE submissions. Across all settings, a substantial number of HTA submissions were based on single arm phase II trials. The majority of HTA submissions relied on the same trial used to support regulatory approval.

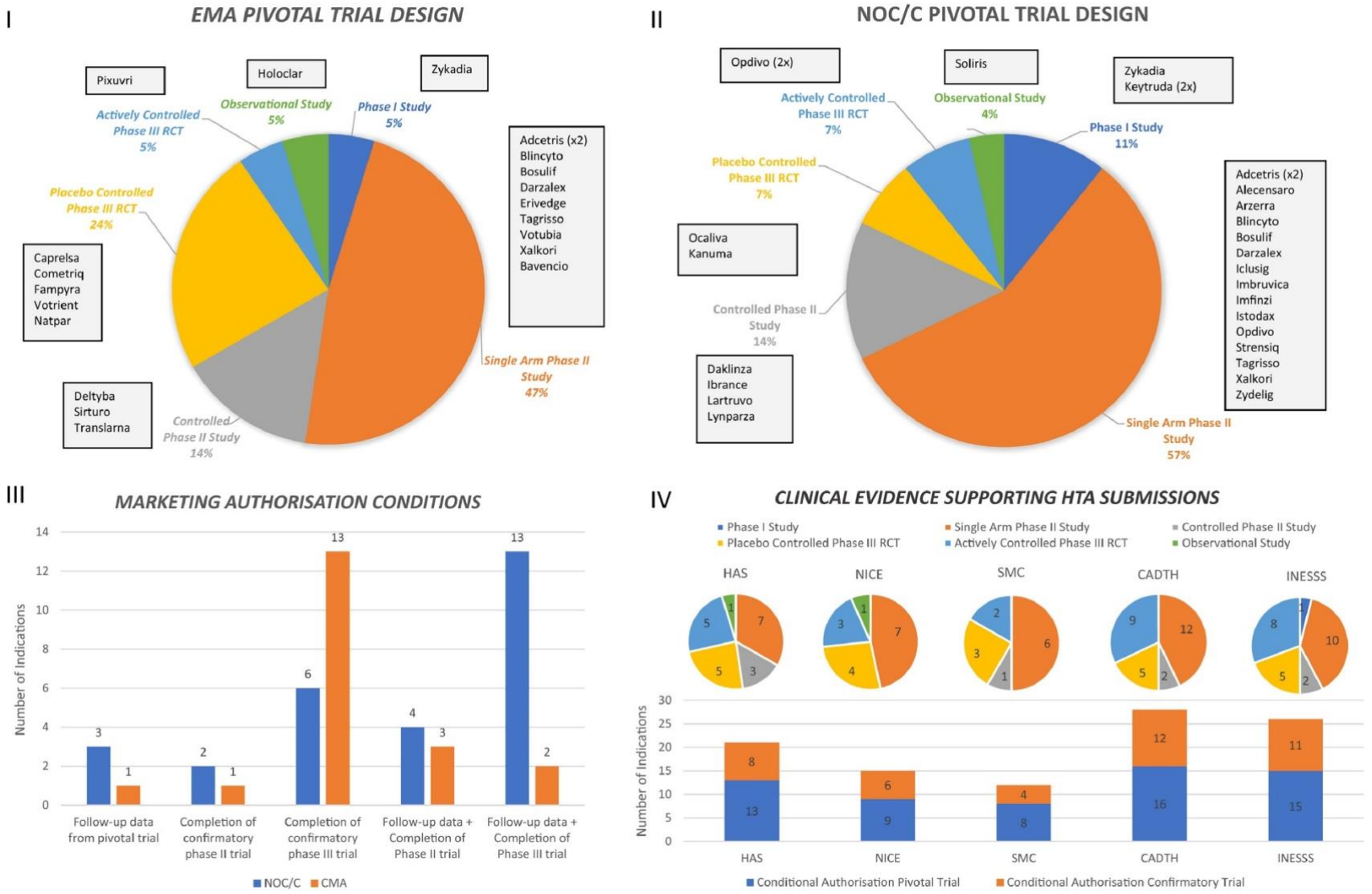


Figure 2.1 - Clinical Evidence Supporting Marketing Authorisation and HTA Approval of Accelerated Access Products

I – Pivotal trial design of EMA conditional marketing authorisation approvals between 2010 and 2017 with at least one HTA evaluation in France, England or Scotland. II – Pivotal trial design of Health Canada notice of compliance with conditions approvals between 2010 and 2017 with at least one HTA evaluation in Ontario (CADTH/PCODR) or Quebec (INESSS). III – Evidence generation conditions set by EMA and Health Canada for conditional marketing authorisation approvals and notice of compliance with conditions. IV – Characteristics of main clinical trial supporting HTA submissions for conditional marketing authorisation approvals and notice of compliance with conditions. Part A provides an overview of the study designs for the main trial supporting HTA approval. Part B outlines the extent to which clinical evidence supporting HTA is based on the conditional authorisation pivotal trial or based on pivotal trial confirmatory trials.

However, evidence from confirmatory trials (the conditions for marketing authorisation), was available in 38% of HAS submissions, 40% for NICE submissions, 33% of SMC submissions, 43% of CADTH submissions, and 42% of INESSS submissions. Out of the 24 medicine-indication pairs that received a negative HTA recommendation across all settings, 45.8% were based on single arm phase II trials, 42% were based on randomised phase III trials, 8% were based on controlled phase II trials, and 4% were based on phase I trials.

2.3.5 Impact of clinical uncertainties on HTA outcomes–agency-level analysis

A total of 738 clinical uncertainties were identified across the entire sample of CMA and NOC/C medicine-indication pairs (See **Figure 2.2**). Across all settings the most common type of clinical uncertainty raised related to the magnitude of clinical benefit (HAS, NICE, SMC and CADTH) or poor study design (INESSS).

Within HAS, uncertainty in the magnitude of clinical benefit, lack of clinical evidence, study design, and relevance to local clinical practice were the most common issues raised (47%, 15%, 18%, and 14% respectively). Over 85% of clinical uncertainties raised by HAS were not addressed in the assessment and were considered to be limitations in the clinical evidence submitted. Marginal differences in the average number and type of clinical uncertainties are present when comparing products by HTA outcome. On average, products given an ASMR rating of V had a larger number of uncertainties that were not overcome and a smaller number of addressed uncertainties relative to products given an ASMR rating of IV or III. In particular, products with an ASMR rating of V had a greater number of unaddressed uncertainties relating to evidence on the magnitude of clinical benefit and relating to issues with poor study design.

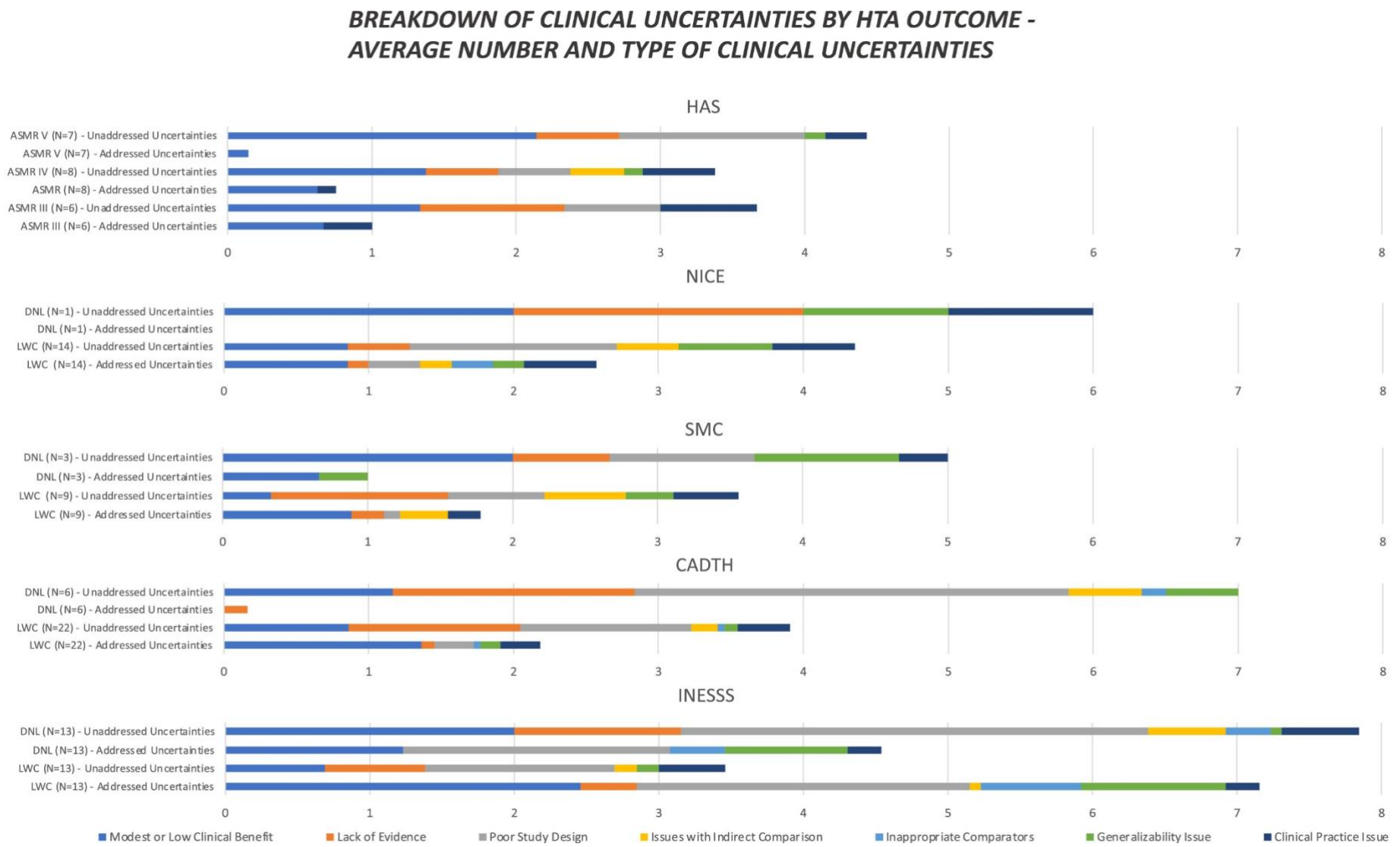


Figure 2.2 - Average Number and Type of Clinical Uncertainties Raised in the Assessment of CMA Approvals between 2010-2017 in France (HAS), England (NICE), and Scotland (SMC) and of NOC/C approvals in Ontario (CADTH) and Quebec (INESSS)

Clinical uncertainties are categorised according to whether or not they have been addressed or remain unaddressed in the context of a decision. Data is presented at country level and according to HTA outcome: LWC = HTA recommendation to list with conditions, DNL = HTA recommendation to not list a product. ASMR = Amélioration du Service Médical Rendu (Scale of added clinical benefit ranging from V – non-existent to I – Major).

The key clinical uncertainties raised during NICE assessments of CMA products included uncertainty in magnitude of clinical benefit (25%), poor study design (24%), relevance to local clinical practice (16%), generalisability of trial population (15%) and lack of evidence (10%). Comparisons between products based on HTA outcome are limited by low sample size. The only CMA medicine-indication pair that received a negative listing decision by NICE was Erivedge for metastatic basal cell carcinoma. A total of six clinical uncertainties were raised during NICE's assessment of Erivedge. Two issues were raised on the magnitude of clinical benefit (no evidence of benefit in a subgroup and low magnitude of survival benefit), two issues on lack of evidence (no direct comparative evidence to best supportive care and no long-term OS data), one issue relating to generalisability (proportion of patients in trial with Gorlin syndrome higher than expected in the UK population), and one issue relating to clinical practice (trial not generalisable to UK clinical practice for patients with basal cell carcinoma).

The key clinical uncertainties raised during SMC assessments of CMA products included uncertainty in magnitude of clinical benefit (29%), lack of evidence (23%), issues in study design (15%), issues in indirect comparison (12%), relevance to local clinical practice (11%), and generalisability of trial population (11%). Unresolved uncertainties relating to magnitude of clinical benefit, poor study design and generalisability of trial population were more common in medicine-indication pairs that received negative recommendations relative to medicine-indications that were conditionally recommended for funding.

Within CADTH, uncertainties in magnitude of clinical benefit, lack of evidence and study design were most common (32%, 22%, and 28% respectively). Unresolved uncertainties relating to poor study design and generalisability of trial population were more common in medicine-indication pairs that received negative recommendations relative to medicine-indications that were conditionally recommended for funding. While the total average number

of uncertainties raised was similar across LWC and DNL groups (7.16 vs 7), clinical uncertainties were more likely to be addressed in assessments with positive outcomes.

Similar to CADTH, uncertainties in magnitude of clinical benefit, lack of evidence and study design were the most common uncertainties raised by INESSS (28%, 10%, and 38%, respectively). Medicine-indication pairs with negative HTA outcomes are more likely to have unresolved clinical uncertainties (magnitude of clinical benefit, lack of evidence and study design) relative to medicine-indication pairs with positive HTA outcomes. Common unresolved issues in study design leading to negative recommendations by INESSS included (small number of patients (n = 5), issues in randomisation (n = 3), inappropriate outcome measure (n = 2), issues in study blinding (n = 4), confounding due to patient crossover (n = 2) and inadequate study duration (n = 2).

2.3.6. Impact of economic uncertainties on HTA outcomes–agency-level analysis

A total of 368 economic uncertainties were identified across the entire sample of CMA and NOC/C medicine-indication pairs (See **Figure 2.3**). Economic analysis was not routinely performed for HAS medicine-indication pairs (only one medicine-indication pair submitted an economic evaluation – a cost-minimisation analysis of Zykadia for ALK positive NSCLC). Only one economic uncertainty was raised in relation to the appropriateness of conducting a cost-minimisation analysis, which was addressed and deemed appropriate.

The most common type of economic uncertainty raised during NICE evaluations related to modelling issues (37% of all economic uncertainties), followed by issues in cost-effectiveness estimate (29%), issues in utility estimates (24%) and issues in cost estimations (12%).

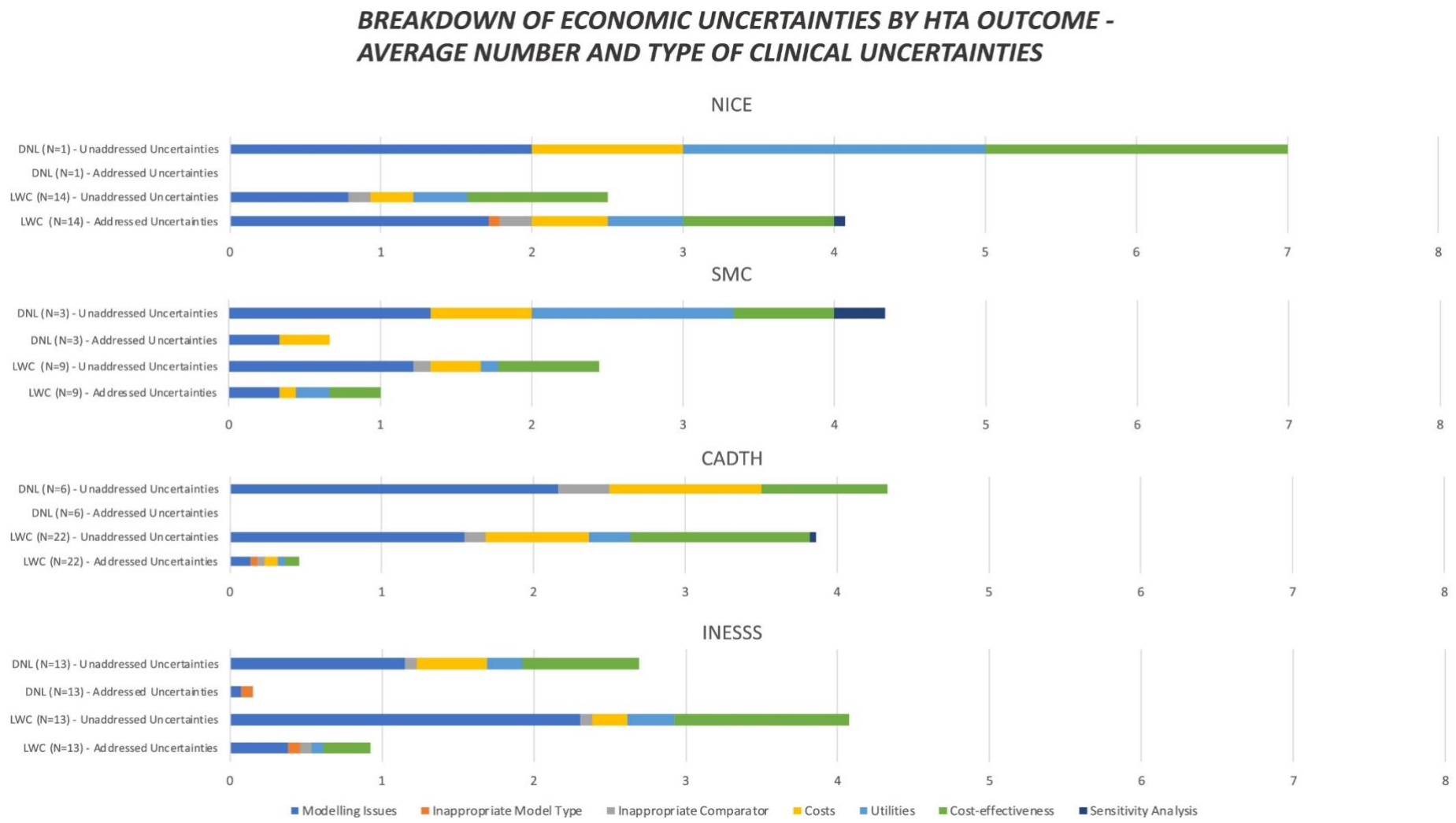


Figure 2.3 - Average Number and Type of Economic Uncertainties Raised in the Assessment of CMA Approvals between 2010-2017 in England (NICE), and Scotland (SMC) and of NOC/C approvals in Ontario (CADTH) and Quebec (INESSS)

Economic uncertainties are categorised according to whether or not they have been addressed or remain unaddressed in the context of a decision. Data is presented at country level and according to HTA outcome: LWC = HTA recommendation to list with conditions, DNL = HTA recommendation to not list a product.

Comparison across medicine-indication pairs by HTA outcome is limited due to sample size. In their negative recommendation for Erivedge, NICE raised two uncertainties on modelling (limitations in clinical evidence used and inappropriate extrapolation method for estimating time to treatment discontinuation), two issues in cost effectiveness (ICER too high after adjustments, ICER highly uncertain), two issues in utilities (utilities not generalisable to UK and uncertainty in quality of life data), and one issue in costs (cost of best-supportive care being over-estimated). The majority of uncertainties raised for medicine-indication pairs with positive NICE outcomes were overcome.

Within Scotland, the most common type of economic uncertainty raised was also related to modelling issues (41%), followed by issues in cost-effectiveness estimates (24%), issues in utility estimates (15%) and issues in cost estimations (15%). Medicine-indication pairs with negative HTA outcomes had a larger average number of unresolved economic uncertainties than medicine-indication pairs with positive HTA outcomes. In particular, issues in cost estimation and utility estimation were more common in the negative outcome group.

Modelling issues were also the most frequently raised type of economic uncertainty by CADTH (41%) and INESSS (50%). Within CADTH, only marginal differences were seen between medicine-indication pairs with positive and negative outcomes. Unresolved uncertainties in modelling and cost estimation were slightly more common in the negative HTA outcome group. In the negative recommendation group (Darzalex, Alecensaro, Arzerra, Imbruvica, Zydelig, and Soliris), unresolved issues in modelling included majority of clinical benefit being derived post-progression (n = 1), uncertainty in treatment duration (n = 3), issues with extrapolation (n = 5), inappropriate time horizon (n = 3), and lack of clinical evidence (n = 1). Within INESSS, unresolved economic uncertainties were more common in the positive HTA outcome group than the negative HTA outcome group. Economic assessment was limited for

a number of medicine-indication pairs in the negative HTA outcome group. For Arzerra, Zykadia, Alecensaro, Darzalex, and Lartuvo, INESSS rejected the economic analysis submitted due to high levels of uncertainty in the clinical evidence submitted.

2.3.7. Impact of social value judgments on HTA outcomes–agency-level analysis

Social value judgments raised in the context of HTA assessments include disease rarity, disease severity, unmet medical need, innovative mechanism of action, short life expectancy for patient population, administration advantages, and special demographics (See **Figure 2.4**). The most commonly raised SVJs in HTA assessments of CMA and NOC/C products across all settings were disease severity and unmet need. Disease severity was raised in the majority of assessments across all agencies, 81% of HAS assessments, 80% in NICE assessments, 73% of SMC assessments, 72% of CADTH assessments, and 89% of INESSS assessments. In NICE, SMC, CADTH and INESS, disease severity was mentioned more frequently in the context of negative HTA outcomes relative to positive HTA outcomes, although the difference was marginal for INESSS and NICE. Unmet need was also raised in the majority of assessments across all agencies, 82% of HAS assessments, 73% in NICE assessments, 92% of SMC assessments, 85% of CADTH assessments, and 93% of INESSS assessments. Unmet need was raised more frequently in positive HTA outcomes in HAS (ASMR III 100% vs ASMR V 57%) and in CADTH (LWC 95% vs DNL 50%).

Across all settings, disease rarity was raised more frequently in the context of positive decisions. This difference was most notable in the HAS (100% of assessments that resulted in an ASMR rating of III vs only 25% for ASMR IV and 14% for ASMR V), CADTH (41% LWC vs 17% DNL), and SMC (44% LWC vs 0% DNL), followed by NICE (21% vs 0%) and INESSS (23% vs 15%).

Figure 2.4 - Key Social Value Judgments (SVJs) Raised in the Assessment of CMA Approvals between 2010 and 2017 in France (HAS), England (NICE), and Scotland (SMC) and of NOC/C approvals in Ontario (CADTH) and Quebec (INESSS)

SVJs are reported in terms of the frequency in which they are raised in the HTA decisions. Data is presented by country and according to HTA outcome: LWC = HTA recommendation to list with conditions, DNL = HTA recommendation to not list a product. ASMR = Amélioration du Service Médical Rendu (Scale of added clinical benefit ranging from V – non-existent to I – Major).

Innovative mechanism of action, short life expectancy, administrative advantage and special demographics were raised less frequently in the assessment of NOC/C and CMA products with a few exceptions. In SMC, innovative mechanism of action was raised in 75% of assessments, while special demographics were mentioned in 50% of assessments. Meanwhile, in INESSS, short life expectancy was raised in 63% of assessments and administration advantage was mentioned in 43% of assessments.

2.4 Discussion

There is a clear disconnect between expedited regulatory pathways that are promoting accelerated access to innovative medicines, and HTA agencies that still require robust clinical evidence to arrive at funding decisions. While evidence from confirmatory trials is available for use in HTA submissions in approximately 30−40% of cases, resubmissions and rejections of conditionally approved products are common, and a wide range and number of unresolved clinical and economic uncertainties are raised in the context of HTA decisions.

This study has enabled a comprehensive evaluation of the key parameters (clinical, economic and additional dimensions of value) that HTA agencies consider in the assessment and appraisal of conditionally approved medicines. Within Europe, CMA products must address an unmet medical need and demonstrate proof that the benefit to public health of the immediate availability of a product outweighs the risk associated with immature data [136]. Within Canada, NOC/C products must be used in serious or life threatening conditions where there is (a) no available therapy or (b) where the product represents a significant improvement over existing products available in Canada [96]. Despite clear criteria for fulfilling unmet medical need in serious or life threatening conditions, HTA outcomes for these products are highly variable across the HAS, NICE, SMC, CADTH and INESSS suggesting that contextual

considerations and SVJs alone, such as disease severity and unmet need, are not sufficient to overcome issues in clinical and economic evidence at HTA level.

Out of the five agencies in our sample, NICE was the most favourable towards conditionally approved products, providing positive recommendations to 93% (14/15) medicine-indication pairs that were appraised. While HAS also had a high frequency of approval in terms of reimbursement (only one product received an SMR rating of "insufficient"), no products received an ASMR of I or II (indicating a "major" or "important" added benefit, respectively) and 33% of medicine-indication pairs received an ASMR rating of V indicating non-existent added benefit or "lack of therapeutic progress". This indicates a clear disconnect between the HAS and EMA on the value of conditionally approved products. Conditionally approved products had mixed success with the SMC, as only half of the products appraised received a positive coverage recommendation upon completion of the process, while an additional 3 products received a positive coverage recommendation following resubmission. CADTH was also relatively favourable towards NOC/C products, although 21% of medicine-indication pairs received a negative recommendation and a further 21% required a resubmission for a positive HTA outcome. INESSS was the least favourable towards conditionally approved products, providing a positive recommendation to only 50%.

It is clear that HTA agencies do not rely on a single metric to arrive at an assessment outcome, but, rather, a combination of multiple parameters. Products with negative HTA outcomes (DNL and SMR insufficient) frequently had several dimensions of value that were remarked upon positively by HTA agencies, most frequently disease severity and unmet need. Nevertheless, SVJs alone, may not compensate for concerns related to clinical and economic evidence. Across the aggregate sample, products with negative HTA outcomes have a high tendency to have unresolved study design issues and unresolved issues in the cost-effectiveness estimates, even for products identified for use in severe diseases with high unmet need.

Within the HAS, uncertainties in magnitude of clinical benefit, issues in study design, disease rarity, and unmet need were key parameters in distinguishing products by ASMR rating. Within NICE, uncertainties in the magnitude of clinical evidence, uncertainties related to lack of evidence, uncertainties in cost estimation, and uncertainties in utilities estimates were notable parameters in the rejection of Erivedge. Within the SMC, uncertainties in magnitude of clinical benefit, issues in study design, issues in generalisability of the trial population, uncertainty in cost estimation, uncertainty in utilities estimates, disease rarity, and administration advantage were key parameters in distinguishing products with positive and negative HTA outcomes. In CADTH, uncertainty in study design, uncertainty in generalisability of trial population, uncertainties in modelling, and unmet need were key parameters in distinguishing products with positive and negative HTA outcomes. Finally in INESSS, uncertainties in magnitude of clinical benefit, uncertainties in study design, uncertainties in cost estimation, innovative mechanism of action and administration advantage were key parameters in distinguishing products with positive and negative HTA outcomes.

The heterogeneity in HTA outcomes reported here is consistent with other empirical studies that have compared HTA assessment and outcomes across settings [148-151], and raise questions around whether or not current frameworks employed by HTA agencies adequately capture all elements of value that a product provides. This is particularly important in the context of conditionally approved products where patients often have no therapeutic alternatives and are suffering from life-threatening or chronically debilitating conditions.

Several policy priorities emerge from our analysis. First, greater alignment between regulatory bodies and HTA agencies is needed on evidence requirements for conditionally approved medicines. The extent to which conditional marketing authorisation pathways reduce clinical development time is currently limited by stringent HTA evidence requirements, resulting in reduced or delayed availability of conditionally approved medicines. HTA agencies and

regulatory bodies serve fundamentally different functions with distinct objectives. While complete harmonisation of evidence requirements is not pragmatic, more can be done to tailor HTA processes to conditionally approved products. Conditional reimbursement pathways, such as England's Cancer Drugs Fund (CDF), provide temporary reimbursement to products with high levels of clinical uncertainty to allow time for evidence maturation and could be implemented more widely [152]. While conditional reimbursement pathways produce greater administrative burden, due to the need for resubmission and reassessment following evidence maturation, their use may be warranted in limited cases for medicines that address an unmet medical in a serious or life-threatening condition.

Second, HTA agencies need to play a more active role in evidence generation planning for conditionally approved medicines. In a recent EMA report on experience with the CMA from 2006-2016, the EMA calls for greater engagement with HTA agencies and increased use of early dialogue [153]. A number of initiatives on joint early dialogue between regulators and HTA agencies and involving multiple HTA agencies have been launched recently in Europe including the EMA-EUnetHTA Parallel Consultation procedure and the EUnetHTA-Multi HTA Early Dialogue procedure [27, 154]. HTA agencies should have more systematic and earlier involvement in joint early dialogue processes to clarify evidence expectations earlier in the clinical development pathway and to help mitigate negative HTA outcomes for conditionally approved medicines.

Finally, there is a need for increased transparency and consistency in HTA decision-making, particularly in the incorporation of parameters beyond clinical and cost effectiveness. SVJs are consistently raised during the HTA decision-making process, providing contextual considerations. However, methods of incorporating social value judgments are not explicitly defined in HTA processes, leading to uncertainty in the impact of these parameters on decision-making. A recent review of HTA systems and methods highlighted that while HTA agencies

routinely consider economic and clinical evidence, other elements of value are often considered implicitly [21]. Novel approaches to HTA such as multiple criteria decision analysis (MCDA) could help to improve the transparency of decision-making through explicit consideration and weighting of a range of different value dimensions [155]. While MCDA could help to clarify questions around what constitutes value in the context of conditionally approved medicines, it does not guarantee that different HTA agencies or regulatory agencies will align on their definition of value. Alternatively, HTA agencies should explore alternative mechanisms of explicitly scoring or weighting social value parameters, with clearly defined criteria and impact on decision-making (e.g. sliding cost-effectiveness thresholds).

There are several limitations in the present study which highlight areas for future research. First, while the analytical framework employed in the present study allows for the identification of the frequency with which a particular parameter is raised in the context of HTA, the weight of particular parameters on the final decision may be variable. In particular, the relative impact of clinical vs non-clinical parameters (social value judgments) on the final decision remains unknown. For instance, the level of unmet need and ethical obligations to fund a novel medicine is unlikely to uniform across all disease areas. By extension, the extent to which unmet need modifies HTA outcomes is likely to vary from medicine-to-medicine. As such, while the results presented here help to explain some of the heterogeneity seen across settings in the evaluation of conditionally approved products and what parameters are likely to be important, they do not fully account for the discrepancies seen across settings. Second, the results are unique to the HTA agencies considered and to conditionally approved products approved between 2010-2017, and, as such, are not generalisable to other HTA agencies or types of products including those with standard regulatory approval. While outside the scope of the present study, which was limited to the characteristics, evidence and evaluation of conditionally approved products, an evaluation of how HTA agencies compare in their assessment of standard vs conditionally

approved products would present a natural extension and offer further clarity on how HTA agencies balance uncertainties in clinical and economic evidence with additional dimensions of value such as disease severity and unmet need. There would also be added value in considering the impact of alternative regulatory pathways including priority review and authorisation under exceptional circumstances. Third, while the Health Canada NOC/C pathway and the EMA CMA pathway are not asimilar, they each have distinct eligibility criteria, as evidenced by differences in the products that received conditional approval in the respective settings. As a result, it is possible that the differences identified across HTA agencies in the evaluation of conditionally approved products are partially caused to differences at regulatory level, rather than differences in evidence thresholds and consideration of uncertainty and additional dimensions of value. Finally, marketing authorisation for a small number of conditionally approved products was withdrawn and, because of that, they were excluded due to redaction of HTA reports. This may bias the results slightly in favour of products with positive HTA outcomes.

2.5 Conclusion

This study explored the disconnect between regulatory and health technology assessment agencies on the value of conditionally approved products through application of a mixed-methods analytical framework. Significant heterogeneity was noted in terms of parameters considered by HTA agencies and HTA outcomes. The push for accelerated access to medicines for serious and life-threatening conditions by regulatory agencies is often stalled by HTA agencies that require robust evidence to inform resource allocation recommendations or decisions. As more innovative and life-saving medicines are developed, it will be critical to improve the dialogue between all stakeholders in order to clarify evidence requirements and avoid delays in patient access.

2.6 Appendix

Table 2.4 - Comparison of Expedited Regulatory Approval Pathways

Type of Expedited Regulatory Pathway	Description	Mechanism for Accelerating Access	Examples
Conditional Approval	Approval based on immature or surrogate clinical evidence on the condition that confirmatory studies are performed to validate the safety and efficacy of a product. For products which address an unmet need and are used in serious, chronically debilitating or life-threatening diseases.	Shifts clinical development from pre-approval to post-approval	EMA – Conditional Marketing Authorisation FDA – Accelerated Approval Health Canada – Notice of Compliance with Conditions TGA – Provisional Approval
Exceptional Circumstances	Approval of products where it is unethical or unfeasible to undertake complete evidence development.	Not applicable. Provides authorisation in circumstances where it would otherwise not be possible	EMA – Marketing Authorisation Under Exceptional Circumstances FDA – Animal Rule
Priority Review	Reduction of marketing authorisation review time. No changes to evidence thresholds for authorisation. For products of major interest to public health and that address an unmet need.	Reduces regulatory review time	EMA – Accelerated Assessment FDA – Priority Review Health Canada – Priority Review TGA – Priority Review
Enhanced Regulatory Support	Enhanced early dialogue, scientific advice or engagement with marketing authorisation officials in order to improve evidence generation plans. For products that are used in serious or life-threatening diseases and which have shown early evidence of improvement over existing therapeutic alternatives.	Informs evidence generation and avoids delays in regulatory approval	EMA – PRIME FDA – Fast-Track, Breakthrough Therapy Designation
Verification Review	Reduction in marketing authorisation review time based on prior approval in one or more designated overseas regulatory agencies.	Reduces regulatory review time	Health Canada – Access to Drugs Under Exceptional Circumstances TGA – Abbreviated review based on overseas regulator

Abbreviations: EMA – European Medicines Agency, FDA – U.S. Food and Drug Administration, TGA – Australian Therapeutic Goods Administration

Source: The authors based on [1-5].

Table 2.5 - List of Expedited Approval Drug-Indication Pairs

CMA Drug-Indication Pairs

Molecule name	Brand name	Indication	HAS Outcome	NICE Outcome	SMC Outcome
Ataluren	Translarna	For the treatment of Duchenne muscle dystrophy, resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients 5 years of age or more	Moderate, IV	LWC	DNL
Avelumab	Bavencio	As monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).	Important, IV	LWC	LWC
Bedaquiline	Sirturo	For use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.	Important, III	NS	NS
Blinatumomab	Blincyto®	For previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia	Important, III	LWC	LWC
Bosutinib	Bosulif ®	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	Important, V	LWC - RESUB	LWC - RESUB
Brentuximab Vedotin-1	Adcetris ®	For the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.	Important, III	LWC	LWC
Brentuximab Vedotin-2	Adcetris®	For the treatment of adult patients with relapse or refractory systemic large cell anaplastic lymphoma (sALCL).	Important, III	LWC - RESUB	NS
Cabozantinib-2	Cometriq®	For the treatment of medullary thyroid carcinoma in adult patients with progressive, non-resectable, locally advanced or metastatic disease.	Important, IV	LWC	DNL

Ceritinib	Zykadia®	For treating adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib	Important, IV	LWC	LWC
Crizotinib-1	Xalkori®	For the treatment of advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kynase (ALK+) for adult patients previously treated with at least one other lung cancer treatment	Important, III	LWC - RESUB	LWC - RESUB
Daratumumab	Darzalex	As a monotherapy for the treatment of adult patients with recurrent and refractory multiple myeloma who have already been treated with a proteasome inhibitor and an immune modulator and have shown a disease progression during the last therapy.	Important, V	LWC	LWC - RESUB
Delamanid	Deltyba	for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.	Important, III	NS	NS
Everolimus-4	Votubia®	For the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.	Important, V	NS	NS
ex vivo expanded autologous human corneal epithelial cells containing stem cells	Holoclar	Treatment of patients with moderate-severe (superficial corneal neovascularisation in at least two quadrants) limbal stem cell deficiency, unilateral or bilateral with a minimum of 1-2 mm2 of undamaged limbus, due to ocular burns.	Important, IV	LWC	NS
Fampridine	Fampyra®	For the improvement of walking ability of adult patients with multiple sclerosis (MS) with walking impairment (EDSS 4-7).	Low, V	NS	DNL
Osimertinib	Tagrisso	For the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy	Important, IV	LWC	LWC
parathyroid hormone	Natpar	For adjuvant therapy in adult patients with chronic hypoparathyroidism which cannot be adequately controlled by conventional treatment alone.	Low, V	NS	NS

Pazopanib-1	Votrient®	In adults for the first-line treatment of advanced renal-cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.	Insufficient, V	LWC	LWC
Pixantrone	Pixuvri®	As monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non Hodgkin B cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.	Low, V	LWC	NS
Vandetanib	Caprelsa®	For the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease	Important, IV	NS	NS
Vismodegib	Erivedge®	Erivedge is indicated for the treatment of adult patients with: - symptomatic metastatic basal cell carcinoma or - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy	Important, IV	DNL	NS
NOC/C Drug-Indication Pairs					
Molecule name	**Brand name**	**Indication**	**CADTH OUTCOME**	**INESSS OUTCOME**	
Alectinib	Alecensaro	As monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK) positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	DNL	DNL	
Asfotase alfa	Strensiq	As long-term enzyme therapy in patients with hypophosphatasia in the childhood and adolescent age to treat the bone manifestations of the disease.	LWC	DNL	
Blinatumomab	Blincyto®	Previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia	LWC - RESUB	LWC	
Bosutinib	Bosulif ®	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)	LWC	DNL	

		previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options		
Brentuximab Vedotin-1	Adcetris ®	For the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.	LWC	LWC- RESUB
Brentuximab Vedotin-2	Adcetris®	For the treatment of adult patients with relapse or refractory systemic large cell anaplastic lymphoma (sALCL).	LWC	LWC
Ceritinib	Zykadia®	For treating adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib	LWC - RESUB	DNL
Crizotinib-1	Xalkori®	For the treatment of advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kynase (ALK+) for adult patients previously treated with at least one other lung cancer treatment	LWC - RESUB	LWC
Daclatasvir	Daklinza®	In combination with sofosbuvir (SOF), be reimbursed for the treatment of patients with genotype 3 chronic hepatitis C (CHC)	LWC - RESUB	LWC - RESUB
Daratumumab	Darzalex	As a monotherapy for the treatment of adult patients with recurrent and refractory multiple myeloma who have already been treated with a proteasome inhibitor and an immune modulator and have shown a disease progression during the last therapy.	DNL	DNL
Durvalumab	Imfinzi	As a monotherapy for the treatment of stage non-small cell lung cancerlocally advanced and inoperable in people:•whose disease has not progressed after chemoradiotherapy based on a platinum salt;and•whose previous chemoradiotherapy treatment has ended in the last 6weeks;and•whose performance status according to ECOG is 0 or 1	LWC	LWC
eculizumab	Soliris	For the treatment of patients with atypical hemolytic uremic syndrome (atypical HUS) to inhibit complement-mediated thrombotic microangiopathy	DNL	NS
Ibrutinib-2	Imbruvica	For the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL)	DNL	DNL - RESUB
Idelalisib-2	Zydelig®	For the treatment of relapsed/refractory follicular lymphoma (FL) that has progressed despite prior treatment with rituximab and an alkylating agent.	DNL	NS

Nivolumab	Opdivo	For the treatment of adult patients with classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after: autologous stem cell transplantation (ASCT) and brentuximab vedotin, or 3 or more lines of systemic therapy including ASCT,	LWC	DNL
Nivolumab-1	Opdivo®	As a monotherapy in adults for the treatment of advanced (non-resectable or metastatic) melanoma.	LWC	LWC
Nivolumab-6	Opdivo®	In adults for the treatment of advanced (non-resectable or metastatic) melanoma in combination with ipilimumab	LWC	DNL
Obeticholic Acid	Ocaliva	For treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.	LWC	LWC
Ofatumumab	Arzerra®	To treat, in combination with chlorambucil or bendamustine, patients with CLS who have not received prior treatment and who are not suitable for fludarabine-based treatment (a type of cellular toxicity)	DNL	DNL
Olaparib	Lynparza	As a monotherapy (alone) for maintenance therapy for ovarian cancer recurrence in patients with a specific mutation, BRCA	LWC - RESUB	LWC - RESUB
Olaratumab	Lartruvo	In combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin	LWC	DNL
Osimertinib	Tagrisso	Used in patients with non-small cell lung cancer whose cancer is advanced or has spread and has a particular mutation called T790M. The mutation is a change in the gene of the protein epidermal growth factor receptor, EGFR	LWC	LWC
Palbociclib	Ibrance	Used in patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer	LWC - RESUB	DNL
Pembrolizumab-1	Keytruda®	As a monotherapy for the treatment of advanced (non-resectable or metastasizing) melanoma in adults.	LWC	LWC
Pembrolizumab-2	Keytruda®	For the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with PD-L1 expressing tumours after prior chemotherapy in adults. Patients with EGFR- or ALK-	LWC	DNL

		positive tumour mutations should already have received a therapy approved for these mutations prior to therapy with KEYTRUDA.		
Ponatinib	Iclusig	For the treatment of two types of blood cancer, chronic myeloid leukemia (KML) and Philadelphia chromosomal acute lymphocytic leukemia (Ph + ALL)	LWC	LWC
Romidepsin	Istodax	For the treatment of recurrent peripheral T lymphoma orrefractory, in people:•who are not eligible for a hematopoietic stem cell transplant attime of initiation of treatment;and•whose performance status according to ECOG is 0 to 2	LWC	LWC
Sebelipase alfa	Kanuma	For the treatment of infants, children, and adults diagnosed with LAL deficiency.	LWC	DNL

Source: The Authors.

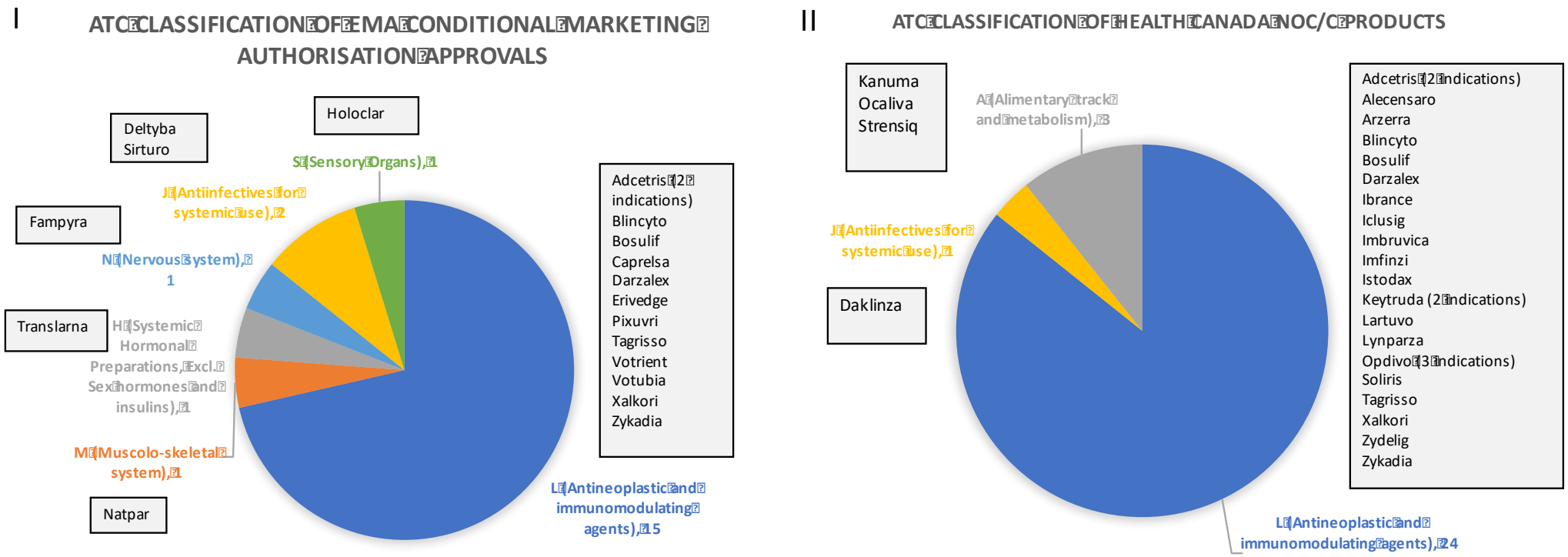
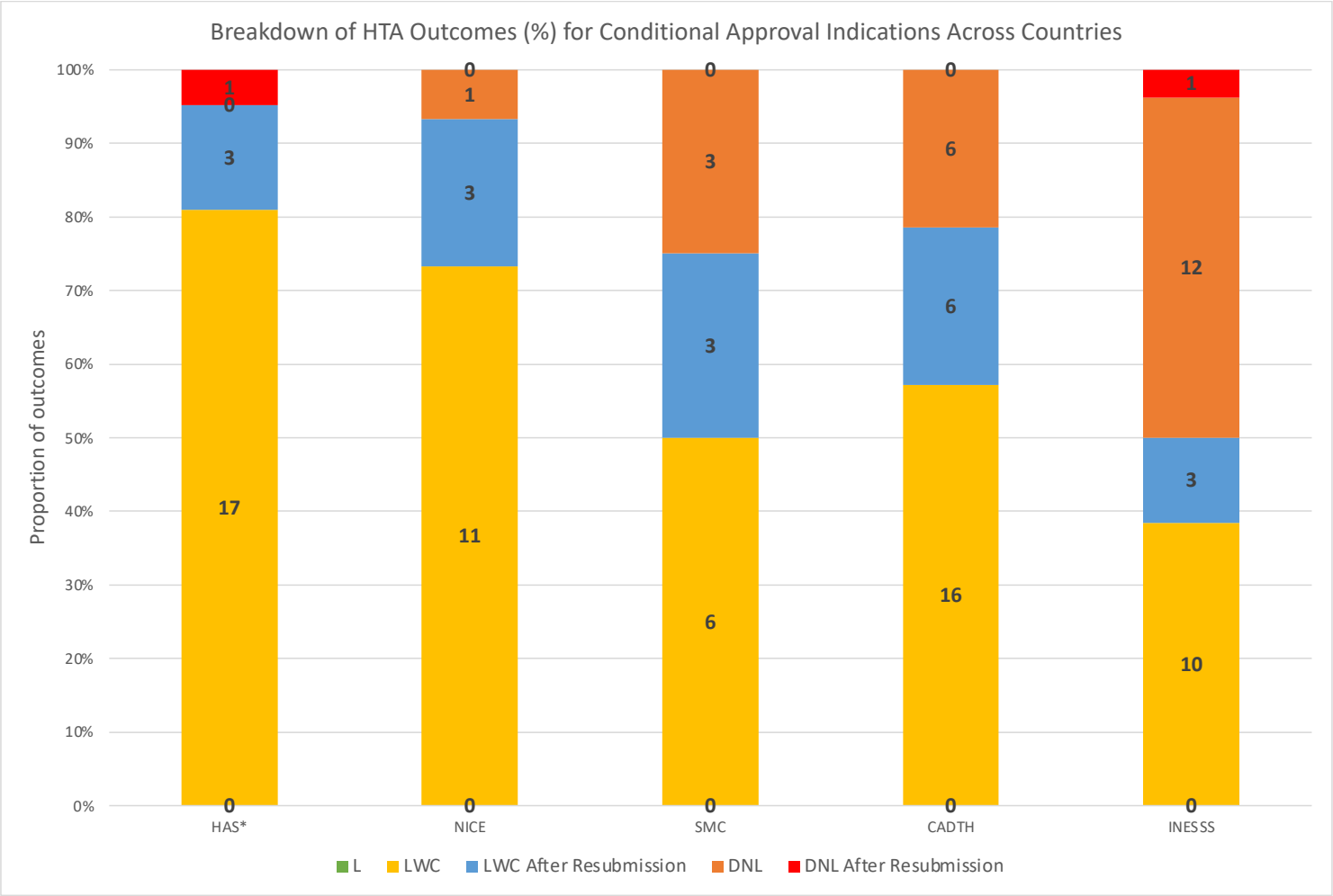


Figure 2.5 - Sample overview.

I – Therapeutic areas of EMA conditional approval marketing authorisation approvals between 2010-2017 with at least one HTA submission in England (NICE), Scotland (SMC) or France (HAS). II – Therapeutic areas of Health Canada notice of compliance with conditions approvals between 2010-2017 with at least one HTA submission in Ontario (CADTH) or Quebec (INESSS)



*HAS – Products classified as L, LWC or DNL based on SMR and ASMR ratings. DNL= SMR rating of insufficient, L= SMR rating of important and ASMR rating of I or II, LWC = All other classifications.

Figure 2.6 - HTA Outcomes for Accelerated Approval Indications in Europe and Canada

L = Listed, LWC= Listed with economic or clinical conditions, LWC after resubmission = listed with condition through a resubmission following an initial rejection, DNL = do not list, DNL After Resubmission = do not list through a resubmission following an initial rejection

3. LAUNCH SEQUENCING OF PHARMACEUTICALS WITH MULTIPLE THERAPEUTIC INDICATIONS: EVIDENCE FROM SEVEN COUNTRIES[3]

[3] **Citation:** Mills M, Michaeli D, Miracolo A, Kanavos P. Launch sequencing of pharmaceuticals with multiple therapeutic indications: evidence from seven countries. *BMC Health Services Research.* 2023 Feb;23(1):150. DOI: 10.1186/s12913-023-09095-2. PMID: 36782175; PMCID: PMC9923892.

ABSTRACT

Background. New medicines are increasingly being identified as efficacious across multiple indications. The impact of current pricing and reimbursement policies on launch decisions across these indications remains unclear.

Objective. This paper, first, maps marketing authorisation and HTA coverage recommendation sequences of multi-indication medicines across Germany, France, England, Scotland, Canada, Australia, and the USA, and second, evaluates the clinical characteristics, clinical development time and coverage recommendation time of multi-indication medicines, drawing comparisons between the first and subsequent indications of an approved molecule.

Methods. Medicine approvals by the Food and Drug Administration between 2009-2019 were screened to identify multi-indication products with approved oncology indications. Data on clinical trial characteristics, clinical performance and HTA outcomes were extracted from publicly available regulatory approval and HTA reports.

Results. Relative to subsequent indications, first indications were more likely to receive conditional marketing authorisation, have an orphan designation, have a single arm phase II pivotal trial and lower MCBS score. Subsequent indications had faster HTA coverage recommendation times in England and Canada. While the majority of first indications received HTA coverage recommendations across all settings, the proportion of subsequent indications with HTA coverage recommendations was lower and uptake varied considerably across settings.

Conclusions. Discordance in the value of first versus subsequent indications can pose major challenges in systems that define price based on the initial indication. Current pricing and reimbursement systems generate significant fragmentation in the approval and availability of multi-indication products across settings.

3.1 Background

In 2018, over two-thirds of cancer medicines were approved for use in multiple indications [102]. Developing an established medicine for use in a new indication carries a number of advantages over de novo development, including reduced R&D costs and regulatory advantages in terms of secondary patents and extension of marketing exclusivity [103, 156]. Oncology medicines in particular may be good candidates for follow-on innovation, as similar underlying causes may be present across cancer types. Multi-indication products generate interesting challenges for health insurance systems, which typically assign prices at product level, rather than indication level. Given differences in disease stage, disease pathology, and available therapeutic alternatives, the added value a product provides can vary significantly across its respective therapeutic indications [157]. There has been considerable debate about the best method to finance multi-indication medicines [61-64]. Approaches include a single price per molecule, a weighted pricing model, differential discounting and indication-based pricing [61]. While economists argue that providing separate prices for each use of a molecule is the optimal approach for maximising welfare, most countries opt for indirect methods such as weighted pricing or differential discounting due to regulatory barriers and administrative burden [62, 64].

Indication-based pricing, also known as indication-specific pricing or multi-indication pricing, is a form of price discrimination whereby each indication for a molecule is priced separately according to the incremental value it provides above the standard of care in that particular indication. Under a single-price-per-molecule system, the price is anchored at the first indication launched for a molecule and manufacturers may not launch indications with lower incremental value in order to avoid price erosion and a loss of producer surplus in the higher value indication. Under an indication-based pricing model, price differentiation across

indications ensures that the price is linked to the incremental value each indication provides relative to the standard of care. In theory, this removes incentives to withhold the launch in subsequent indications, which improve health, but not necessarily to the same extent as the first indication, increases the number of patients that have access to the medicine in question and maximises social welfare. Economists have argued both in favour and against this type of model for pricing pharmaceuticals [61, 64]. While indication-based pricing represents a method for manufacturers to maximise their producer surplus and the overall value they receive from a medicine [64], it can also provide short-term benefits in terms of increased patient access to medicines, and long-term benefits in terms of incentivising research and development of a wider range of therapeutic indications (including lower value indications) [65].

Countries have taken different approaches to differentiating the (therapeutic) value of multiple indications for a single medicine. While no countries implement a pure form of indication-based pricing (e.g. different list prices for each indication of a molecule), a number of indirect indication-based pricing policies have been implemented [66]. Specifically, there are four broad mechanisms for implementation of indication-based pricing: a) blended or weighted pricing, b) differential discounting, c) different brand names for different indications, or d) outcomes-based reimbursement models (See Appendix A for a full overview of indication-based pricing mechanisms).

Contrary to single indication drugs, the impact of current pricing and reimbursement strategies on manufacturer launch decisions and patient access to multiple indications remains unclear. Current literature exploring issues surrounding multi-indication medicines and indication-based pricing are limited to discussions on economic theory [61-64], simulations or economic evaluations of individual multi-indication medicines[63, 158], or reviews of pricing and reimbursement policies [66, 159].

In light of the above, the aim of the paper is to analyse the extent to which current pricing and reimbursement policies in select developed countries lead to indication launch sequencing, the order in which pharmaceutical firms develop, launch and market the use of medicines in different therapeutic indications across jurisdictions. The specific objectives are twofold: first, to map the marketing authorisation and HTA coverage recommendation sequence of multi-indication oncology medicines with the view to understanding patterns in indication launch and whether these hold across different health care systems. Second, to compare and contrast the first indication launched for a medicine, with the subsequent indications in terms of clinical trial characteristics, regulatory approval timelines, coverage decisions and HTA coverage recommendation timelines and access to market in order to understand how manufacturers prioritise development indications. By focusing on oncology indications, the paper contributes to the literature on indication-based pricing in 3 ways: first, it introduces a conceptual framework for the analysis of multi-indication medicines with specific focus on market entry dynamics and clinical characteristics; second, it provides a comprehensive empirical analysis with rich descriptive evidence on the clinical characteristics of multi-indication oncology medicines; and, third, it adopts a comparative and international perspective by examining marketing authorisation and HTA coverage recommendation patterns and sequence across selected countries in order to identify whether launch strategies vary depending on differences in regulatory settings or display similarities, despite these differences.

3.2 Methods

3.2.1 Conceptual framework

The launch of a specific indication for a medicine can be considered at both a global and local level. In the first instance, manufacturers must make a decision about whether to invest in

research and development for a specific use of a new molecule. Global launch is triggered by receipt of marketing authorisation in at least one setting (often the U.S. Food and Drug Administration (FDA) is targeted first) [160]. Following development of a product for an indication and global launch (or at times in parallel to global launch), decisions are made about launch of the same product-indication in other markets. Local launch involves submission for MA and, depending on the context, may or may not require an HTA coverage recommendation.

Sequencing the launch of different indications is a function of the expected value of the indication and extent to which it contributes to return on investment and profit maximisation. Manufacturers may sequence the launch of different indications in two ways, which can be inter-connected: pre-development sequencing and post-development sequencing.

A. Pre-development sequencing (pre-pivotal trial)

Pre-development sequencing relates to the decision on whether or not to pursue global launch for a particular indication and occurs prior to full development or submission to a regulatory authority. Under pre-development sequencing, manufacturers may prioritise initiation of a pivotal trial for indications with high perceived value for a specific molecule and may elect not to develop or delay the development of indications with a low perceived value. Early clinical data (or evidence of therapeutic advantage), price benchmarking, unmet need, and/or market size are factors which may contribute to the perceived value of an indication and influence decisions to develop and/or register a new medicine. Manufacturers may face a trade-off between price and market size and may opt to develop first in a niche or orphan designation, where budget constraints may be smaller, in order to establish a target benchmark price before expanding into indications with larger patient populations. The impact of competitors developing medicines in similar indications can also influence sequencing strategies.

B. Post-development sequencing

Post-development sequencing relates to decisions to launch indications in local markets following development and global launch. A combination of clinical, economic and ethical considerations contributes to post-development decision making. Local launch decisions apply to both first and subsequent indications for a molecule, however price benchmarking and coverage of an initial indication within a specific setting may influence decisions to launch subsequent indications. Under a system where current pricing and reimbursement policies do not adequately capture the incremental value of individual indications, manufacturers may choose not to launch of an indications. Typically, this could occur in cases where there are comparable alternative treatments available to patients and if the introduction of a subsequent indication would lead to substantial price erosion based on the presence of previous indications, lower perceived therapeutic advantage or higher uncertainty over therapeutic advantage. Manufacturers may adopt different strategies across countries based on variations in the perceived value of an indication across settings (e.g. due to differences in the HTA approaches or differences in unmet need). Decisions not to launch an indication in a particular jurisdiction can occur through one of three mechanisms: first, a manufacturer may elect not to submit for regulatory approval; second, a manufacturer may receive regulatory approval for an indication but elect not to submit for HTA review; and third, a manufacturer may receive regulatory approval for an indication and submit for HTA review. If there is failure to reach agreement with a payor on an acceptable or cost-effective price (depending on the setting), the manufacturer may choose not to launch an indication.

Additional consideration is given to the nature of the multi-indication medicines being developed. Multi-indication medicines can be broadly grouped into three categories depending on the extent to which the various indications are similar. At the broadest level, a molecule can

have multiple indications that span distinct therapeutic areas (e.g. oncology vs ophthalmology). Second, a molecule can have multiple indications across different diseases within a specific therapeutic area (e.g. melanoma vs lung cancer). Third, a molecule can have multiple indications that span different lines of therapy for a particular disease (e.g. 1st line vs 2nd line metastatic castrate resistant prostate cancer). The association between unmet need and market size may vary across type of multi-indication medicines. For molecules with multiple indications across different lines of therapy within a specific disease, unmet need tends to be highest in late stage relapsed/refractory patient populations that have exhausted other treatment alternatives. Fundamentally, the patient population in late stage disease will likely be smaller and clinical trials may be shorter for later-line therapies, with possible reduced life expectancy. However, the same association may not be present when developing indications across multiple types of cancer or across different therapeutic areas.

3.2.2 Sample selection and data sources

FDA marketing authorisations were screened between January 1st, 2009 and January 1st, 2019 to identify a recent sample of multiple indication medicines that have launched globally. Medicines with a first approval after January 1st, 2009 and a second indication approved prior to January 1st, 2019, were identified. The study cut-off date was selected to provide sufficient follow-up time to track indication approvals after the initial approval. The scope of the study was restricted to multi-indication medicines used in oncology, a therapeutic area that is a) of high interest to decision-makers given burden of disease, high treatment costs and challenges in evidence development [161] and b) increasingly subject to follow-on indication [102]. The study scope is also restricted to multi-indication monotherapy treatments to limit the impact of combination therapies. Inclusion criteria were: 1) a minimum of one approved indication for

the treatment of oncology during the study period (regardless of whether this is a first approval or subsequent); and 2) a minimum of two monotherapy indications approved during the study period. A flow chart detailing sample selection is included in Appendix B.

The countries in scope included England, Scotland, France, Germany, Canada, Australia, and the USA. Country selection was based on public availability of marketing authorisation reports, public availability of health technology assessment (HTA) reports, and language (English, French, and German). Regulatory agency websites were screened to identify marketing authorisation reports for all indications approved for the included multi-indication medicines. This included the U.S. FDA [162], the European Medicines Agency (EMA) [83], Health Canada [85], and the Australian Therapeutic Goods Administration (TGA) [84]. Characteristics of pivotal clinical trials were screened via clinicaltrials.gov [163]. The European Society of Medical Oncology website was screened to identify corresponding evidence on the magnitude of clinical benefit scale (MCBS). Indications without an MCBS score were graded in accordance with the validated MCBS scorecard methodology based on clinical trial performance[164]. Finally, HTA agency websites were screened to identify HTA recommendations issued for all indications for the selected multi-indication medicines. This included the National Institute of Health and Care Excellence (NICE - England) [129], the Scottish Medicines Consortium (SMC – Scotland) [130], the Federal Joint Committee (G-BA - Germany) [132], the Haute Authorité de Santé, (HAS - France) [131], the Canadian Agency for Drugs and Technologies in Health (CADTH) [134], and the Pharmaceutical Benefits Advisory Committee (PBAC - Australia) [133]. Regulatory approvals and HTA approvals for included indications were tracked for an additional two years beyond the cut-off date for first approval (01/01/2019). The data collection cut-off date for the sample is 01/01/2021.

3.2.3 Data extraction

For all included indications, and based on country-specific (regulatory and/or HTA) information, data extraction included general information (molecule name, brand name and therapeutic indication), regulatory variables (MA date, MA type, and orphan designation), clinical variables (study design of pivotal trial, pivotal trial size, pivotal trial initiation date, type of primary endpoint, primary endpoint outcome, and MCBS Score), and HTA variables (HTA outcome and whether a molecule has been approved for listing (L), listing with criteria or restrictions (LWC) or it has been rejected (do not list – DNL), HTA submission date (where available), and HTA recommendation date). (See **Table 3.1**).

Table 3.1 - List of Variables Extracted

General Information	
Variable	Description
Molecule name	International Non-proprietary Name (INN) of medicine
Brand name	Company branded name of marketed medicine
Therapeutic indication	Approved therapeutic label of marketed medicine, designating the intended and authorised use of a medicine in a specific patient population. For the included molecules, all approved therapeutic indications recorded from each regulatory agency (FDA, EMA, Health Canada, TGA).
Regulatory Variables	
Variable	Description
Marketing authorisation date	The approval date for marketing authorisation of a specific medicine - indication pair (dd/mm/yyyy). Recorded for each regulatory agency across all included medicine - indication pairs.
Marketing authorisation type	The type of marketing authorisation granted for a specific medicine - indication pair. Categorised as standard approval, priority review, or conditional authorisation. Standard approval includes FDA standard approval, EMA standard approval, TGA standard approval and Health Canada notice of compliance (NOC). Priority review includes FDA priority review, EMA accelerated assessment, TGA priority review, and Health Canada priority review. Conditional authorisation includes FDA accelerated approval, EMA conditional marketing authorisation, TGA provisional approval, and Health Canada, notice of compliance with conditions (NOC/C).
Orphan designation	Medicine – therapeutic indication received an orphan designation by relevant regulatory agency (0 = no, 1 = yes). Orphan designations indicate the therapeutic indication applies to a rare or orphan disease patient population. Orphan designation criteria vary across settings. The EMA and TGA orphan designations requires a prevalence of less than 5 in 10,000. The FDA orphan designation requires that the condition affects less than 200,000 in the USA. Health Canada does not have an orphan designation.
Clinical Variables	
Variable	Description
Study design of pivotal trial	The study design of the pivotal trial used to support conditional regulatory approval. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled)
Pivotal trial size	The number of patients enrolled in the pivotal trial
Pivotal trial initiation date	The initiation date of the pivotal trial (per clinicaltrials.gov)
Type of primary endpoint	The type of primary endpoint used within the pivotal trial (0 = surrogate endpoint, 1 = clinical endpoint). Surrogate endpoints provide an indication or prediction of clinical benefit and provide early signals of a medicines efficacy. The following endpoints have been classified as surrogate within this study: progression free survival (PFS), overall response rate (ORR), subependymal giant cell astrocytoma (SEGA) volume, angiomyolipoma response rate, best observed response (BOR), Primary response (PR), Spleen volume reduction, remission free survival (RFS), complete response rate (CR), duration of response (DOR), major cytogenic response (MCyR), major molecular response (MMR) best-corrected visual acuity (BCVA), forced vital capacity (FVC). Clinical endpoints are hard clinical outcomes that provide an objective measure of clinical benefit. The following endpoints have been classified as clinical within this study: overall survival (OS), maintenance of vision, and seizure frequency.
Primary endpoint outcome	The performance of the primary endpoint defined based on the trial protocol. Includes performance of active arm, performance of control arm, hazard ratio, confidence intervals, and significance (p value). For oncology indications, primary endpoints are predominantly either median progression-free survival (months) or median overall survival (months).
MCBS Score	The magnitude of clinical benefit scale (per www.esmo.org/guidelines/esmo-mcbs). The MCBS scale is 5 category ranking scale outlining the strength of evidence from 1 (low benefit) to 5 (high benefit). A ranking of 4 or 5 indicates substantial magnitude of benefit. The scale is based predominantly based on the performance of the primary endpoint, and is adjusted for quality of life improvements or changes in toxicity.
HTA variables	
Variable	Description

HTA Outcome	HTA outcomes are classified as List (L), List with conditions (LWC), Do not list (DNL), or No HTA submission. In Germany, the G-BA added benefit ratings determine pricing, rather than the listing of a drug. We classify "lesser benefit" or "no proof of added benefit" ratings as DNL, "Proof of major or significant added benefit" as L, and all other ratings as LWC. Note that medicines with lesser or no proof of added benefit may still be reimbursed in Germany based on reference pricing. In France, the medical service rendered (SMR) rating determines the rate of reimbursement, while the improvement in medical service rendered (ASMR) determines pricing. We classify medicines with an SMR of insufficient as DNL, medicines with an SMR of Important and an ASMR of Major or Important as L, and all other ratings as LWC.
HTA recommendation date	The HTA coverage recommendation date (dd/mm/yyyy)
HTA submission date	The date in which manufacturers filed their submission for health technology assessment. Only available for NICE, SMC and CADTH.

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; EMA – European Medicines Agency; FDA – Food and Drug Administration (USA); GBA – Federal Joint Committee (Germany); HAS – Haute Autorité de Santé (France); HC – Health Canada; HTA – health technology assessment; NICE – National Institute of Health and Care Excellence (England and Wales); PBAC – Pharmaceutical Benefits Advisory Committee (Australia); SMC – Scottish Medicines Consortium (Scotland); TGA – Therapeutic Goods Administration (Australia)

Source: The authors

3.2.4 Analysis

Data was extracted into a dataset in Microsoft Excel and imported into STATA SE Version 15.1. for analysis. The first indication for a molecule to receive FDA approval was classified as the "first indication" and all subsequent indications were classified as "subsequent indications".

The following research endpoints were studied: first, *the alignment between global launch sequence, national regulatory approval and HTA recommendation sequence* was examined through a mapping of global launch, regulatory approval and HTA recommendation in each of study countries. For each molecule, codes were assigned to each indication launched based on launch sequence across FDA, EMA, Health Canada, and TGA. The global launch date (date of first approval in one of FDA, EMA, Health Canada or TGA), total number of distinct indications identified, the proportion of indications with regulatory approval in each jurisdiction and the proportion of indications with positive HTA coverage recommendations are tabulated to identify differences in regulatory and HTA approval across settings. Separately, the global launch sequence and HTA approval sequence are compared and tabulated in order to identify instances of post-development sequencing.

Second, *differences in regulatory approval and clinical characteristics of first vs second indications* were explored through descriptive statistics with the aim of understanding how manufacturers are prioritising development of indications. The regulatory approval pathway and regulatory designations provide an indication of the extent to which disease severity, unmet need, and market size are prioritised. Clinical characteristics are considered in terms of quality of clinical evidence (pivotal trial design, trial size, and type of primary endpoint) and the MCBS score of a medicine, which provides an aggregate measure of the strength and quality of evidence. Categorical variables (MA type, orphan designation, trial design, type of endpoint,

and MCBS score) were analysed using Pearson Chi-squared tests. Mean trial size was analysed using two sample t-tests.

Third, *differences in HTA outcome of first vs subsequent indications* are also explored through descriptive statistics (Pearson Chi-Squared tests) to identify whether subsequent indications are less likely to receive HTA coverage recommendations. Additionally, the association between HTA outcome and MCBS score is calculated for each HTA agency (Pearson Chi-Squared test).

Fourth, clinical development time and HTA coverage recommendation time was evaluated through survival analysis through a comparison first and subsequent indications. Clinical development time was defined as T1-T0, where T0 represents pivotal clinical trial initiation date, and T1 represents MA approval date. T1 is defined for each country based on the relevant regulatory agency, such that clinical development time (T1-T0) for a specific medicine-indication pair may vary across Europe, Canada, Australia, and the FDA. HTA coverage recommendation timelines were defined as T2-T1, where T2 represents HTA coverage recommendation date. Kaplan Meier plots were produced for both clinical development time and HTA coverage recommendation time. Log-rank tests were used to identify differences in survival plots of first indications and subsequent indications. Subgroup analysis was performed at country level and according to type of multi-indication medicine. Additional analysis was performed to evaluate time from marketing authorisation to HTA submission for CADTH, G-BA and NICE, where data on HTA submissions is available. Mean time from marketing authorisation to HTA submission for first vs subsequent indications was calculated using two sample t-tests.

3.3 Results

3.3.1 Sample Overview

Out of 90 multi-indication medicines identified in the study period, 31 medicines met the inclusion criteria for the study (See Appendix B). Of these 31 medicines a total of 118 distinct therapeutic indications were identified. Four medicines had multiple indications approved across therapeutic areas ibrutinib, nintedanib, aflibercept, and everolimus) corresponding to 18% of total indications (n=22). Sixteen medicines had multiple indications across different types of cancer (cabozantinib, pazopanib, tisagenlecleucel, regorafenib, remucirumab, avelumab, atezolizumab, eribulin, ruxolitinib, nivolumab, pembrolizumab, brentuximab vedotin, ipilimumab, romidepsin, vemurafenib, and lenvatanib), corresponding to 58% indications (n=68). Eleven medicines had multiple indications across different lines of therapy within the same disease (abiraterone acetate, afatinib, blinatumomab, enzalutamide, rucaparib, osimertinib, crizotinib, bosutinib, alectinib, and ceritinib, ofatumumab), corresponding to 24% of total indications (n=28). Out of the 118 indications identified, 32 were classified as "first indications" and 86 were classified as "subsequent indications" (brentuxiumab vedotin had two initial indications approved). A full list of indications included is provided in Appendix C.

3.3.2 Sequence alignment between global launch, national regulatory approval and HTA recommendation

The FDA approved the highest proportion of indications, with 115 approvals (97%) followed by the EMA with 96 approvals (81%), Health Canada with 94 (80%) and TGA with 93 (79%). In a limited number of cases, applications for marketing authorisations were withdrawn (5 indications for EMA, 1 indication for Health Canada, and 1 indication for TGA) or refused (1

indication for EMA. The first launch of each indication was predominantly in the FDA (106 indications had their first approval in the FDA vs 12 in the EMA, and 0 in Health Canada or the TGA).

HTA outcomes for multi-indication products were highly variable at both indication and molecule level. No multi-indication medicine had a positive HTA coverage recommendation for all globally launched indications. First indications had a high frequency of positive HTA recommendations across settings. Out of 32 first indications evaluated, positive recommendations were identified for 29 (91%) by Germany, 28 (88%) by HAS, 27 (84%) by NICE, 26 (81%) by SMC, 25 (78%) by PBAC and 23 (72%) by CADTH. Subsequent indications had a lower frequency of positive HTA recommendations across all settings. Out of 86 subsequent indications evaluated, positive HTA recommendations were identified for 60 (70%) by HAS, 58 (67%) by GBA, 48 (56%) by NICE, 50 (58%) by SMC, 50 (58%) by PBAC, and 51 (59%) by CADTH (See **Table 3.2**).

Table 3.2 - Marketing Authorisation and HTA Approvals of Multi-Indication Oncology Products in England, Scotland, France, Germany, Ontario, and Australia

			Regulatory Approvals				HTA Approvals					
Molecule	**First indication approval date[1]**	**Total number of distinct indications identified[2]**	**FDA approvals n (%)**	**EMA approvals n (%)**	**HC approvals n (%)**	**TGA approvals n (%)**	**NICE approvals n (%)**	**SMC approvals n (%)**	**HAS approvals [3] n (%)**	**GBA approvals [4] n (%)**	**CADTH approvals n (%)**	**PBAC approvals n (%)**
Ibrutinib	13/11/2013	**6**	6 (100%)	4 (67%)	6 (100%)	4 (67%)	3 (50%)	3 (50%)	4 (67%)	3 (50%)	3 (50%)	3 (50%)
Nintedanib	25/09/2014	**2**	1 (50%)	2 (100%)	1 (50%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	2 (100%)	1 (50%)	1 (50%)
Aflibercept	20/09/2011	**7**	5 (71%)	6 (86%)	6 (86%)	6 (86%)	5 (71%)	6 (86%)	6 (86%)	1 (14%)	4 (57%)	5 (71%)
Everolimus	30/03/2009	**7**	7 (100%)	7 (100%)	7 (100%)	6 (86%)	4 (57%)	3 (43%)	7 (100%)	1 (14%)	3 (43%)	5 (71%)
Cabozantinib	29/11/2012	**4**	4 (100%)	4 (100%)	3 (75%)	3 (75%)	3 (75%)	1 (25%)	3 (75%)	3 (75%)	2 (50%)	1 (25%)
Pazopanib	19/10/2009	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)	0 (0%)	1 (50%)	2 (100%)
Tisagenlecleucel	30/08/2017	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	0 (0%)	0 (0%)
Regorafenib	27/09/2012	**3**	3 (100%)	3 (100%)	3 (100%)	3 (100%)	2 (67%)	2 (67%)	3 (100%)	2 (67%)	2 (67%)	0 (0%)
Ramucirumab	21/04/2014	**3**	3 (100%)	3 (100%)	1 (33%)	1 (33%)	0 (0%)	0 (0%)	2 (67%)	1 (33%)	1 (33%)	1 (33%)
Avelumab	23/03/2017	**2**	2 (100%)	1 (50%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
Atezolizumab	18/05/2016	**3**	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	1 (33%)	2 (67%)	2 (67%)	1 (33%)	2 (67%)
Eribulin	15/11/2010	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	2 (100%)	1 (50%)	1 (50%)	2 (100%)
Ruxolitinib	16/11/2011	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)
Nivolumab	22/12/2014	**13**	13 (100%)	10 (77%)	10 (77%)	11 (85%)	9 (69%)	9 (69%)	9 (69%)	7 (54%)	8 (62%)	7 (54%)
Pembrolizumab	04/09/2014	**16**	16 (100%)	11 (69%)	10 (63%)	12 (75%)	8 (50%)	8 (50%)	8 (50%)	7 (44%)	8 (50%)	7 (44%)
Brentuximab vedotin	19/08/2011	**6**	6 (100%)	5 (83%)	6 (100%)	4 (67%)	3 (50%)	3 (50%)	4 (67%)	3 (50%)	6 (100%)	4 (67%)
Ipilimumab	25/03/2011	**5**	5 (100%)	3 (60%)	3 (60%)	3 (60%)	3 (60%)	3 (60%)	3 (60%)	2 (40%)	3 (60%)	3 (60%)
Romidepsin	01/05/2009	**2**	2 (100%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)

Vemurafenib	17/08/2011	**2**	2 (100%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)
Lenvatanib	13/02/2015	**3**	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	1 (33%)	2 (67%)	2 (67%)	2 (67%)
Abiraterone Acetate	28/04/2011	**3**	3 (100%)	3 (100%)	3 (100%)	3 (100%)	2 (67%)	3 (100%)	3 (100%)	3 (100%)	1 (33%)	1 (33%)
Afatinib	12/07/2013	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
Blinatumomab	03/12/2014	**3**	3 (100%)	3 (100%)	3 (100%)	3 (100%)	2 (67%)	3 (100%)	2 (67%)	3 (100%)	2 (67%)	2 (67%)
Enzalutamide	31/08/2012	**3**	3 (100%)	3 (100%)	3 (100%)	3 (100%)	2 (67%)	2 (67%)	3 (100%)	2 (67%)	3 (100%)	1 (33%)
Rucaparib	19/12/2016	**2**	2 (100%)	2 (100%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)
Osimertinib	13/11/2015	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	2 (100%)	1 (50%)	2 (100%)	1 (50%)
Crizotinib	26/08/2011	**3**	3 (100%)	3 (100%)	2 (67%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)	2 (67%)	2 (67%)	2 (67%)
Bosutinib	04/09/2012	**2**	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)
Alectinib	11/12/2015	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	1 (50%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)
Ceritinib	29/04/2014	**2**	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	2 (100%)	0 (0%)	1 (50%)	1 (50%)
Ofatumumab	26/10/2009	**4**	4 (100%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; EMA – European Medicines Agency; FDA – Food and Drug Administration (USA); GBA – Federal Joint Committee (Germany); HAS – Haute Autorité de Santé (France); HC – Health Canada; HTA – health technology assessment; NICE – National Institute of Health and Care Excellence (England and Wales); PBAC – Pharmaceutical Benefits Advisory Committee (Australia); SMC – Scottish Medicines Consortium (Scotland); TGA – Therapeutic Goods Administration (Australia)

1 The date in which a molecule first received a marketing authorisation in one of the FDA, EMA, TGA or Health Canada. A detailed list of included indications is provided in Appendix C.
2 The total number of distinct indications identified with approval in one or more of the FDA, EMA, TGA or Health Canada for a specific multi-indication molecule during the study period (01/01/2009 – 01/01/2019).
3 In France, indications which receive an SMR rating of insufficient are categorised as having a negative HTA outcome (DNL)
4 In Germany, indications which receive a rating of lesser benefit or no proof of added benefit are categorised as having a negative HTA outcome (DNL). In practice, these indications may still be reimbursed at a price determined based on reference pricing, and the HTA approval sequence does not necessarily reflect the order in which indications are launched within the country.

Concordance between global launch sequence (defined based on first approval in one of FDA, EMA, Health Canada and TGA) and HTA coverage recommendation sequence was variable (See Appendix C - **Table 3.7**).

Medicines with multiple indications across distinct therapeutic areas (typically received HTA coverage recommendations in a similar sequence to global launch sequence. Exceptions included ibrutinib, where the second indication launched globally (chronic lymophicytic leukemia) was approved by NICE, CADTH and PBAC prior to the first indication launched globally (mantle cell lymphoma) and everolimus, where the 5th indication approved globally (advanced breast cancer) was the first to receive NICE approval and the 2nd indication approved globally (subependymal giant cell astrocytoma) was the first to receive PBAC approval.

Concordance between global launch sequence and HTA coverage recommendation sequence for medicines with multiple indications across different oncologic diseases was mixed. HTA coverage recommendation of indications for pazopanib, tisagenlecleucel, regorafenib, ramucirumab, avelumab, eribulin, ruxolitinib, and ipilimumab typically followed global launch sequence, although a number of indications for all molecules were not approved. Cabozantinib, ibrutinib, nivolumab, pembrolizumab, brentuximab vedotin, and lenvatinib all had instances of global launch sequence not matching HTA recommendation sequence.

Medicines with multiple indications across different lines of therapy within a disease had a lower average number of indications. Concordance between HTA coverage recommendation sequence and global launch sequence was high, although a number of indications either were either not assessed by HTA agencies or received a negative recommendation.

3.3.3 Differences in regulatory approval and clinical characteristics of first vs subsequent indications

First and subsequent indications were compared in terms of type of MA, orphan status, pivotal trial design, type of primary endpoint, trial size, MCBS score and HTA outcomes (See **Table 3.3**).

Relative to subsequent indications, first indications were more likely to be approved based on a conditional marketing authorisation pathway (34 of 119 (29%) first indications vs 39 of 279 (14%) subsequent indications, p = 0.001). These results remain significant when excluding EMA from analysis (where conditional approval is only available for first-indications). First indications are also more likely to have an orphan designation (55 of 119 (46%) vs 65 of 279 (23%), p<0.001) more likely to have a phase II single arm trial design (42 of 119 (35%) vs 56 of 279 (20%), p=0.009), and are more likely to receive a low MCBS score (54 of 111 (48%) vs 88 of 253 (35%), p = 0.012). MCBS scores within individual multi-indication drugs were highly variable across indications (see Appendix C - **Table 3.6**), with only 11 (33%) of medicines showing similar scoring across indications (everolimus, tisagenlecleucel, ramucirumab, avelumab, eribulin, rucolitinib, romidepsin, lenvatinib, blinatumomab, abiraterone, and bosutinib). No significant differences were identified between first and subsequent indications, for type of endpoint, trial size.

Subgroup analysis by type of multi-indication medicine was consistent with aggregate results with the following exceptions. Relative to subsequent indications, first indications for medicines with multiple indications across different therapeutic areas no longer show statistical significance for conditional approval (3 of 16 (18.75%) vs 6 of 60 (10%), p=0.423), phase II pivotal trial design (n=3 of 16 (18.75%) vs 10 of 60 (16.67), p=0.505) or low MCBS score (3 of 8 (37.50%) vs 7 of 34 (21%), p=0.418) and are more have a larger number of average

patients in the pivotal trial (591 vs 371, p=0.031). Relative to subsequent indications, first indications for medicines with multiple oncologic indications have a lower number of average patients in the pivotal trial (469 vs 588, p=0.039) and no longer show significance for conditional approval (15 of 63 (23%) vs 29 of 163 (18%), p =0.144 or low MCBS score (25 of 63 (40%) vs 62 of 163 (38%), p = 0.682). Relative to subsequent indications, first indications for medicines with multiple indications across different lines of therapy no longer show statistical significance for orphan designation (15 of 40 (38%) vs 18 of 56 (32%), p = 0.584).

Table 3.3 - Clinical Evidence Characteristics and HTA Outcomes of First vs Subsequent Indications

Category	Variable	First indication n (%)	Subsequent indication n (%)	P value
REGULATORY APPROVAL				
Type of MA granted (all agencies)	Standard	61 (51%)	207 (74%)	0.001
	Conditional	34 (29%)	39 (14%)	
	Priority review	24 (20%)	33 (12%)	
Type of MA granted (excluding EMA)	Standard	47 (53%)	146 (69%)	0.032
	Conditional	24 (27%)	36 (16%)	
	Priority review	18 (20%)	31 (15%)	
Orphan Designation[1]	Yes	55 (46%)	65 (23%)	<0.0001
	No	64 (54%)	214 (77%)	
CLINICAL EVIDENCE				
Pivotal trial design	Phase II single arm	42 (35%)	56 (20%)	0.009
	Phase III placebo RCT	30 (25%)	76 (27%)	
	Phase III head-to-head	39 (33%)	129 (46%)	
	Other	8 (7%)	18 (6%)	
Type of primary endpoint	Clinical	28 (24%)	49 (18%)	0.221
	Surrogate	81 (68%)	194 (69%)	
	Co-primary	10 (8%)	36 (13%)	
Trial size	Number of enrolled patients Mean [95% CI]	486 [421 – 550]	555 [504 -605]	0.125
MCBS[2]	Score of 1	54 (48%)	88 (35%)	0.012
	Score of 2 or 3	22 (20%)	85 (34%)	
	Score of 4 or 5	35 (32%)	80 (31%)	
HTA OUTCOMES				
G-BA	Proof of added benefit	25 (86%)	26 (45%)	0.004
	Lesser/no added benefit	4 (14%)	32 (57%)	
HAS	Reimbursed	27 (96%)	54 (90%)	0.299
	Not-reimbursed	1 (4%)	6 (10%)	
NICE	List/List with Criteria	26 (96%)	43 (90%)	0.304
	Do not list	1 (4%)	5 (10%)	
SMC	List/List with Criteria	23 (88%)	43 (86%)	0.763

	Do not list	3 (12%)	7 (14%)	
	List/List with Criteria	22 (96%)	41 (84%)	
CADTH				0.152
	Do not list	1 (4%)	8 (16%)	
	List/List with Criteria	23 (92%)	33 (66%)	
PBAC				0.015
	Do not list	2 (8%)	17 (34%)	

p-values calculated based on $\chi 2$ -test (for categorical variables) and two sample t-tests (for mean comparisons)

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; GBA – Federal Joint Committee (Germany); HAS – Haute Autorité de Santé (France); HTA – health technology assessment; MA – marketing authorisation, NICE – National Institute of Health and Care Excellence (England and Wales); PBAC – Pharmaceutical Benefits Advisory Committee (Australia) PFS – progression-free survival; SMC – Scottish Medicines Consortium (Scotland); TGA – Therapeutic Goods Administration (Australia)

1 Results presented are aggregated across all countries. The requirements for orphan designations vary across settings. For the FDA, the disease or condition must (A) affect less than 200,000 persons in the United States, or (B) affect more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug. For the EMA, the prevalence of condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development. For the TGA, one of the following criteria must apply: a) the condition affects fewer than 5 in 10,000 individuals in Australia when the application is made; b) if it were included in the Register, would not be likely to be supplied to more than 5 in 10,000 individuals in Australia during each year that it is included in the Register; or c) it is not likely to be financially viable for the sponsor to market the medicine in Australia. Health Canada does not have an orphan designation.

2 The magnitude of clinical benefit scale is a ranking of clinical benefit derived by the European Society for Medical Oncology, to grade the magnitude of benefit provided by a clinical trial. Ranking ranges from 1 (low) to 5 (high) clinical benefit. MCBS scores are grouped in terms of low benefit (1), moderate benefit (2 or 3) and substantial benefit (4 or 5). [22]

3 Excludes indications that are not submitted for HTA approval. In Germany, indications which receive a rating of lesser benefit or no proof of added benefit are categorised as having a negative HTA outcome (DNL). In practice, these indications may still be reimbursed at a price determined based on reference pricing, and the HTA approval sequence does not necessarily reflect the order in which indications are launched within the country. In France, indications which receive an SMR rating of insufficient are categorised as having a negative HTA outcome (DNL)

4.3.4 Differences in HTA outcome of first vs subsequent indications

With the exception of Australia and Germany, no significant differences were identified in HTA outcomes across settings , defined as the proportion of medicines evaluated by HTA agencies that received a positive HTA recommendation. In Australia, first indications were more likely to receive a positive recommendation: 23 of 25 (92%) of first indications evaluated vs 33 of 50 (66%) subsequent indications evaluated (p=0.015). Within Germany, first indications were more likely to show evidence of added benefit than subsequent indications: 25 of 29 (86%) first indications evaluated vs 26 of 58 (45%) subsequent indications evaluated (p = 0.04).

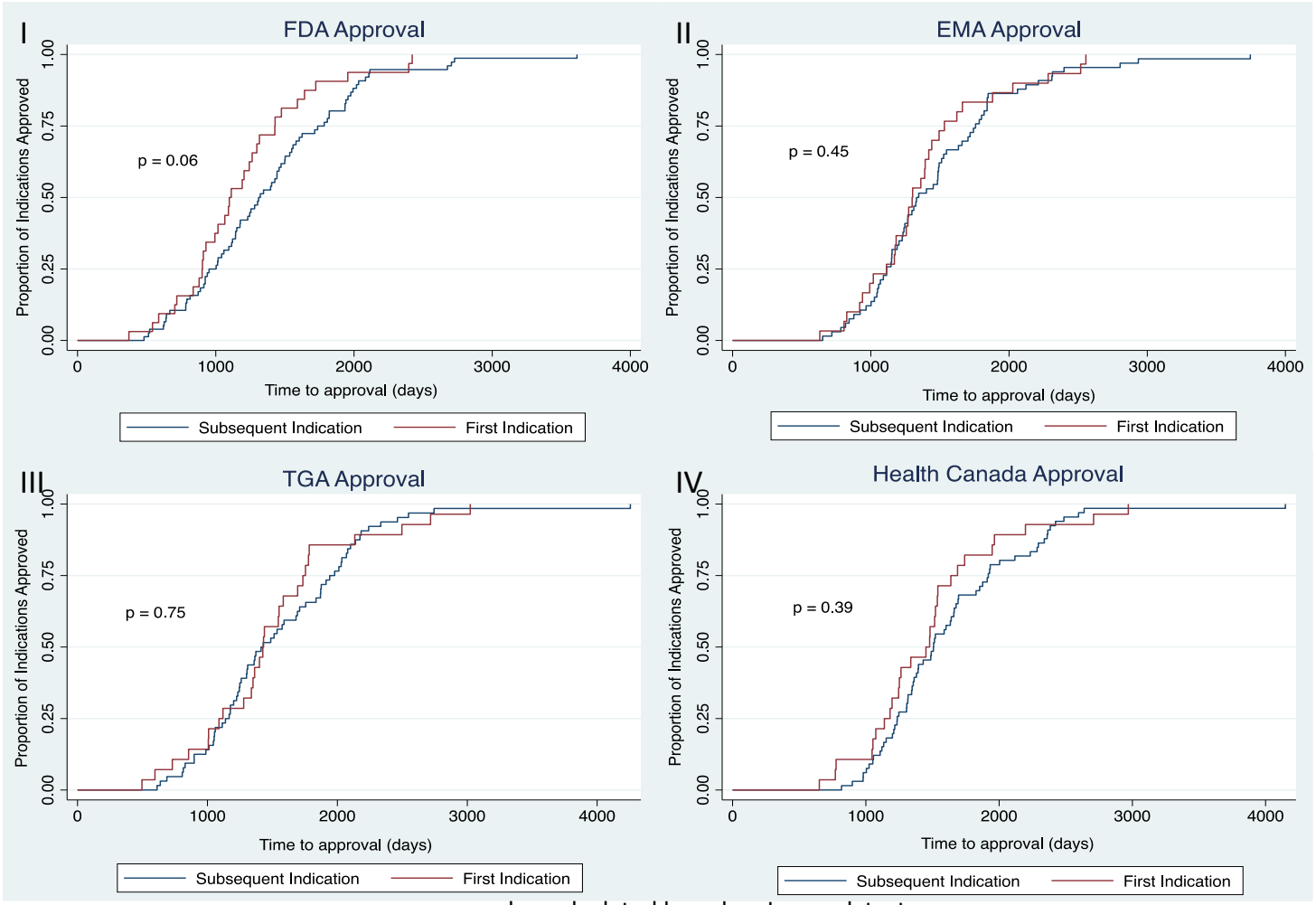
Within Germany and France, HTA outcomes are significantly associated with MCBS score. In Germany 25 of 56 (45%) of indications with a low or moderate MCBS score (1, 2 or 3) received a rating of no added benefit vs 5 of 31 (16%) with an MCBS score of 4 or 5, p = 0.007. Within France 7 of 44 (14%) indication with a low or moderate MCBS score (1, 2 or 3) received an SMR of insufficient vs 0 of 28 (0%), p = 0.040. No significant differences in HTA outcome vs MCBS score were identified in NICE, SMC, CADTH or PBAC.

3.3.5 Clinical development time and HTA coverage recommendation time

Survival analysis of first and subsequent indications in terms of clinical development time did not yield any statistically significant differences between the two groups (See **Figure 3.1**). Little to no separation of survival curves was seen in the USA, Europe, Canada, and Australia. Median clinical development times were fastest in the USA (median time 1,098 days vs 1,310 days, p=0.06), followed by the EMA (median time 1,299 days vs 1,331 days, p=0.45), the TGA (median time 1,426 days vs 1,413 days, p=0.75) and Health Canada (median time 1,451 days vs 1,507 days, p=0.39) for first vs subsequent indications respectively.

HTA coverage recommendation timelines of first and subsequent indications varied across settings (See **Figure 3.2**). In England and Canada, HTA coverage recommendation timelines were significantly longer for first indications than for subsequent indications. In England, median HTA coverage recommendation time was 506 days for first indications and 335 days for subsequent indications (p=0.007). None of the indications studied were assessed under NICE's fast track assessment procedure introduced in 2017. In Canada, median HTA coverage recommendation time was 289 days for first indications and 183 days for subsequent indications (p=0.02). Within France, first-indications received approval marginally faster than subsequent indication (258 days vs 300 days, p = 0.04). No significant differences across first and subsequent indications were detected for HTA coverage recommendation timelines in Australia, Germany and Scotland.

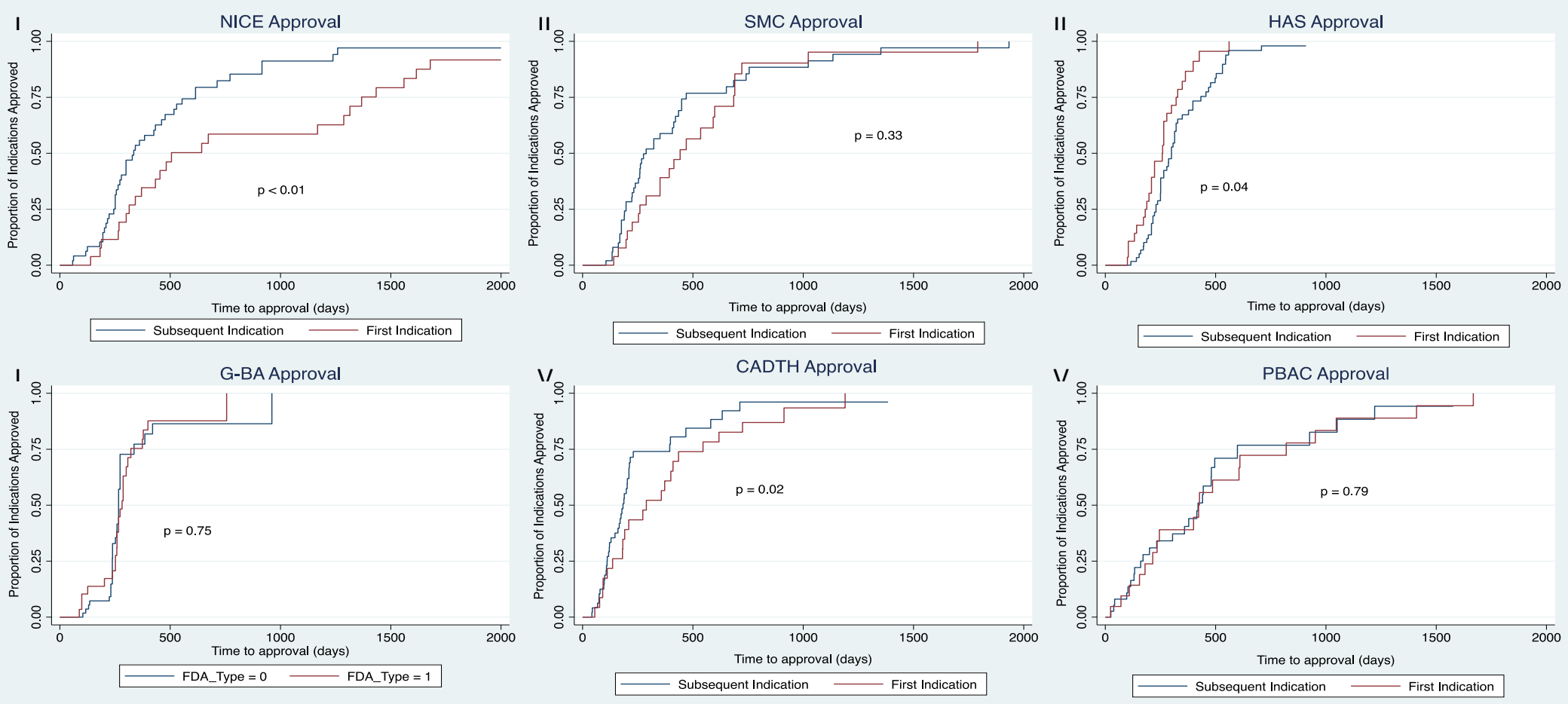
HTA recommendation timelines were further evaluated in terms time from marketing authorisation to HTA submission across CADTH, G-BA, and NICE. Time from marketing authorisation to NICE submission was significantly longer for first indications vs subsequent indications (427 days vs 76 days, p=0.01). No significant differences were detected across first vs subsequent indications for time from marketing authorisation to HTA submission in CADTH or G-BA, although time to submission was faster than NICE in both settings: 146 days for first indications vs 46 days for subsequent indications (p=0.09) for CADTH; and 105 days for first indications vs 69 days for subsequent indications.



p-value calculated based on Log rank tests

Figure 3.1 - Kaplan Meier plots of clinical development time for multi-indication products, defined as time from pivotal trial initiation to regulatory approval.

I – Clinical development time of first vs subsequent indications in the USA. II – Clinical development time of first vs subsequent indications in Europe. III – Clinical development time of first vs subsequent indications in Canada. IV – Clinical development time of first vs subsequent indications in Australia. Abbreviations: EMA – European Medicines Agency, FDA – Food and Drug Administration (USA), TGA – Therapeutic Goods Administration (Australia)



p-value calculated based on Log rank tests

Figure 3.2 - Kaplan Meier plots of HTA approval time for multi-indication products, defined as time from regulatory approval to HTA approval.

I – HTA approval time of first vs subsequent indications in England. II – HTA approval time of first vs subsequent indications in Scotland. III – HTA approval time of first vs subsequent indications in France. IV – HTA approval time of first vs subsequent indications in Germany. V – HTA approval time of first vs subsequent indications in Canada. VI - HTA approval time of first vs subsequent indications in Australia. Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health, G-BA – Federal Joint Committee, HAS – Haute Autorité de Santé (HAS), NICE – National Institute of Health and Care Excellence, PBAC – Pharmaceutical Benefits Advisory Committee, SMC – Scottish Medicines Consortium.

3.4 Discussion

Decisions to prioritise the development of one indication for a medicine over another and decisions to launch a medicine in local settings following development are multifaceted. Manufacturers face a wide range of clinical, ethical and economic challenges when preparing a valuation for the new use of a medicine, which can vary significantly across both disease and country settings. From the evidence generated above it is clear that there is no uniform approach towards the development and marketing of multi-indication medicines. Nevertheless, a number of interesting observations can be identified in terms of how manufacturers are prioritising the development and launch of multi-indication medicines and in terms of how medicines become available in a given health care setting.

First, manufacturers show a tendency to prioritise development of niche indications, with high disease severity and unmet need for the first indication of multi-indication medicines. To a considerable degree this strategy seems to resonate with the objectives of health systems prioritising treatments that address significant unmet need and disease severity. Relative to subsequent indications, first indications were more likely to be based on conditional approval or priority review, indicative of a prioritisation of patient populations with high disease severity and unmet need for the first indication. Further, a higher proportion of first indications received an orphan designation. These results remain consistent when excluding EMA from analysis (where conditional approval is only granted to new drug submissions, rather than indication extensions).

Second, the evidence base of subsequent indications tends to be based on more robust study designs. Subsequent indications are more likely to be approved on the basis of phase III head-to-head trial designs, while first indications are more dependent on phase II, single arm trials. These findings are aligned with a higher proportion of conditional approvals and lower MCBS

scores in first indications and a tendency to develop indications with high disease severity and unmet need in the first indication. In theory, development of indications that address unmet need and treat life threatening or chronically debilitating diseases can provide advantages to both patients, through access to a new treatment in the absence of therapeutic alternatives, and manufacturers, through lower requirements for market entry and reduced competition at the time of market entry. A further consideration relates to first-mover advantages, as manufacturers may prioritise development of indications which could result in being first to market, but based on less robust evidence of clinical evidence. However, no significant differences were detected in time from pivotal trial initiation to marketing authorisation across first and subsequent indications. In theory, development time would be shorter for subsequent indications if the safety and toxicity of a medicine has been established in the first indication [103]. However, this may not be reflected in the length of the pivotal trial, particularly if subsequent indications tend to be based on later phase clinical trials. Further research on earlier stages of clinical development could help to clarify this issue.

Third, while HTA coverage recommendation rates are similar across first and subsequent indications submitted for assessment, a number of indications do not launch in local settings. Mapping of marketing authorisation and HTA coverage recommendation sequence highlighted discordance between the total number of indications launched globally, the total number of indications with marketing authorisation individually within the EMA, TGA and Health Canada, and the total number of indications with HTA coverage recommendation. Results suggest that post-development sequencing typically manifests through non-launch of indications, frequently through absence of marketing authorisation. Only 81%, 80% and 79% of globally launched indications had authorisation in the EMA, TGA and Health Canada. Of the indications which did not launch, only a small number of withdrawals or refusals were identified, indicating that in most cases of non-approval manufacturers are electing not to

submit for marketing approval. A number of authorised indications also failed to receive positive HTA coverage recommendations, however, with the exception of Australia and Germany, no significant differences were detected in HTA coverage recommendation rates across first and subsequent indications submitted for assessment.

HTA coverage recommendation sequence and HTA coverage recommendation rates should be interpreted with caution as variations in the role and scope of HTA are present across settings (See **Table 3.4**). Within England HTA recommendations by NICE are binding and positively recommended products must be made available within the NHS [165]. In Scotland, the SMC issues recommendations to NHS boards, who make final decisions on reimbursement [146]. In both settings, non-reimbursed products can still be purchased privately or be made available through private insurance schemes. Within Canada, reimbursement of medicines is primarily the responsibility of individual provinces, who rely on CADTH recommendations in an advisory capacity to inform pricing and reimbursement decisions [166]. Prior to launch, products are subject to an assessment by the Patented Medicines Pricing Review Board (PMPRB), who set a maximum allowable price, that applies to both the private and public market (where further discounts are negotiated) [167]. Similarly, PBAC in Australia serves an advisory role to the Ministry of Health for reimbursement in the Public Benefits Scheme [168]. Non-reimbursed products can be purchased privately following TGA approval. In Germany, new medicines are subject to the Act to Reorganise the Pharmaceuticals Market in the Statutory Health Insurance (AMNOG) procedure [169]. It is mandatory for newly marketed medicines to submit a benefit dossier with the Federal Joint Committee (G-BA) before commercialisation in Germany. Benefit assessment and subsequent price negotiations must take place within one year of authorisation. During this time medicines receive free pricing and are made available to patients [126]. Finally, the HAS in France conducts HTA on all new drugs receiving marketing authorisation, and provides recommendations to the economic committee for

Table 3.4 - Role of HTA and Requirements for Launch of New Indications Across Germany, France, England, Scotland, Canada, and Australia

Country	HTA agency	Type of assessment	Role of HTA	Requirements for public reimbursement
Germany	Federal Joint Committee (G-BA)	Relative clinical benefit assessment	Informs pricing negotiations with the National Association of Statutory Health Insurance Funds	EMA authorisation
France	Transparency Committee - Haute Autorité de Santé (HAS)	Relative clinical benefit assessment	Informs pricing (ASMR) and reimbursement rate (SMR)	EMA authorisation and SMR rating above insufficient
England	National Institute of Health and Care Excellence (NICE)	Clinical and cost-effectiveness	Issues binding reimbursement recommendations. Indirectly influences pricing through cost-effectiveness thresholds	EMA authorisation and NICE approval*
Scotland	Scottish Medicines Consortium (SMC)	Clinical and cost-effectiveness	Informs pricing and reimbursement decisions by NHS boards. NHS boards not required to follow recommendation, but must wait for an SMC assessment to be issued.	EMA authorisation and SMC assessment
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH) and pan-Canadian Oncology Drug Review (pCODR)	Clinical and cost-effectiveness	Informs provincial pricing and reimbursement. Provinces are not required to follow recommendation and negotiate either jointly or individually with manufacturers.	Health Canada authorisation and CADTH/PCODR assessment**
Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	Clinical and cost-effectiveness	Informs pricing and reimbursement in Pharmaceutical Benefit Scheme (PBS). Minister of Health makes final decision following positive PBAC recommendation	TGA authorisation and PBAC approval

Source: The authors from [30-38]

Abbreviations: ASMR – Amélioration du Service Médical Rendu (France), EMA – European Medicines Agency, HTA – Health Technology Assessment, NHS – National Health Service, SMR – Service Médical Rendu (France), TGA – Therapeutic Goods Administration (Australia)

* NHS organisations are able to start using a new drug prior to NICE guidance but uptake is low and commissioning groups typically wait for NICE guidance to be issued. Since 2019, NICE evaluates all new drugs launched in the UK.
** Provinces are able to fund drugs without CADTH/PCODR assessments but uptake is low and CADTH/PCODR recommendations typically inform negotiations. The province of Quebec does not rely on CADTH recommendations and has its own health technology assessment agency for informing pricing and reimbursement decisions.

healthcare products (CEPS), the national health insurance funds (UNCAM) and ministry of health [127, 170].

Finally, HTA coverage recommendation timelines tend to be faster for subsequent indications. Interestingly, subsequent indications had a tendency to have faster HTA coverage recommendation timelines, in England and Canada. This could partly be explained by higher quality pivotal clinical trial designs and increased proportion of standard approvals seen in the subsequent indication group. Another possibility is that first indications face higher barriers to entry. HTA agencies may receive efficiency gains from prior evaluations of a medicine in previous indications. Within England, differences in approval of first vs subsequent indications appears to be partly driven by delays in HTA submission of the first indication, perhaps indicating that manufacturers also receive efficiency gains in preparing HTA submissions for subsequent indications or alternatively reflecting increased challenges in preparing submissions with lower quality evidence and potentially higher uncertainty.

Our analysis is not without limitations. First, the present analysis is limited to indications that have received marketing approval, and thus no conclusions can be drawn about decisions not to develop indications pre-development; future research may explore this. Second, our analysis is limited to the USA, Europe, Canada and Australia. While these settings are frequently targeted first for global launch of medicines [160], we cannot exclude the possibility that medicines launch first in other jurisdictions. As such, it is possible that small differences exist between our classification of global launch sequence and true global launch sequence. Third, the results presented here predominantly reflect oncology medicines with multiple indications; further research is needed to establish whether our findings apply to multi-indication medicines in other therapeutic areas. Fourth, the impact of secondary patents and market exclusivity extensions was not explored in the analysis. The current patent regime enables drug innovators

to pursue secondary patents for new uses of existing pharmaceuticals, while regulatory agencies may grant extensions in market exclusivity [79, 105]. These benefits may impact the timing of decisions to launch a product locally and could contribute to differences seen across settings in the timing and availability of indication extensions. Fifth, data was not collected on completion of confirmatory studies for conditional approvals. This may influence the strength of evidence at the time HTA evaluation or decisions to launch subsequent indications, an interesting topic that merits further research. Finally, reforms to HTA systems during the study period may influence results. For instance, the AMNOG process in Germany was not introduced until 2011, meaning no HTA reports were available prior to that [169]; further, NICE introduced reforms to their HTA timelines in 2016 as part of their change to the Cancer Drugs Fund (CDF), committing to processing all HTA submissions in 90 days after regulatory approval [165]. This could contribute to the decrease in HTA coverage recommendation time and submission time seen for subsequent indications in England, but moreover, could influence launch decisions based on integration of the CDF into NICE recommendations [165].

3.5 Conclusion

The development and marketing of multi-indication oncology medicines requires balancing a variety of factors that must be adjusted to the specific characteristics of a clinical setting. Manufacturers show a tendency to launch first in niche indications with high disease severity and unmet need, a strategy that seems to be compatible with what health systems demand, however, a number of examples are present of molecules which do not follow this trend. Of the 118 indications identified only 71% had marketing authorisation across each of the FDA, EMA, TGA and Health Canada, indicative of post-development sequencing. Substantial heterogeneity in HTA outcomes is present across settings although few significant differences were detected across first versus subsequent indications. Overall, discordance in the value of

first vs subsequent indications can be a major challenge in systems that define price based on the initial indication, resulting in fragmented launch and availability of multi-indication products.

3.6 Appendices

Appendix A – Country specific approaches to pricing multi-indication products.

There are four broad mechanisms for implementation of indication-based pricing: a) blended or weighted pricing, b) differential discounting, c) different brand names for different indications, or d) outcomes-based reimbursement models

In some countries, such as Germany, France and Australia a weighted pricing system is used to indirectly achieve indication-based pricing. Under a weighted pricing system, the price of a medicine is re-negotiated after the launch of a new therapeutic indication [61]. Weighted pricing can apply to the list price of a molecule, or to the net price of a molecule in settings where confidential discounting takes place. The price is calculated based on the respective value of each indication and weighted according to the expected utilisation. In theory, this would generate the same level of sales as an indication-based pricing system. In practice, however, the weighted price may not reflect the true value or utilisation of respective indications (e.g. if a competitor launched in one indication and reduced utilisation). As a result, manufacturers may still be reluctant to launch lower value indications under a weighted pricing system unless a retrospective adjustment provision is in place to reflect actual patient volumes. This however, requires robust data capabilities and may be associated with high administrative burden [61].

In settings such as the UK, Switzerland and Italy different confidential discount rates can be applied off a single list price to individual indications for a molecule, particularly if the epidemiology or expected use varies substantially across indications. In these settings, regulatory and legal systems allow for the rate of reimbursement for a molecule to vary according to each indication's value relative to the standard of care [159]. A payer's willingness to provide differential discounts may be limited by issues in data capability and financial flow

through distribution networks. Differential discounting requires tracking of a molecule's use by indication and can be associated with substantial administrative burden. Wholesale distribution may lead to complexities in managing payments across indications [65].

Alternatively, regulatory and legal requirements may require that single price be used for each branded molecule [171]. Using different brand names for individual indications may provide flexibility to assign prices according to brand name. However, implementation of multiple brand names when indications are similar (e.g. for a molecule with multiple cancer indications) may be too confusing and burdensome for healthcare providers and patients [61]. Further, strict monitoring would be required to prevent off-label use of the lower-priced brand, a practice that is common in oncology where there is often high unmet need and patients may be more willing to use a medicine where definitive efficacy and safety have yet to be established [172].

Outcome-based reimbursement models have also been proposed as a potential solution to single pricing system. Outcome-based reimbursement models directly link payment to the real-world value that a medicine provides to patients. Effective outcomes-based reimbursement models could solve the disconnect between single payment models and the incremental value of multiple indications. In a recent study, authors evaluated the potential of outcomes-based payments to address issues in indication-based pricing of trastuzumab for breast cancer and for gastric cancer. Based on clinical trial efficacy, the expected value of trastuzumab in breast cancer and gastric cancer was $3.50 per mg and $0.93 per mg, respectively. However, based on data from an observational cohort, the expected value of trastuzumab in breast cancer and gastric cancer was $8.66 per mg and $0.20 per mg, respectively [63].

Appendix B – Sample selection flowchart and data sources

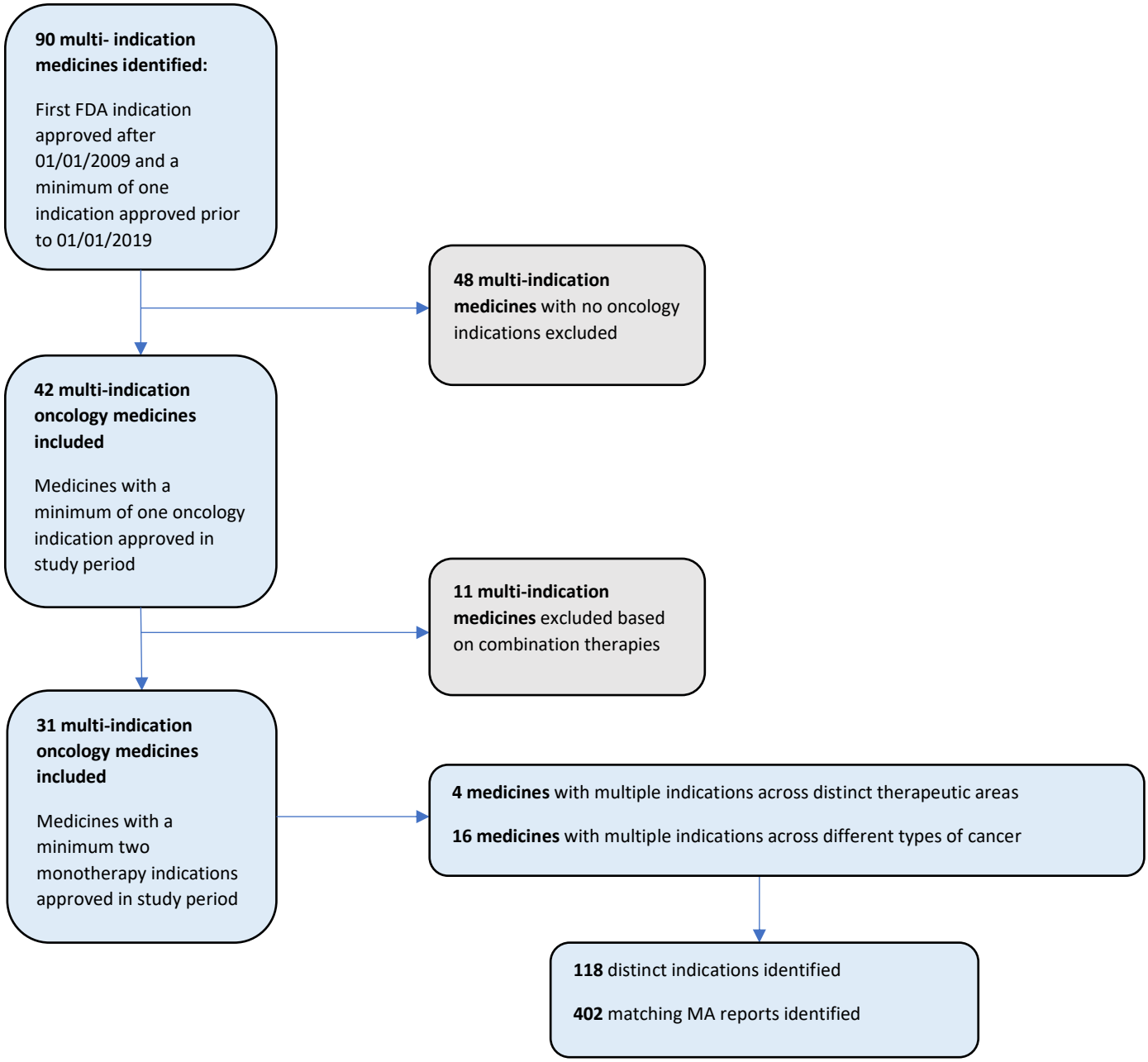


Figure 3.3 - Sample Selection of Medicines With Multiple FDA Approved Therapeutic Indications Between January 1st, 2009 and January 1st, 2019.

Inclusion criteria included a) a minimum of one oncology/cancer indication and b) a minimum of two monotherapy indications. Following sample identification, matching marketing authorisation (MA) and health technology assessment (HTA) reports were identified across England, Scotland, France, Germany, Canada and Australia for included therapeutic indications. Marketing authorisation reports were identified from the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, and the Australian Therapeutic Goods Administration (TGA). HTA reports were identified from the National Institute of Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Federal Joint Committee (G-BA), the Haute Authorité de Santé, (HAS), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Pharmaceutical Benefits Advisory Committee (PBAC).

B2 – DATA SOURCES

Table 3.5 - Marketing Authorisation Report and Health Technology Assessment Report Data Sources

Marketing Authorisation Agencies		
Country/Region	**Agency**	**Website**
Europe	European Medicines Agency (EMA)	https://www.ema.europa.eu/en
USA	U.S. Food and Drug Administration (FDA)	https://www.fda.gov/
Canada	Health Canada	https://www.canada.ca/en/ health-canada.html
Australia	Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/
HTA Agencies		
England	National Institute of Health and Care Excellence (NICE)	https://www.nice.org.uk/
Scotland	Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/
France	Haute Authorité de Santé, (HAS)	https://www.has-sante.fr/
Germany	Federal Joint Committee (G-BA)	https://www.g-ba.de/english/
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/
Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	https://www.pbs.gov.au/pbs/industry/listing/participants/pbac

Appendix C – List of included medicines and indications

Table 3.6 - List of Included Therapeutic Indications, First Approval Date, Pivotal Trial Design And MCBS Scores

Molecule name	Therapeutic Indication	First Marketing Authorisation Date	First Agency to Approve	Pivotal Trial Design	Primary Endpoint (s)	MCBS Score
MEDICINES WITH MULTIPLE INDICATIONS ACROSS DIFFERENT THERAPEUTIC AREAS						
Ibrutinib	For the treatment of patients with mantle cell lymphoma who have received at least one prior therapy	13/11/2013	FDA	Single Arm Phase II	ORR	1
	For the treatment of Chronic lymphocytic leukemia who have received at least one prior therapy	12/02/2014	FDA	Phase III RCT - Active Comparator	PFS	3
	Chronic lymphocytic leukemia with 17p deletion	28/07/2014	FDA	Phase III RCT - Active Comparator	PFS	3
	Waldenström's macroglobulinemia	29/01/2015	FDA	Single Arm Phase II	ORR	1
	Marginal zone lymphoma who require systemic therapy and have received at least one prior anti-CD20-based therapy	18/01/2017	FDA	Single Arm Phase II	ORR	1
	Chronic graft versus host disease after failure of one or more lines of systemic therapy	02/08/2017	FDA	Single Arm Phase II	ORR	N/A
Nintedanib	In combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first-line chemotherapy.	25/09/2014	EMA	Phase III RCT - Placebo Controlled	PFS	2
	For the treatment of idiopathic pulmonary fibrosis.	15/10/2014	FDA	Phase III RCT - Active Comparator	FVC	N/A
Aflibercept	For the treatment of Neovascular (Wet) Age-Related Macular Degeneration	20/09/2011	EMA	Phase III RCT - Active Comparator	Maintenance of vision	N/A
	In combination with 5-fluorouracil, leucovorin, irinotecan, is indicated for patients with metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen.	03/08/2012	FDA	Phase III RCT - Placebo Controlled	OS	4
	For the treatment of Macular Edema following Central Retinal Vein Occlusion	21/09/2012	FDA	Phase III RCT - Active Comparator	BCVA change	N/A

	For the treatment of visual impairment in adult patients with Diabetic Macular Edema (DME)	26/06/2014	EMA	Phase III RCT - Active Comparator	BCVA change	N/A
	For the treatment of adult patients with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)	22/01/2015	EMA	Phase III RCT - Active Comparator	BCVA change	N/A
	For the treatment of patients with Diabetic Retinopathy (DR) in Patients with DME	25/03/2015	FDA	Phase III RCT - Active Comparator	BCVA change	N/A
	For the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV)	24/09/2015	EMA	Phase III RCT - Active Comparator	BCVA change	N/A
	For the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.	30/03/2009	FDA	Phase III RCT - Placebo Controlled	PFS	3
	For the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection	29/10/2010	FDA	Single Arm Phase II	SEGA volume	N/A
	For the treatment of progressive neuroendocrine tumours of pancreatic origin (PNET) that is unresectable, locally advanced or metastatic.	05/05/2011	FDA	Phase III RCT - Placebo Controlled	PFS	3
Everolimus	For the treatment of adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery	26/04/2012	FDA	Phase III RCT - Placebo Controlled	angiomyolipoma response rate	N/A
	For the treatment of hormone receptor-positive advanced breast cancer, in combination with an aromatase inhibitor, in postmenopausal women previously treated with endocrine therapy	21/06/2012	EMA	Phase III RCT - Placebo Controlled	PFS	3
	For the treatment of non-functional neuroendocrine tumours (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic.	26/02/2016	FDA	Phase III RCT - Placebo Controlled	PFS	3
	For adjunctive treatment of patients aged 2 years and older with refractory seizures associated with tuberous sclerosis complex (TSC)	15/12/2016	FDA	Phase III RCT - Placebo Controlled	Seizure frequency	N/A
MEDICINES WITH MULTIPLE THERAPEUTIC INDICATIONS ACROSS DIFFERENT TYPES OF CANCER						
Cabozantinib	For the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma	29/11/2012	FDA	Phase III RCT - Placebo Controlled	PFS	3

	For the treatment of advanced renal cell carcinoma (RCC) in patients who have received one prior therapy	25/04/2016	FDA	Phase III RCT - Active Comparator	PFS	3
	For the treatment of advanced renal cell carcinoma the 'treatment naïve adults with intermediate or poor risk per IMDC criteria	19/12/2017	FDA	Controlled Phase II	PFS	2
	For the treatment of advanced hepatocellular carcinoma in adults following prior systemic therapy	20/09/2018	EMA	Phase III RCT - Placebo Controlled	OS	4
Pazopanib	For the treatment of patients with advanced renal cell carcinoma	19/10/2009	FDA	Phase III RCT - Active Comparator	PFS	3
	For the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy.	26/04/2012	FDA	Phase III RCT - Placebo Controlled	PFS	3
Tisagenlecleucel	For the treatment of patients up to 25 years of age with Bcell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.	30/08/2017	FDA	Single Arm Phase II	ORR	1
	For the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma	01/05/2018	FDA	Single Arm Phase II	ORR	1
Regorafenib	For the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.	27/09/2012	FDA	Phase III RCT - Placebo Controlled	OS	4
	For the treatment of locally advanced, unresectable or metastatic gastrointestinal stromal tumour (GIST) who have been previously treated with imatinib mesylate and sunitinib malate	25/02/2013	FDA	Phase III RCT - Placebo Controlled	PFS	3
	For the treatment of hepatocellular carcinoma (HCC) who have been previously treated with sorafenib	27/04/2017	FDA	Phase III RCT - Placebo Controlled	OS	4
Ramucirumab	For the treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after prior chemotherapy	21/04/2014	FDA	Phase III RCT - Placebo Controlled	OS	4
	In combination with docetaxel, for treatment of metastatic non small cell lung cancer with disease progression on or after platinum-based chemotherapy.	12/12/2014	FDA	Phase III RCT - Placebo Controlled	OS	4

	In combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.	24/04/2015	FDA	Phase III RCT - Placebo Controlled	OS	4
Avelumab	For the treatment of adult patients with metastatic Merkel cell carcinoma (MCC)	23/03/2017	FDA	Single Arm Phase II	BOR	1
	For the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy etastatic urothelial carcinoma (UC)	09/05/2017	FDA	Phase 1 Trial	ORR	1
Atezolizumab	For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy.	18/05/2016	FDA	Phase III RCT - Active Comparator	ORR	1
	For the treatment of metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy.	18/10/2016	FDA	Phase III RCT - Active Comparator	OS	5
	In combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment, of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations	06/12/2018	FDA	Phase III RCT - Active Comparator	OS, PFS	5
Eribulin	For the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease.	15/11/2010	FDA	Phase III RCT - Active Comparator	OS	4
	For the treatment of unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.	28/01/2016	FDA	Phase III RCT - Active Comparator	OS	4
Ruxolitinib	for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.	16/11/2011	FDA	Phase III RCT - Placebo Controlled	Spleen volume reduction	1
	For the treatment of polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea	04/12/2014	FDA	Phase III RCT - Active Comparator	PR	1
Nivolumab	For the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor	22/12/2014	FDA	Phase III RCT - Active Comparator	OS	4
	For the treatment of metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy	04/03/2015	FDA	Phase III RCT - Active Comparator	OS	5

	For the treatment of metastatic non-small cell lung cancer in patients with progression on or after platinum-based chemotherapy	09/10/2015	FDA	Phase 1 Trial	OS	4
	For the treatment of advanced renal cell carcinoma in patients who have received prior antiangiogenic therapy	23/11/2015	FDA	Phase III RCT - Active Comparator	OS	5
	In combination with ipilimumab, for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma	23/11/2015	FDA	Phase III RCT - Active Comparator	PFS	3
	For the treatment of classical hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post transplantation brentuximab vedotin	17/05/2016	FDA	Single Arm Phase II	ORR	1
	For the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy	10/11/2016	FDA	Phase III RCT - Active Comparator	OS	5
	For the treatment of locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	02/02/2017	FDA	Single Arm Phase II	ORR	1
	For the treatment of adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.	31/07/2017	FDA	Single Arm Phase II	ORR	1
	For the treatment of hepatocellular carcinoma who have been previously treated with sorafenib	22/09/2017	FDA	Single Arm Phase II	ORR	1
	For the treatment of melanoma with lymph node involvement or metastatic disease who have undergone complete resection	20/12/2017	FDA	Phase III RCT - Active Comparator	RFS	1
	For the treatment of intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab	16/04/2018	FDA	Phase III RCT - Active Comparator	OS, PFS, ORR	5
	For the treatment of patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy	16/08/2018	FDA	Single Arm Phase II	ORR	1
Pembrolizumab	For the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor	04/09/2014	FDA	Phase III RCT - Active Comparator	PFS, OS	4

For the treatment of metastatic NSCLC whose tumours express PD-L1 and who have disease progression on or after platinum-containing chemotherapy	02/10/2015	FDA	Phase III RCT - Active Comparator	PFS, OS	5
For the treatment of recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy	05/08/2016	FDA	Phase III RCT - Active Comparator	OS	4
For previously untreated patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) whose tumours express PD-L1	24/10/2016	FDA	Phase III RCT - Active Comparator	PFS	3
For the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy	14/03/2017	FDA	Single Arm Phase II	ORR	1
In combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic non-squamous NSCLC	10/05/2017	FDA	Phase III RCT - Placebo Controlled	OS, PFS	5
For the treatment of 2nd line Metastatic Urothelial Carcinoma	18/05/2017	FDA	Phase III RCT - Active Comparator	OS, PFS	4
For the treatment of locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy	18/05/2017	FDA	Single Arm Phase II	ORR	1
For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	23/05/2017	FDA	Single Arm Phase II	ORR	1
For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1	22/09/2017	FDA	Controlled Phase II	ORR	5
For the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1	12/06/2018	FDA	Single Arm Phase II	ORR	1
For the treatment of refractory PMBCL, or for patients who have relapsed after 2 or more prior lines of therapy	13/06/2018	FDA	Single Arm Phase II	ORR	1
Adjuvant treatment of melanoma with involvement of lymph node(s) following complete resection	18/10/2018	EMA	Phase III RCT - Placebo Controlled	RFS	A
In combination with carboplatin and either paclitaxel or nabpaclitaxel, as first-line treatment of patients with metastatic squamous NSCLC.	30/10/2018	FDA	Phase III RCT - Active Comparator	PFS, OS	5

	For the treatment of patients with HCC who have been previously treated with sorafenib	09/11/2018	FDA	Single Arm Phase II	ORR	1
	For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma	19/12/2018	FDA	Single Arm Phase II	ORR	1
	For the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates	19/08/2011	FDA	Single Arm Phase II	ORR	1
	The treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen	19/08/2011	FDA	Single Arm Phase II	ORR	1
	For the treatment of classical HL at high risk of relapse or progression as post-auto-HSCT consolidation.	17/08/2015	FDA	Phase III RCT - Placebo Controlled	PFS	3
Brentuximab vedotin	For the treatment of primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30- expressing mycosis fungoides (MF) who have received prior systemic therapy	09/11/2017	FDA	Phase III RCT - Active Comparator	ORR	1
	Previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy	20/03/2018	FDA	Phase III RCT - Active Comparator	ORR	1
	Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone	16/11/2018	FDA	Phase III RCT - Active Comparator	PFS	3
	For the treatment of unresectable or metastatic melanoma	25/03/2011	FDA	Phase III RCT - Active Comparator	OS	4
	Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy	28/10/2015	FDA	Phase III RCT - Placebo Controlled	RFS	1
Ipilimumab	In combination with nivolumab, for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma	23/11/2015	FDA	Phase III RCT - Active Comparator	PFS	3
	For the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab	16/04/2018	FDA	Phase III RCT - Active Comparator	ORR,OS,PFS	4
	For the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)	10/07/2018	FDA	Controlled Phase II	ORR	1

	metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab					
Romidepsin	Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy	1/05/2009	FDA	Single Arm Phase II	ORR	1
	Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy	16/06/2011	FDA	Single Arm Phase II	ORR	1
Vemurafenib	For the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation	17/08/2011	FDA	Phase III RCT - Active Comparator	OS, PFS	4
	For the treatment of patients with ErdheimChester Disease with BRAF V600 mutation.	06/11/2017	FDA	Single Arm Phase II	ORR	1
Lenvatinib	For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer	13/02/2015	FDA	Phase III RCT - Placebo Controlled	PFS	2
	For the treatment of Renal Cell Cancer (RCC): in combination with everolimus, for patients with advanced RCC following one prior anti-angiogenic therapy.	13/05/2016	FDA	Controlled Phase II	PFS	2
	For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).	15/08/2018	FDA	Phase III RCT - Active Comparator	OS	2
MEDICINES WITH MULTIPLE INDICATIONS ACROSS DIFFERENT LINES OF THERAPY						
Abiraterone Acetate	For the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel	28/04/2011	FDA	Phase III RCT - Placebo Controlled	OS	5
	For the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy.	15/11/2012	EMA	Phase III RCT - Placebo Controlled	PFS, OS	5
	For the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSCP) in adult men in combination with androgen deprivation therapy (ADT) for Zytiga plus prednisone or pednisolone	12/10/2017	EMA	Phase III RCT - Active Comparator	PFS, OS	5
Afatinib	For the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations	12/07/2013	FDA	Phase III RCT - Active Comparator	PFS	3

	Treatment of patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy	25/02/2016	EMA	Phase III RCT - Active Comparator	PFS	2
Blinatumomab	For the treatment of philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).	03/12/2014	FDA	Single Arm Phase II	Rate of CR	1
	For the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children	11/07/2017	FDA	Single Arm Phase II	Rate of CR	1
	For the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission	05/03/2018	FDA	Single Arm Phase II	MRD rate	1
Enzalutamide	For the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.	31/08/2012	FDA	Phase III RCT - Placebo Controlled	OS	5
	For the treatment of patients with metastatic castration-resistant prostate cancer.	10/09/2014	FDA	Phase III RCT - Placebo Controlled	OS, PFS	4
	For the treatment of patients with castration-resistant prostate cancer	13/07/2018	FDA	Phase III RCT - Placebo Controlled	MFS	1
Rucaparib	For the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies	19/12/2016	FDA	Single Arm Phase II	ORR	1
	For the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	06/04/2018	FDA	Phase III RCT - Placebo Controlled	PFS	3
Osimertinib	For the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutationpositive non-small cell lung cancer (NSCLC)	13/11/2015	FDA	Single Arm Phase II	ORR	1
	First-line treatment of patients with metastatic NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations	18/04/2018	FDA	Phase III RCT - Active Comparator	PFS	3
Crizotinib	For the treatment of previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	26/08/2011	FDA	Phase 1 Trial	ORR	1
	First-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	27/09/2013	TGA	Phase III RCT - Active Comparator	PFS	3
	For the treatment of metastatic NSCLC whose tumours are ROS1-positive	11/03/2016	FDA	Phase 1 Trial	ORR	1

Bosutinib	For the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy	04/09/2012	FDA	Single Arm Phase II	MCyR	1
	For the treatment of newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML)	19/12/2017	FDA	Phase III RCT - Active Comparator	MMR	1
Alectinib	For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	11/12/2015	FDA	Single Arm Phase II	ORR	1
	For the treatment of anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC)	12/10/2017	EMA	Phase III RCT - Active Comparator	PFS	3
Ceritinib	For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.	29/04/2014	FDA	Phase 1 Trial	ORR, DOR	1
	First-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	18/05/2017	EMA	Phase III RCT - Active Comparator	PFS	3
Ofatumumab	For the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab	26/10/2009	FDA	Single Arm Phase II	ORR	1
	in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate	17/04/2014	FDA	Phase III RCT - Active Comparator	PFS	3
	for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL.	19/01/2016	FDA	Phase III RCT - Placebo Controlled	PFS	3
	in combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL	30/08/2016	FDA	Phase III RCT - Active Comparator	PFS	3

Abbreviations: BCVA - best-corrected visual acuity; BOR - best observed response; CR – complete response rate; DOR - duration of response; FVC - forced vital capacity; MCyR - major cytogenic response; MMR - major molecular response; ORR - overall response rate; OS – overall survival; PFS - progression free survival; PR – primary response; RFS -remission free survival,, SEGA - subependymal giant cell astrocytoma

Table 3.7 - Alignment of Regulatory Approval and HTA Approval Sequence

Molecule	Approved Indications (Brief version)	Regulatory Approval Sequence	HTA Approval Sequence					
			NICE	SMC	HAS	G-BA	CADTH	PBAC
Ibrutinib	2nd line Mantle Cell Lymphoma	**1**	3rd	1st	1st	1st	2nd	2nd
	2nd Line Chronic lymphocytic leukemia	**2**	1st	2nd	2nd	2nd	1st	1st
	1st Line Chronic lymphocytic leukemia	**3**	NS	NS	3rd	3rd	3rd	3rd
	Waldenström's macroglobulinemia	**4**	2nd	3rd	4th	NAB	DNL	NS
	2nd Line Marginal zone lymphoma	**5**	NM	NM	NM	NM	NS	NM
	Chronic graft versus host disease	**6**	NM	NM	NM	NM	NS	NM
Nintedanib	2nd line NSCLC	**1**	1st	1st	INS	1st	NM	DNL
	Idiopathic Pulmonary Fibrosis	**2**	2nd	2nd	1st	2nd	1st	1st
Aflibercept	Neovascular Age-Related Macular Degeneration	**1**	1st	1st	1st	NAB	1st	1st
	Combination metastatic colorectal cancer	**2**	DNL	2nd	2nd	1st	DNL	DNL
	Central Retinal Vein Occlusion	**3**	2nd	3rd	3rd	NAB	T 2nd	2nd
	Diabetic Macular Edema	**4**	3rd	4th	4th	NAB	T 2nd	3rd
	Branch Retinal Vein Occlusion	**5**	5th	5th	5th	NAB	4th	4th
	Diabetic Retinopathy	**6**	NM	NM	NM	NM	NM	NM
	Myopic choroidal neovascularisation	**7**	4th	6th	6th	NAB	NS	5th
Everolimus	Advanced renal cell carcinoma	**1**	2nd	DNL	1st	1st	NS	T 3rd
	Subependymal giant cell astrocytoma	**2**	NS	NS	2nd	NS	DNL	1st
	Pancreatic progressive neuroendocrine tumours	**3**	T 3rd	1st	3rd	NS	1st	T 3rd
	Renal angiomyolipoma and tuberous sclerosis complex	**4**	NS	NS	4th	NS	NS	NM
	Advanced breast cancer	**5**	1st	2nd	5th	NS	2nd	2nd
	Neuroendocrine tumours of GI or lung origin	**6**	T 3rd	3rd	6th	NS	3rd	NS
	Tuberous sclerosis complex associated seizures	**7**	NS	NS	7th	NS	NS	5th
Cabozantinib	Metastatic medullary thyroid cancer	**1**	2nd	DNL	1st	1st	NM	NM
	2nd line renal cell carcinoma	**2**	1st	1st	2nd	2nd	1st	1st
	1st line renal cell carcinoma	**3**	3rd	DNL	INS	NAB	NS	DNL
	2nd line hepatocellular carcinoma	**4**	NS	NS	3rd	3rd	2nd	DNL
Pazopanib	Advanced renal cell carcinoma	**1**	1st	1st	INS	NS	1st	1st
	Advanced soft tissue sarcoma	**2**	NS	DNL	1st	NS	DNL	2nd
Tisagenlecleucel*	R/R acute lymphoblastic leukemia	**1**	1st	1st	1st	1st	NS	NS
	R/R diffuse large B-cell lymphoma	**2**	2nd	2nd	2nd	2nd	NS	NS
Regorafenib	2nd Line metastatic colorectal cancer	**1**	NS	NS	1st	1st	DNL	DNL
	2nd Line metastatic gastrointestinal stromal tumour	**2**	1st	1st	2nd	NAB	1st	DNL
	2nd Line hepatocellular carcinoma	**3**	2nd	2nd	3rd	2nd	2nd	DNL

Ramucirumab	2nd line gastric cancer	**1**	DNL	NS	1st	1st	1st	1st
	2nd Line NSCLC	**2**	DNL	NS	NS	NAB	NM	NM
	2nd Line metastatic colorectal cancer	**3**	NS	NS	2nd	NAB	NM	NM
Avelumab	Metastatic Merkel cell carcinoma	**1**	1st	1st	1st	1st	1st	1st
	Metastatic urothelial carcinoma	**2**	NM	NM	NM	NM	NS	NM
Atezolizumab	2nd Line urothelial carcinoma	**1**	1st	DNL	NS	2nd	NS	NS
	2nd Line NSLCLC	**2**	2nd	1st	1st	1st	1st	1st
	Combination 1st Line NSCLC	**3**	3rd	DNL	2nd	NAB	DNL	2nd
Eribulin	3rd line metastatic breast cancer	**1**	1st	1st	1st	1st	1st	1st
	2nd line liposarcoma	**2**	NS	NS	2nd	NAB	NS	2nd
Ruxolitinib	Myelofibrosis	**1**	1st	1st	1st	1st	1st	1st
	Polycythemia vera	**2**	NS	NS	2nd	2nd	2nd	NS
Nivolumab	2nd Line Melanoma	**1**	1st	2nd	1st	1st	1st	1st
	2nd Line squamous NSCLC	**2**	T 5th	1st	T 3rd	2nd	2nd	T 2nd
	2nd Line non-squamous NSCLC	**3**	T 5th	3rd	T 3rd	T 3rd	NS	T 2nd
	2nd Line Renal Cell Carcinoma	**4**	3rd	5th	2nd	T 3rd	3rd	T 2nd
	Combination 1st Line Melanoma	**5**	2nd	4th	6th	NAB	5th	6th
	Classical Hodgkin Lymphoma	**6**	4th	6th	5th	NAB	6th	NS
	Metastatic squamous cell carcinoma of the head and neck	**7**	7th	7th	7th	5th	4th	5th
	2nd Line Urothelial carcinoma	**8**	DNL	DNL	NS	NAB	NM	NS
	Combination Microsatellite Instability-High Cancer	**9**	NM	NM	NM	NM	NM	NM
	Hepatocellular carcinoma	**10**	NM	NM	NM	NM	DNL	NS
	Adjuvant Melanoma	**11**	8th	8th	8th	6th	7th	DNL
	Combination 1st Line Renal Cell Carcinoma	**12**	9th	9th	9th	7th	8th	NS
	2nd Line SCLC	**13**	NM	NM	NM	NM	NM	NM
Pembrolizumab	2nd Line Metastatic Melanoma	**1**	1st	1st	1st	1st	1st	1st
	2nd Line Metastatic NSCLC	**2**	2nd	2nd	2nd	2nd	2nd	DNL
	2nd Line Metastatic HNSCC	**3**	NS	9th	6th	NAB	NM	DNL
	1st line Metastatic NSCLC	**4**	3rd	3rd	3rd	3rd	3rd	T 3rd
	Relapsed/Refractory classical Hodgkin Lymphoma	**5**	6th	5th	5th	NAB	4th	2nd
	Combination 1st Line Non-squamous NSCLC	**6**	NS	NS	NS	T 5th	6th	DNL
	2nd line Metastatic Urothelial Carcinoma	**7**	4th	4th	4th	4th	5th	T 3rd
	1st line Metastatic Urothelial Carcinoma	**8**	5th	DNL	NS	NAB	DNL	NS
	2nd Line - Microsatellite Instability-High Cancer	**9**	NS	NS	NS	NS	NS	DNL
	3rd line Metastatic Gastric Cancer	**10**	NM	NM	NM	NM	NM	NM
	2nd line Cervical Cancer	**11**	NM	NM	NM	NM	NM	NM
	3rd line Primary Mediastinal Large B-Cell Lymphoma	**12**	NM	NM	NM	NM	NM	T 6th
	Adjuvant Treatment Melanoma	**13**	7th	7th	7th	T 5th	7th	T 6th
	Combination 1st Line Squamous NSCLC	**14**	8th	8th	8th	T 5th	8th	5th
	2nd Line Hepatocellular Carcinoma	**15**	NM	NM	NM	NM	NM	NM

	Metastatic Merkell Cell Carcinoma	**16**	NM	NM	NM	NM	NM	NM
Brentuximab vedotin	3rd line Hodgkin lymphoma	**1**	1st	T 1st	T 1st	T 1st	1st	T 2nd
	2nd line systemic anaplastic large cell lymphoma	**1**	2nd	T 1st	T 1st	T 1st	2nd	1st
	Classical Hodgkin lymphoma at high risk of relapse	**3**	NS	NS	3rd	NAB	3rd	T 2nd
	Primary cutaneous anaplastic large cell lymphoma	**4**	3rd	3rd	4th	3rd	T 5th	4th
	1st line classical Hodgkin lymphoma	**5**	NS	NS	INS	NAB	T 5th	NM
	1st line systemic anaplastic large cell lymphoma	**6**	NM	NM	NM	NM	4th	NM
Ipilimumab	Advanced melanoma	**1**	1st	1st	1st	1st	1st	1st
	Adjuvant treatment of melanoma	**2**	NM	NM	NM	NM	NM	NM
	Combination melanoma	**3**	2nd	2nd	2nd	NAB	2nd	2nd
	Combination renal cell carcinoma	**4**	3rd	3rd	3rd	3rd	3rd	3rd
	Combination Microsatellite Instability-High Cancer	**5**	NM	NM	NM	NM	NM	NM
Romidepsin	Cutaneous T-cell lymphoma	**1**	NM	NM	NM	NM	NM	NM
	Peripheral T-cell lymphoma	**2**	NM	NM	NM	NM	1st	DNL
Vemurafenib	Metastatic melanoma	**1**	1st	1st	1st	1st	NS	DNL
	Erdheim-Chester Disease	**2**	NM	NM	NM	NM	NM	NM
Lenvatanib	Thyroid cancer	**1**	2nd	1st	1st	1st	1st	1st
	Renal Cell Carcinoma	**2**	1st	3rd	INS	2nd	DNL	DNL
	Hepatocellular carcinoma	**3**	3rd	2nd	INS	NAB	2nd	2nd
Abiraterone Acetate	2nd line metastatic castrate-resistant prostate cancer	**1**	1st	1st	1st	1st	NS	1st
	1st line metastatic castrate resistant prostate cancer	**2**	2nd	2nd	2nd	2nd	1st	DNL
	Metastatic high-risk castration-sensitive prostate cancer	**3**	NS	3rd	3rd	3rd	NS	NS
Afatinib	1st line NSCLC	**1**	1st	1st	1st	1st	1st	1st
	2nd line NSCLC	**2**	NS	NS	INS	NAB	NS	DNL
Blinatumomab	R/R B-cell precursor ALL (Ph-)	**1**	1st	1st	1st	1st	1st	1st
	R/R B-cell precursor ALL	**2**	NS	2nd	2nd	2nd	NS	NS
	First or second complete remission B-cell ALL	**3**	2nd	3rd	NS	3rd	3rd	3rd
Enzalutamide	2nd line metastatic castrate-resistant prostate cancer	**1**	1st	1st	1st	1st	1st	1st
	1st line metastatic castrate resistant prostate cancer	**2**	2nd	2nd	2nd	2nd	2nd	DNL
	Castrate resistant prostate cancer	**3**	DNL	DNL	3rd	NAB	3rd	NS
Rucaparib	3rd Line Ovarian, Fallopian, Peritoneal Cancer	**1**	NS	NS	NS	NAB	NM	NM
	Maintenance treatment ovarian, fallopian, peritoneal Cancer	**2**	1st	1st	1st	NAB	NM	NM
Osimertinib	1st line NSCLC	**1**	1st	1st	1st	NAB	1st	1st
	2nd line NSCLC	**2**	DNL	DNL	2nd	1st	2nd	DNL

Crizotinib	2nd line NSCLC	**1**	2nd	1st	1st	1st	1st	1st
	1st line NSCLC	**2**	1st	2nd	2nd	2nd	NM	NS
	1st line NSCLC (ROS1 +)	**3**	3rd	3rd	3rd	NAB	2nd	2nd
Bosutinib	2nd Line Ph+ chronic myelogenous leukemia	**1**	1st	1st	1st	1st	1st	1st
	1st Line Ph+ chronic myelogenous leukemia	**2**	NS	NS	2nd	NAB	NS	NM
Alectinib	2nd line NSCLC	**1**	NS	NS	1st	1st	1st	1st
	1st line NSCLC	**2**	1st	1st	2nd	2nd	2nd	NS
Ceritinib	2nd line NSCLC	**1**	1st	1st	1st	NAB	1st	1st
	1st line NSCLC	**2**	2nd	NS	2nd	NAB	NS	NS
Ofatumumab	2nd line chronic lymphocytic leukemia	**1**	NM	NM	NM	NM	NM	NS
	Combination 1st line chronic lymphocytic leukemia	**2**	NM	NM	NM	NM	NM	1st
	Maintenance treatment chronic lymphocytic leukemia	**3**	NM	NM	NM	NM	NM	NM
	Combination 2nd line chronic lymphocytic leukemia	**4**	NM	NM	NM	NM	NM	NM

Abbreviations: ALL – acute lymphoblastic leukemia; NSCLC – Non-small cell lung cancer.. HNSCS – Head and Neck Squamous cell carcinoma.

Legend: NS = No submission (Indicates that no HTA decision was identified for this indication during the study period); NM = Not marketed (indication does not have marketing authorisation within respective jurisdiction); DNL = Do not list (HTA agency in England, Scotland, Canada or Australia issued a negative coverage recommendation), INS = Insufficient (The HAS in France gave an SMR rating of insufficient), NAB = No added Benefit (the G-BA in Germany gave a rating of no proof of added benefit).

4. HEALTHCARE PAYER PERSPECTIVES ON THE ASSESSMENT AND PRICING OF ONCOLOGY MULTI-INDICATION PRODUCTS: EVIDENCE FROM NINE OECD COUNTRIES[4]

[4] **Citation:** Mills M, Kanavos P. Healthcare Payer Perspectives on the Assessment and Pricing of Oncology Multi-Indication Products: Evidence from Nine OECD Countries. *Pharmacoecon Open.* *2*023 Mar 23. doi: 10.1007/s41669-023-00406-1.

ABSTRACT

Background: New pharmaceuticals are increasingly being developed for use across multiple indications. Countries across Europe and North America have adopted a range of different approaches to capture differences in the value of individual indications.

Objective: The three aims of this study were: 1) to review the price-setting practice over the past 5 years for multi-indication products across England, France, Italy, Spain, Belgium, Switzerland, Turkey, Canada and the USA; 2) to assess the impact of current practices on launch strategy; and 3) to identify issues in the implementation of indication-based pricing

Methods: Ten current and former members of health insurance organisations, healthcare payer organisations, or health technology assessment agencies with expertise on pharmaceutical purchasing were invited to participate in semi-structured interviews. Interview transcripts were imported into NVivo 12 for thematic analysis.

Results: The majority of countries studied require full assessments upon launch of a new indication. Five different approaches to pricing were identified: *weighted pricing, differential discounting, mandatory discount, price anchoring, and free pricing.* Manufacturers show a tendency to launch first in niche indications with high unmet need to achieve a high price. Stakeholders from England, France, Italy, Belgium, and Switzerland consider their current system fit-for-purpose, while other countries expressed concern over the administrative burden of monitoring products at indication level.

Conclusions: Given high administrative burden, it is questionable whether indication-based pricing would provide additional public benefit above and beyond current weighted dynamic single pricing and differential discounting practices for multi-indication products.

4.1 Background

Pharmaceuticals are increasingly being developed for use across multiple therapeutic indications [102, 157, 172, 173]. This has been particularly prevalent in the field of oncology, where improvements in our understanding of tumour pathology and molecular genetics have spurred the development of tumour agnostic therapies and where an increasing number of older non-oncology medicines are being repurposed as anti-neoplastic medicines [102, 157, 172]. In 2018, over two thirds of cancer drugs were approved for use across multiple indications [173]. Developing a product across multiple therapeutic indications or repurposing an older product for use in different patient populations can be considerably cheaper than developing a product from scratch, given that many early R&D activities only need to be performed once [103].

As multi-indication products have become more prevalent, questions have emerged on whether current regulations for the assessment, pricing, and reimbursement of pharmaceuticals are fit-for-purpose [62, 174]. It is generally accepted that the price of pharmaceutical should be linked to the value it provides [66, 175]. In the case of multi-indication products, the value of each respective indication can be variable, given differences in therapeutic effect, patient population, disease pathway, and standard of care. It follows that under single-pricing systems, where only a single price can be set per product, the incremental value that individual indications provide is disconnected from the price. Under single-pricing systems, firms may elect not to launch products with lower value to avoid price erosion in the higher value indication. Instead, economists argue that a system of price discrimination, or indication-based pricing, whereby a different price is assigned to each therapeutic indication, would maximise social welfare [64, 176, 177].

Countries across Europe and North America have adopted different value-based approaches to address the disconnect in value and price in multi-indication products, although no formal indication-based pricing systems have been implemented [65, 159]. France and Spain employ weighted pricing, whereby the price of product is renegotiated upon the launch of an additional indication for a previously reimbursed product [62, 66]. The renegotiated price represents the average price of the various indications, weighted according to disease prevalence. Within the UK, current regulations do not enable different prices at list price level. Differential discounting is possible whereby the confidential discount rate, and by extension the net reimbursement price, can vary at indication level [62, 66]. However, the current voluntary scheme for branded medicine pricing and access (VPAS) is largely regulated on a per-product basis (a product specific sales cap of £20 million applies) and the Department of Health expresses a preference against multiple net prices for a single medicine, due to the complexity it would create for the NHS [178]. The USA remains a single price per product system, whereby manufacturers can freely set the price of a product and payers have limited capacity to push back on prices [65]. Barriers to implementation of indication-based pricing in the USA include regulation around Medicaid best-price law and anti-kickback statutes, along with insufficient data systems for monitoring product use at indication level [61, 171]. The Medicaid best price law requires manufacturers to provide a product-specific rebate to state Medicaid programmes equivalent to either 23.1% of the average pharmacy retail price or to the "best price" in the event a discount offered by manufacturers exceeds 23.1%. No provisions currently exist for multi-indication products, meaning that an indication specific discount could trigger a new "best price". Further, it is unclear if indication-based pricing may violate antikick-back statutes, which prohibit the offering of renumeration to induce or reward prescription of medicines, due to concerns that manufacturers may "accept" the risk of off-label use of lower price indications to obtain coverage [61].

Despite an increasing number of publications on the pricing of multi-indication products, overall evidence on the subject remains scarce, both in terms of peer-reviewed literature and public documents [179]. A key gap is that the hypothetical scenarios describing single pricing systems evaluated in economic papers on indication-based pricing [62, 64, 157, 176, 177] do not accurately reflect current practices for pricing multi-indication products. While an indication-based pricing model maximises social welfare relative to a single pricing model that is anchored according to the price of a single indication, the social welfare implications of a dynamic weighted single pricing model or differential discounting model (indirect forms of indication-based pricing) have not been explored. Given widespread implementation of these measures for pricing multi-indication products [159, 179], it remains unclear if advocacy for formal systems of indication-based pricing, with different list prices for individual indications, is justified. On the other hand, recent analysis on a cohort of multi-indication oncology products has provided preliminary evidence that manufacturers show a tendency to sequence the development and launch of products according to clinical value and disease prevalence, highlighting the need to further explore the potential benefits of indication-based pricing over existing pricing practices for multi-indication products [180, 181]. This is an important finding given that the presence of previously launched indications has typically not been considered in empirical literature on pharmaceutical firm entry [59, 68, 71-73]. Overall, there is a lack of clarity on whether existing indirect indication-based pricing approaches adequately safeguard public and patient interest in the development and use of multi-indication oncology products and on the value and practicalities of implementing a more formal version of indication-based pricing.

This paper builds an analytical framework surrounding policy developments in multi-indication products and uses this framework to gather and present insights from current and former members of health insurance organisations and health technology assessment agencies

with expertise in pharmaceutical purchasing across nine OECD countries. In doing so, the objective of this paper is threefold: first, to review current practices (over the period of the past 5 years) of price-setting and paying for medicines with multiple distinct indications with emphasis on oncology; second, to assess the impact of said pricing practices on firm entry and the launch of multi-indication products; and third, to identify issues around the practicality of indication-based pricing implementation relating to political willingness, legal/regulatory structures, administration, and/or data infrastructure.

4.2 Methods

4.2.1 Analytical framework

The evidence informing this study is based on primary sources. To address the study objectives an analytical framework was created with associated endpoints which were separated into three groups: first, current practices for multi-indication products; second, impact of pricing regulation on manufacturer launch strategy; and third, future expectations on indication-based pricing. The analytical framework was jointly developed by study co-authors, based on identified gaps in existing literature on indication-based pricing. The identified endpoints are provided in **Table 4.1**, alongside brief definitions.

4.2.2 Semi-structured interviews

i) *Development of a semi-structured interview guide*

A semi-structured interview guide was developed to collect primary evidence on current assessment and pricing methods, monitoring challenges, industry launch strategy and

expectations for future reform on multi-indication products. Interview respondents were asked to predominantly consider assessment and pricing of multi-indication oncology products, however we're also invited to comment on pricing practices of multi-indication products in general. The interview guide consisted of 10 questions, as shown in **Table 4.2**.

ii) *Stakeholder Selection*

Current and former members of health insurance organisations, healthcare payers organisations or health technology assessment agencies responsible for pharmaceutical purchasing in 13 countries (France, England, Switzerland, Italy, Spain, Belgium, Germany, Russia, Poland, Turkey, Australia, the USA, and Canada) were invited to participate in semi-structured interviews. All experts identified had a minimum of 10 years of experience working on pharmaceutical policy and had extensive knowledge of pharmaceutical pricing and reimbursement practices in their respective settings. Specific candidates for participation were identified from our research group's network of affiliated institutions and pharmaceutical policy experts, which includes, among others, members from the EU funded ADVANCE HTA consortium, the IMPACT HTA consortium, and WHO Europe Collaborating Centres, along with contacts from health insurance/payers organisations and HTA agencies, stemming from several years of collaboration and work with these institutions (including a series of WHO Europe workshops on strategic procurement for innovative medicines, which were attended by representatives from health insurance organisations from over 21 EU members states).

Table 4.1 - Analytical Framework and Key Endpoints

Key Themes of Analytical Framework	Key indicators/endpoints	Aim of framework and associated indicators
Current Practices for Multi-Indication Products	▪ Assessment policy for multi-indication products ▪ Pricing and reimbursement policy for multi-indication products ▪ Monitoring capacity/Data infrastructure for multi-indication products	Discusses current approaches to the assessment, pricing, reimbursement, and monitoring of multi-indication products in order understand how countries manage the launch of an indication extension for a previously reimbursed product.
Impact on Manufacturer Launch Strategy	▪ Characteristics of first indications ▪ Withholding of indications	Assesses the impact of current practices on manufacturer launch sequence through an examination of whether notable differences are present between the first indication to launch for a product and subsequent indications and whether there is evidence of developed indications being withheld from the market.
Future Expectations on Indication-Based Pricing	▪ Performance of current system ▪ Barriers to implementation of Indication-Based Pricing	Examines whether current pricing practices generate perverse incentives for launch sequencing, whether they adequately safeguard patient and public interests in the development and use of multi-indication products and whether there is scope and interest to move towards an indication-based pricing model.

Table 4.2 - Semi-Structured Interview Guide

Indication-Based Pricing – Semi-Structured Interview Guide
1. How does your country conduct HTA for/assess indication extensions? Does each indication require a full submission and evaluation? 2. How does your country deal with pricing for multi-indication products? a. Is it possible for a molecule to have multiple list prices for different indications? What about products with different brand names? b. If you are not making provisions for different list prices, do you differentiate between indications at reimbursement level with different reimbursement strategies, including different prices? 3. Do you apply a weighted pricing model for multi-indication products, whereby the price for a molecule is adjusted when a new indication launches? Can you explain the procedure for adjusting the price when a new indication is launched? Is weighting based on expected disease prevalence or based on market share? In practice does the price change significantly upon launching a new indication? Can the price ever increase following launch of a new indication? Have companies ever withdrawn/not launched an indication due to disagreement over the adjusted price? 4. Does your country apply differential discounting for multiple indications of a molecule? Are there any challenges in terms of reimbursement with different confidential prices by indication? 5. Has your country implemented any outcomes-based payment arrangements for multi-indication products? Can effective outcomes-based payments models eliminate the need for indication-based pricing? What are the key barriers associated with implementing outcomes-based payment models? 6. Are you in a position to monitor with a good degree of accuracy the prescribing and utilisation of the same molecule across different indications? Are you facing any challenges there? 7. Do you think the current pricing and reimbursement system is fit-for-purpose with multi-indication products in your country? Can you provide any examples where the current system hasn't worked? Do you believe the current system incentivises launch sequencing or decisions to withhold authorised indications of a product? If so, why? Is there any desire to move towards an indication-based pricing model or approach if you haven't one already? 8. Considering a molecule with multiple indications, do you have an opinion on what kind of characteristics would the first indication have that is submitted to your country for assessment? (probes can be rarest, most high-priced, highest unmet need/no available therapies, severe condition, etc) 9. Considering a molecule with multiple indications, do you apply different pricing and reimbursement procedures for a) products with multiple indications across different therapeutic areas (E.g. ophthalmology and cancer), b) products with multiple indications across different diseases within a broader therapeutic area (E.g. melanoma vs lung cancer), or c) products with multiple indications across different lines of therapy within a defined disease (e.g. 1st vs 2nd line treatment for advanced metastatic prostate cancer)? **10.** What are the key challenges and barriers associated with implementing an indication-based pricing model in your country?

Abbreviations: HTA – Health Technology Assessment

A total of two experts from each country were identified and invited to participate. Countries were selected to include: a) both high- and middle-income countries; b) countries with large and small populations; and c) countries with different health financing systems. Invitations for interviews were sent between April 2020 and June 2020.

iii) *Data collection*

Interviews were conducted between June 2020 and October 2020. All interviews took place virtually using Zoom software. Interview respondents were provided with a participant information sheet and were asked to sign a consent form in advance of the interviews. All interviews were anonymised to protect the identity of respondents. The evidence collected represent the views of the individual stakeholders participating, rather than official positions of healthcare organisations within included settings. The duration of interviews was 45 minutes to 60 minutes. All interviews were recorded to facilitate transcription and analysis of the results. Prior to interviews, the research methodology was subject to standard institutional ethics review processes. No significant ethical issues were raised by the research.

iv) *Data analysis*

All interview recordings were transcribed using Rev transcription service (https://www.rev.com). Interview transcripts were imported into NVivo 12 for coding and thematic analysis. Interview text was coded according to the research endpoints outlined in the analytical framework and insights were analysed across three main themes:

The first theme related to current practices in the assessment, pricing, and monitoring of multi-indication products**.** The assessment of multi-indication products was coded in terms of whether differences exist across original indications and indication-extensions in the

requirements for health technology assessment. Pricing was coded in terms of whether a setting employs indication-based pricing, weighted pricing, differential discounting, a single pricing model or an alternative pricing scheme for multi-indication products. Additional codes were assigned based on whether price increases can occur following the introduction of a new indication with higher effectiveness. Monitoring was coded in terms of how effectively a country can monitor a product's use at indication level (low, medium, high, or very high). A country with low monitoring capacity has no ability to differentiate the use of a product across different therapeutic indications. A country with very high monitoring capacity routinely and actively collects data on the use of a product at indication level.

The second theme related to perspectives on launch strategy and characteristics of first indications. Characteristics of first indications was coded in terms of the salient features of the first indication to launch, including disease prevalence, disease severity, price, unmet need, or disease stage. Additional codes were assigned for evidence of withholding the launch of subsequent indications.

Finally, the third thematic area focused on future expectations for pricing of multi-indication products. Performance of the current system was coded in terms of whether current pricing practices are fit-for-purpose for multi-indication products. Specifically, this relates to the extent to which current pricing practices: a) adequately capture the incremental value of multi-indication products; b) generate perverse incentives for manufacturers in terms of the development and launch of multi-indication products; and c) adequately safeguard patient and public interests in the development and use of multi-indication products. Barriers to implementation of indication-based pricing were coded in terms of feasibility, technical/legal requirements, and willingness to implement.

4.3 Results

4.3.1 Interview results

A total of ten experts across nine countries accepted invitations for semi-structured interviews. The countries included in analysis are England, France, Spain, Italy, Belgium, Switzerland, Canada, the USA, and Turkey. Two expert stakeholders from the USA were interviewed.

4.3.2 Assessment, pricing and monitoring of multi-indication products

Most countries conduct full HTA assessments for indication extensions of a previously reimbursed molecule. England, France, Italy, Spain, Belgium, Switzerland, and Canada all employ HTA as a key tool for informing pricing and reimbursement decisions and require separate evaluations for each approved therapeutic indication for a given molecule (See **Table 4.3**). Each assessment is conducted independently of previous submissions. Each indication is evaluated on the merits of the clinical and economic evidence submitted against the relevant standard of care within the defined therapeutic indication.

Table 4.3 - Current Practices for the Assessment and Pricing of Multi-Indication Products

Countries	Do new indications require full HTA submissions?	Pricing method for multi-indication products	Ability to monitor product use at indication level?	Can price increase upon launch of a new indication?
England	Yes[1]	*Differential discounting: A* separate PAS can be negotiated for each indication	Medium	Free pricing subject to NICE threshold and VPAS threshold
France	Yes	*Weighted pricing:* Price renegotiated based on ASMR, price of standard of care and prevalence	Medium	In theory, but no examples identified
Italy	Yes	*Mandatory discounts[2]:* New indications are subject to existing price volume agreements or must renegotiate the discount rate	Very High	Mandatory price cuts based on added revenue
Spain	Yes	*Weighted pricing:* Reimbursement price renegotiated based on price of competitor and prevalence	High	In theory, but no examples identified
Belgium	Yes	*Weighted pricing:* Renegotiation of list price or of terms of conditional reimbursement	Very High	In theory, but no examples identified
Switzerland	Yes	*Differential discounting:* A single list price applies, but indications can be reimbursed at different rates.	Very High	In theory, but no examples identified
Turkey	No	*Price set by first indication[3]*	Medium	No
USA	No	*Free pricing:* PBM discounts may be renegotiated	Low	Free pricing
Canada	Yes[1]	*Weighted pricing:* Price renegotiated at provincial level following CADTH assessment of new indication	High	In theory, but no examples identified

1 Pricing and reimbursement can technically be negotiated prior to HTA evaluation but uptake is low

2 Discount level determined through deliberative process which considers level of unmet need, added clinical value, and quality of evidence.

3 Products under the alternative reimbursement pathway may be eligible for price renegotiations

Abbreviations: ASMR – Improvement in medical benefit rendered (France), CADTH – Canadian Agency for Drug Technology Assessment, HTA – Health Technology Assessment, NICE – National Institute of Health and Care Excellence (England), PBM – Pharmacy Benefit Manager (USA), VPAS – Voluntary Pricing and Access Scheme

Five different approaches to the pricing of multi-indication medicines were identified across the included countries:

France, Spain, Belgium and Canada employ *weighted pricing*, whereby the price of a molecule is renegotiated upon launch of a new indication. Within France, the Transparency committee in Haute-Authorite Sante (HAS) conducts HTA on all newly approved therapeutic indications (both original indications and indication extensions). The Transparency Committee assigns a benefit rating (Medical Service Rendered – SMR), which determines the reimbursement rate for an indication and assigns an added benefit rating (Additional Medical Service Rendered – ASMR), which is used by the French medicine pricing committee (CEPS) to inform price negotiations. Within Spain, The Spanish Agency of Medicines and Medical Devices (AEMPS) conducts a clinical assessment of all new indications and produces a therapeutic position report (IPT). The Inter-Ministerial Pricing Commission negotiates both the official list price for a medicine and the discounted reimbursement price based on the IPT. Within (Belgium), the reimbursement committee within the National Institute for Health and Disability (RIZIV-INAMI) assesses all new therapeutic indications and provides a reimbursement recommendation to the Minister of Social Affairs. The Minister of Social Affairs makes a final decision on the reimbursement and sets the reimbursement price. In Canada, the Canadian Agency for Drugs and Technologies in Health assesses newly approved therapeutic indications (CADTH) and issues reimbursement recommendations. Provincial reimbursement committees undertake pricing negotiations with manufacturers for each therapeutic indication.

England and Switzerland employ *differential discounting* models, whereby different discount rates can be negotiated for each individual indication. Within England, the National Institute of Health and Care Excellence (NICE) conducts HTA on newly approved therapeutic indications (both original indications and indication extensions) and makes reimbursement recommendations to NHS England. Reimbursement recommendations are frequently

conditioned on indication specific patient-access schemes negotiated between the manufacturer and NHS England, which may involve confidential discounts or other financial agreements. Deviations from uniform net pricing are typically reserved for cases where the level of clinical effectiveness is highly variable across indications. Differential discounts, when implemented, result in different net prices which can either be achieved through indication-specific procurement processes or through ex-post rebates based on tracking of product use at indication level. Within Switzerland, the Federal Office of Public Health (BAG) assesses products approved by SwissMedic for inclusion on the positive reimbursement list. The assessment from the Federal Office of Public Health is subsequently appraised by the Federal Drug Commission (FDC), which provides a recommendation to the BAG on three criteria ("WZW" criteria: appropriateness, effectiveness, and cost-effectiveness). Effectiveness relates to the scientific evidence base of the product and includes assessment of both the clinical evidence considered in Swissmedic approval and real-world evidence. Both the total benefit of the product and the relative clinical benefit of the product are considered. Appropriateness relates to all pharmacological and formulation aspects of the product (e.g. packet size). Cost-effectiveness or economic efficiency relates to the economic impact of funding a technology within the Swiss health insurance system in terms of opportunity cost, budget impact and efficiency). The BAG then makes a final determination on pricing and reimbursement based on these recommendations and negotiations with the manufacturer.

In Italy, launch of a subsequent indication is now subject to a *mandatory price discount*, proportional to the increase in patient population. The specific level of discount is subject to a deliberative process which considers three criteria: a) unmet need, b) added clinical value, and c) quality of evidence. Indication extensions which address an unmet medical need, have high therapeutic value, or launch in a niche indication may receive minimal or no discounts on the net product price. Conversely, competition (either currently available alternatives or

competitors in development), marginal added clinical benefit, low quality of evidence, and high disease prevalence will increase the level of discount required. The scientific committee (CTS) within the Italian Medicines Agency (AIFA) assesses the unmet need, added clinical value and quality of evidence for all newly approved therapeutic indications. The CTS provides recommendations to the price reimbursement committee (CPR) which has the mandate to conduct pricing negotiations. Italy has the capacity to implement unique risk-sharing schemes at indication-level, however, has begun to shift away from this practice in favour of simpler financial agreements.

In Turkey, *prices are anchored by the first indication* assessed and approved for reimbursement. The launch of a new indication does not trigger a price revision. The Social Security Agency (SGK) assesses newly approved drugs for reimbursement following regulatory approval by the Ministry of Health. There are two routes for reimbursement. Pricing under the general procedure requires a statutory discount of 40% on the retail price of the drug (determine through external reference pricing). Recently, an alternative reimbursement mechanism was implemented (predominantly for very expensive drugs) which allows companies to negotiate confidential discounts or risk sharing schemes with the SGK.

The USA operates predominantly under a *free pricing* model as payers have limited capacity to push back on the prices of drugs. The USA healthcare market is highly fragmented with a range of public and private health insurers. HTA is not formally used within the USA to inform pricing and reimbursement of pharmaceuticals. Publicly funded plans include Medicare (for adults above the age of 65), Medicaid (for low-income adults and families), and the Veterans Health Administration. Nearly 70% of the population is covered through private insurance plans. Reimbursement and pricing criteria for pharmaceuticals vary across insurance plans. While list prices are set freely, pharmacy benefit managers can negotiate confidential discounts with manufacturers in private insurance markets and legislation ensures Medicaid and VA

prices represent a price floor. These price floors are set at molecule level, according to the national drug code. In theory, PBM discounts may be renegotiated upon launch of a new indication through a weighted pricing approach, although this is not routinely done. It may also be possible for manufacturers to obtain separate drug codes, provided a product is launched under different brand. This is likely only feasible for products with multiple indications across different therapeutic areas (e.g. older non-oncology medicines repurposed as anti-neoplastic agents with new brand names).

Countries vary significantly in their capacity to monitor product at use at indication level. Italy, Belgium and Switzerland have very high capacity to monitor product use at indication level. Healthcare systems have extensive digital infrastructure which enables routine collection of prescribing data, including detail on the specific use of indications. Canada and Spain also have a high ability to monitor product use at indication level, however some disparities are present across provinces/regions. France, England and Turkey have established eprescribing infrastructure, but interview respondents indicated limitations in accessibility, extent of use, accuracy of information and/or granularity of information. Within the NHS England, central logging of sales only includes data on drug name and dosage, although separate datasets may facilitate tracking of product use at indication level for specific therapeutic areas. Within the USA, eprescribing infrastructure is in place (e.g. transactional databases for commercial plans and Medicare part D). However, data is not recorded and collected in a way to enable monitoring of products at indication level. Changes in legislation would be needed enabling drug codes to be assigned at indication level or enabling greater granularity in the collection of prescribing data.

No examples of prices increasing upon launch of an indication extension were identified across the included countries. In theory, weighted pricing systems (France, Spain, Belgium, and Canada) allow for an increase in price if a subsequent indication achieves a higher price than the first indication. An increase in price is also possible in Switzerland, although in practice separate prices are only given to indications if the subsequent indication has a lower therapeutic value. Within England, manufacturers can set prices freely as long as they meet NICE cost-effectiveness requirements and the Voluntary Scheme for branded medicines (VPAS) requirements, but it is unlikely for the overall list price of a molecule to rise after commercial access agreements have been agreed for original indications. Within Italy, indication extensions trigger a mandatory discount. It is possible for the price to stay flat if the disease prevalence of the subsequent indication is very small or if high unmet need and therapeutic advantage is demonstrated. In Turkey, the price is set based on the first indication and is unlikely to change upon launch of a subsequent indication. In the USA, manufacturers may raise the list price of products freely and this process is independent of the launch of new indications. In theory, the net price of a product negotiated with PBMs could increase upon launch of a new indication, but no examples were identified.

4.3.3 Perspectives on launch strategy and characteristics of first indications

All countries identified highest price as the defining characteristic of first indications launched for multi-indication products (See **Table 4.4**). The majority of interviewees identified a tendency for first indications to be for smaller populations (England, France, Spain, Italy, Switzerland, USA, Canada). Additional characteristics of first indications identified include highest clinical effectiveness (France, USA), high unmet need (England, France, Switzerland, Turkey, USA), highest disease prevalence (Turkey) and late-stage disease (England).

Three interviewees (France, Italy, Belgium) identified instances where no agreement could be reached on the pricing and reimbursement of an indication extension, leading to a manufacturer electing not to launch a specific indication. However, each country expressed that the withholding of indications would typically only occur when there were concerns over the therapeutic benefit and the patient population had alternative treatment options. Interviewees from France, Italy, and Belgium all expressed confidence that the current pricing and reimbursement system would facilitate access for indications that had significant therapeutic advantages over the current standard of care.

Table 4.4 - Payer Perspectives on the Characteristics of First Indication Launched for Multi-Indication Oncology Products

Characteristics of first indication									
Highest price	✓	✓	✓	✓	✓	✓	✓	✓	✓
Highest clinical effectiveness		✓						✓	
Small population	✓	✓	✓	✓		✓		✓	✓
High disease prevalence							✓		
High unmet need	✓	✓				✓	✓	✓	
Late-stage disease	✓								

4.3.4 Future expectations for pricing of multi-indication products

The majority of interviewees considered their current system fit-for-purpose for the pricing and reimbursement of multi-indication products (England, France, Italy, Belgium, and Switzerland) (See **Table 4.5**). In France, Belgium and Italy, interviewees expressed confidence that weighted pricing models sufficiently capture the incremental value of indications and facilitate access to therapeutic indications that offer true therapeutic advantages. Within England and Switzerland, interviewees expressed confidence that differential discounting methods adequately capture the incremental value of subsequent indications in cases where there are substantial differences across indications.

All interviewees indicated that a key barrier to implementation of indication-based pricing was administrative complexity. While many countries have high capacity to monitor product use at indication level, these countries still express a preference for administrative simplicity. In other countries (England, France, USA), improvements to monitoring capacity would be needed to facilitate indication-based pricing. Another common barrier to implementation identified was difficulty in payment and distribution (England, France, Spain, Italy, Belgium, USA, Canada). Currently, most payment and distribution systems for medicines do not differentiate according to indication use. Many countries use wholesalers to help distribute medicines. While it may be possible to have indication-specific prices if different formulations/brands were used across indications (e.g. for older non-oncology medicines repurposed as anti-neoplastic agents), current systems would not be able to accommodate different prices for different uses of the same formulation (which is frequently the case for tumour agnostic medicines). Parallel trade and off-label use would be difficult to prevent. Additional barriers to implementation included issues with regulatory/legal structure (England, Turkey, USA), and ethical issues for prescribers/patients (France, Spain, Belgium, USA, Canada).

Table 4.5 - Barriers to Implementation of Indication Based Pricing

Barriers to implementation of IBP									
Current system fit-for-purpose / IBP not needed	✓	✓		✓	✓	✓			
Regulatory/legal structure	✓						✓	✓	
Preference for administrative simplicity	✓	✓	✓	✓	✓	✓	✓	✓	✓
Difficulty in monitoring indication use	✓	✓						✓	
Difficulty in payment and distribution	✓	✓	✓	✓	✓			✓	✓
Ethical issues for prescribers/patients		✓	✓		✓			✓	✓

Abbreviations: IBP – Indication-based pricing

4.4 Discussion

The current pricing and reimbursement environment for multi-indication products is highly dynamic. Most health systems considered (France, Belgium, Spain, Italy, England, Canada, and Switzerland), routinely assess the incremental value of new indications and have methods of capturing this value in their pricing system, either through differential discounting or through weighted pricing, consistent with pricing approaches described in a recent systematic review [179]. Even within the USA, pharmacy benefit managers can engage in a "weighted pricing" like model, by renegotiating discounts upon launch of a new indication. This is despite broader issues in the public and private pricing system including the inability for the government to negotiate on Medicare prices, the inflexibility created for contracting due to the Medicaid best price law, and the dynamic between pharmacy benefit managers and manufacturers which has led to consistent price increases to offset confidential discounts.

Two notable exceptions to currently published descriptions of pricing for multi-indication products are the UK and Italy. Within Peckler et al. it was reported that PAS in the UK are negotiated at molecule level and do not support indication-based pricing mechanisms, while our expert reports that PAS are indication and patient group specific [179]. This is consistent with the language in the current VPAS: "In cases where uniform pricing would lead to a reduction in total revenue for a medicine overall from the introduction of additional indications, other forms of commercial flexibility may be considered for medicines with a strong value proposition. In these cases, commercial flexibility would only be considered where the level of clinical effectiveness is highly differentiated, but substantial in all indications under consideration." [178]. Further, while Italy is correctly described as having the legislative capacity and data infrastructure to support indication-specific managed-entry agreements, the finding that they are moving away from value-based indication-specific models towards simple financial models is extremely pertinent in the debate on indication-based pricing. Despite

considerable capacity and experience in managing pharmaceutical purchasing at indication level, a shift towards administrative simplicity is consistent with the over-arching trend in preferences of payer stakeholders in the present study and may be interpreted to represent a shift away from value based-pricing (although unmet need, therapeutic advantage and quality of evidence still play a key role in the deliberative process in Italy).

A primary aim of pharmaceutical policy is to promote timely, equitable, affordable and sustainable access to effective medicines [175]. Policy makers must balance the short-term goal of promoting widespread access to currently available treatment with long term global R&D priorities and the need to develop further treatments for diseases with unmet need [161]. Value-based pricing, or ensuring the price paid for a medicine reflects the value it provides, falls at the intersection of these two objectives. This is provided that sufficient mechanisms are in place to promote widespread access following expiration of intellectual property rights, whereby prices should converge towards marginal cost of production. In the short term, effective value-based pricing helps to ensure that value delivered to patients is maximised given a budget constraint. In the long-run, value-based pricing sends signals to manufacturers and helps align R&D incentives with value. A key policy question emerging from this research is whether a formal indication-based pricing model would achieve these objectives over and above current practices for price setting of multi-indication products including dynamic weighted single pricing models and differential discounting approaches?

Despite indications from several countries that current systems are fit-for-purpose, interview respondents also indicated that these systems generate incentives to sequence or withhold the launch of indications, a finding which is aligned with empirical research on the development and launch of multi-indication products [180, 181]. Proponents of indication-based pricing argue that single price systems may generate perverse incentives not to develop and launch medium or low value indications to avoid price erosion in high value indications [176, 177].

In theory, effective implementation of a dynamic weighted single pricing system or differential discounting addresses this issue by aggregating the incremental value of indications or by facilitating different net prices per indication through confidential discounts. In practice, current systems still incentivise prioritisation of the development and launch of niche indications with high unmet need to obtain a high price for the initial indication. There are several possible explanations for this discrepancy, with important implications in terms of the extent to which existing practices protect overall patient and public interests in oncology treatment development and use.

First, it is possible that current pricing and reimbursement methods are not accurately capturing the incremental value of indications. Weighted pricing relies on the ability to accurately forecast use of a product or the means to retrospectively adjust the price based on actual usage of a product across indications. Currently, weighted pricing models predominantly rely on the former method. Many factors influence ability to forecast usage correctly, including the presence of competitors, changes in patient demographics and poor data infrastructure [182]. Manufacturers may be reluctant to accept a reduction in price through launch of a new indication if there is uncertainty over usage.

Second, it is notable that no examples of price increases where identified, despite increases being theoretically possible. Perceptions of "price stickiness", or the presence of price ceilings may contribute to launch prioritisation of indications that are most likely to achieve the highest price. Within Italy, indication extensions are subject to a mandatory price cut (depending on the level of unmet need, therapeutic advantage, and quality of evidence) that is proportional to the increase in patient volume, such that the payers capture a portion of the increase in revenue.

Third, it is possible that differences in the characteristics of first and subsequent indications are a product of standard R&D strategic decision-making. Launch of an indication is not the result

of a single decision, but rather a series of decisions throughout the various stages of clinical research and development. Given high costs and risks associated with drug development, firms are likely to prioritise development of indications with the highest perceived value and likelihood of success based on early clinical evidence and market projections. By extension it is possible that the highest perceived value indication would be prioritised under both single-pricing and indication-based pricing models.

A separate issue relates to the withholding of indication extensions when no agreement can be reached on pricing and reimbursement. The withholding of indications signals an access failure and disconnect between payers and manufacturers on the value of product within that indication. Interview respondents highlight that the non-launch of an indication typically only occurs when alternative treatment options are available to patients. While disagreements between payers and manufacturers on the value of a product is not unique to multi-indication products, concerns over price erosion of previously reimbursed indications may play a role in the process [66].

Although a formal indication-based pricing could help to address some of the challenges described above, R&D prioritisation of high value indications and disconnects in the value between payers and manufacturers would likely still occur. Willingness to implement a formal indication-based pricing model was low across the studied countries. In some settings (USA, UK, France), data infrastructure and regulatory/legal hurdles represent significant barriers to implementing indication-based pricing, including but not limited to the Medicaid Best Price law (USA) and the Voluntary scheme for branded medicines pricing and access (UK) . In other settings (Italy, Belgium, Switzerland) where monitoring capacity was high and no significant legal or regulatory barriers were identified, implementation of indication-based pricing is still unlikely as payers have expressed a clear desire to avoid administrative burden. Overall, given

the perception of only marginal potential benefits over existing practices and significant barriers to implementation, it is highly unlikely that a formal system of indication-based pricing will be implemented in the near future.

The reluctance to adopt indication-based pricing and, by extension, the low likeliness of seeing formalised indication-based pricing models in the near future, has important potential implications for patients. While healthcare payers may be convinced that current pricing practices adequately safeguard patients against the non-launch of a subsequent indications, given the perception that this typically only occurs if therapeutic alternatives are available, this finding should be validated in future empirical research exploring the conditions surrounding the withholding of indications or non-reimbursement of indications. Importantly, even in the absence of added clinical efficacy, there is value in having multiple treatment options with different tolerability profiles, particularly in oncology where treatments can have severe adverse event profiles [183]. Further, we cannot discount the possibility that the current environment for pricing multi-indication products may fail to generate optimal R&D incentives (although this may be less of a priority in smaller markets) and that some development programmes may not be initiated or may be terminated prematurely due to concerns over price erosion at molecule level. While recent literature has provided us with insights on how frequently multi-indication products are approved at HTA level [181], future research on the conditions surrounding termination of development programmes prior to marketing authorisation would be of value.

Strengths and Weaknesses

This study relies on perceptual analysis of 10 former and current senior members of health insurance organisation, health payor organisations, and health technology assessment agencies with expertise on pharmaceutical purchasing. Adopting a semi-structured interview approach

with senior experts in pharmaceutical policy and purchasing enabled an in-depth exploration of the challenges presented by multi-indication products, approaches taken to mitigate these challenges, and the practicalities of implementing more formal indication-based pricing systems.

The present study is not without limitations. First, participation was limited to a single participant in all but one country. The results presented represent the subjective views of the individuals, rather than official positions of health insurance organisations, health payor organisations and health technology assessments. This reflects the required level of expertise (10 years of experience working in pharmaceutical policy) and the nature of the topic (while the proportion of products with multiple indications is increasing, pricing of products with multiple therapeutic indications remains a niche topic). Second, the study scope was restricted to health insurance and health technology assessment stakeholders. While these actors are potentially in the greatest position to comment on whether indication-based pricing would provide net additional value over and above existing pricing practices, it would be of interest to expand analysis to other stakeholder groups including patients, physicians, pharmacists, manufacturers, and regulators. Third, the characteristics of first vs subsequent indications reflect the subjective opinion of interviewees on the effects of current pricing practices, rather than an objective measure of the characteristics of first vs subsequent indications. Objective evaluations of these characteristics have been performed in other studies [180, 181]. Finally, the issue of combination pricing was not explored during interviews or throughout the study. Within oncology, the optimal therapeutic strategy may involve a combination therapy. Combination therapies are associated with a unique set of challenges from a pricing and assessment perspective. Most notably: a) it may be difficult to attribute the individual contribution of each component of the combination to the overall therapeutic value; and b) combination therapies involving multiple in-patent medicines often fail to reach cost-

effectiveness requirements and may require substantial discounts. In this context, implementation of pricing systems that can support multiple prices by product use (either list or net) may be required to facilitate access [184]. As such, it is possible that there are additional benefits to indication-based pricing, that may not have been fully considered by interview respondents in the context of multi-indication products.

4.5 Conclusion

Current price-setting practices for multi-indication products include weighted pricing, differential discounting, mandatory discounting, single pricing, and free pricing. The majority of countries studied actively capture the incremental value of individual indications through assessment and pricing processes. Interview respondents, perhaps by nature of their direct experience in managing complex managed entry agreements, stressed the need for 'practicality' in managing the introduction of multi-indication products. Overall, respondents predominantly questioned whether an indication-based pricing system (if any) is likely to provide significant benefits above and beyond current practices for the pricing and reimbursement of multi-indication products. Even in settings capable of managing data infrastructure, supply chain issues, and legal/regulatory hurdles, there is poor willingness at payer level to take on the administrative burden associated with monitoring products at indication level.

5. HTA BARRIERS FOR CONDITIONAL APPROVAL DRUGS[5]

[5] Mills, M. HTA Barriers for Conditional Approval Drugs. *PharmacoEconomics* (2023). https://doi.org/10.1007/s40273-023-01248-9

ABSTRACT

Introduction: Conditional approval pathways facilitate accelerated marketing authorisation based on immature clinical evidence for drugs that address an unmet medical need in a life-threatening or chronically debilitating condition. Lowering evidence requirements for marketing authorisation results in higher clinical uncertainty, which may present challenges for the health technology assessment of these products.

Objectives: The objective of this study is to assess whether conditionally approved drugs face higher probabilities of HTA rejection or delays in HTA approval relative to drugs with standard marketing authorisation.

Methods: This paper adopts a mixed-methods approach to provide a meta-analysis of HTA outcomes across 80 drug-indication pairs in France, England, Scotland, and Canada. Differences in the characteristics (i.e. disease rarity and clinical trial design) of conditionally approved drugs and drugs with standard marketing authorisation and drivers of HTA outcomes are assessed through logistics regression. Delays in HTA approval are assessed through survival analysis.

Results: Relative to standard approval drugs, conditionally approved drugs are less likely to include phase III trial designs, less likely to include clinical endpoints, and less likely to include an active comparator. Uncertainties in clinical and economic evidence are raised more frequently by HTA agencies for conditionally approved drugs, which have a marginally lower probability of receiving HTA approval relative to drugs with standard approval. Conditionally approved drugs face moderate delays (an average of 6 months) in receiving HTA approval relative to standard approval drugs.

Conclusion: Overall, conditionally approved drugs likely face increased barriers at HTA level.

KEY POINTS FOR DECISION-MAKERS

- Conditionally approved drugs have high levels of unresolved clinical uncertainties related to the magnitude of clinical benefit, appropriateness of clinical trial design, and adverse event profile.

- Conditionally approved drugs likely face a slightly increased probability of receiving a negative HTA outcome.

- Delays in HTA approval were identified for conditionally approved drugs, although the extent of delay varies across settings.

5.1 Introduction

Firm entry in the pharmaceutical market, and by extension diffusion of innovative medicines to patients, is heavily influenced by the presence and structure of regulatory institutions [22]. In an increasing number of settings globally, innovative medicines must pass through two key milestones before adoption into a healthcare system: marketing authorisation (MA) and health technology assessment (HTA) [26, 67]. Marketing authorisation review is undertaken by regulatory institutions such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration in order to confirm that drugs have a positive benefit-to-risk ratio (i.e. that they are safe and efficacious for human use) [185]. HTA agencies on the other hand, such as the National Institute of Care and Health Excellence (NICE) in England, evaluate the relative clinical and, in some instances, economic effectiveness of a drug in or order to inform resource allocation decisions [145, 186].

The presence of two sets of institutions with distinct objectives increases the transaction costs firms face in overcoming regulatory hurdles [24, 25]. Within the pharmaceutical market, institutional alignment (between MA and HTA agencies) is inversely correlated with transaction cost (i.e. the cost associated with research and development) [67]. Strong alignment between marketing authorisation agencies and HTA agencies on evidence requirements reduces firm evidence generation costs, while poor alignment increases costs.

Potential issues arising from institutional alignment are well illustrated by the case of conditional approval pathways. Conditional approval pathways, a type of marketing authorisation, provide medicines with provisional authorisation in an effort to reduce regulatory delays in instances where medicines address an unmet medical need in a serious, life-threatening or chronically debilitating disease [96, 153]. Approval is granted on the basis of pre-mature or early phase clinical evidence on the condition that evidence generation is

completed post-authorisation; effectively shifting the evidence generation transaction cost from pre-approval to post-approval [28]. Depending on how stringently post-marketing requirements are enforced, transaction costs may be lower; recent research on FDA accelerated approval drugs identified several instances where confirmatory trials were never completed [139].

The extent to which firms benefit from this shift, and by extension the extent to which conditional approval policies achieve their intended effect of accelerating access to drugs that address an unmet medical need, is contingent on whether firms meet evidence requirements at HTA level. However, HTA outcomes and approval timelines for conditionally approved oncology drugs in Europe are extremely fragmented [14].

Fragmented HTA outcomes have important consequences for public health, leading to differences in patient access and time to access of medicines across settings [187, 188]. Differences in HTA methodology across agencies may account for some of the heterogeneity, leading to differences in the interpretation of evidence [21, 39, 189]. Magnitude of clinical efficacy, clinical trial design, disease area and cost-effectiveness, have all been reported as significant determinants of HTA outcomes in single-setting analyses [17, 53-56, 190, 191]. More recently, some empirical studies have attempted to explain difference HTA outcomes across settings through mixed-methods approaches [192, 193], although findings are limited by sample size and the difficulty of quantitatively assessing HTA coverage decisions.

This study has the following objectives:

1) To compare and contrast the health technology assessment of drugs that have received conditional marketing authorisation relative to those that have received standard marketing authorisation.

2) To examine whether differences in the quality and strength of evidence of conditionally approved drugs and standard approval drugs lead to a higher probability of HTA rejection or delays in HTA approval.

Existing literature on conditional approval pathways has predominantly focused on characterising levels of clinical evidence [30, 137, 194, 195], clinical development and approval timelines [29, 137], post-approval safety warnings [138, 196] and completion of confirmatory studies [139, 196, 197]. A small body of literature has begun to explore HTA decision-making on conditionally approved drugs, focusing on single setting evaluations of conditionally approved medicines [198, 199], descriptive analysis of HTA timelines and outcomes [14], and the impact of study design [142] and post-approval studies [200] on HTA outcomes in Europe. The scope of these studies was restricted to conditionally approved drugs, limiting our understanding of whether these drugs face barriers at HTA level over and above drugs with standard marketing authorisation. The present study provides an empirical analysis comparing HTA decision-making on a cohort of conditionally approved and standard approval drugs.

5.2 Methods

This research was undertaken as a follow-up to the IMPACT-HTA Horizon 2020 project [201] as part of a team of researchers tasked with developing methodology on clinical and economic evidence uncertainties in the context of HTA.

5.2.1 Conceptual framework

We employ a mixed-methods approach to the data-collection and meta-analysis of HTA outcomes [39], which accounts for differences in the type of evidence submitted, the

interpretation of evidence, and the impact of interpretation on the final recommendation. The mixed-methods approach involves two stages. In the first stage, publicly available HTA decision reports are qualitatively analysed in order to collect data on the evidence submitted to HTA bodies (both clinical and economic), the interpretation of the evidence from HTA bodies (including the scientific and the social value judgments made) and to identify components of uncertainty as well as elicited and non-elicited additional considerations that may have played a role in the assessment/appraisal process for each drug-indication pair. In the second stage, quantitative analysis is performed to identify key drivers of HTA decision-making. **Table 5.1** provides a conceptual framework which informs model specification.

Table 5.1 - Conceptual Framework for Empirical Analysis of HTA Outcomes

	Negative Effect on HTA Outcome	Ambiguous Effect on HTA Outcome	Positive Effect on HTA Outcome	Hypothesis of predicted impact on HTA outcome
A. Disease Characteristics[1]				
Therapeutic Area (Non-cancer=0, Cancer=1)		X		Evidence generation in oncology is limited by disease severity and short patient expectancy, which create ethical barriers to conducting large head-to-head clinical trials. Higher levels of clinical uncertainty in this disease area are expected to have a negative impact on HTA outcomes. However, disease severity and higher perception of unmet need for new cancer drugs may have a positive effect.
Orphan Status (Non-orphan=0, Orphan=1)		X		Evidence generation in orphan disease is limited by issues in patient recruitment for clinical trials. Higher levels of clinical uncertainty in this disease area are expected to have a negative impact on HTA outcomes. However, a higher perception of unmet need and low budget impact may have a positive effect.
B. Pivotal Trial Characteristics[2]				
Trial Phase (Single arm Phase I/II=0, Randomised Phase III = 1)			X	Phase III trials are larger and longer than phase I or II trials and have greater statistical power to evaluate the clinical efficacy of a product. HTA agencies are predicted to look more favourably on evidence generated from a phase III study relative to phase I or II.
Endpoint (Surrogate=0, Clinical=1)			X	Surrogate endpoints can be both validated or un-validated and are designed to provide an indication that a treatment is working at earlier stages in the treatment pathway. Surrogate endpoints may not always represent true indicators of clinical benefit and as such the inclusion of hard clinical endpoints is expected to have a positive impact on HTA outcomes.
Comparator (Placebo/No comparator=0, Active comparator=1)			X	HTA agencies seek to evaluate the clinical and economic impact of a drug against the current standard of care. Submissions with clinical trials including active comparators are expected to have a positive impact on HTA outcomes.
C. Uncertainties[3]				
Clinical Uncertainties Overcome (Total number)		X		Clinical uncertainties relate to issues raised by HTA agencies on magnitude of clinical benefit, absence of clinical evidence, study design, indirect comparisons, generalisability or safety. Uncertainties coded as overcome were raised by HTA agencies in decision reports, but dismissed based on supplemental data, patient submission, clinical expert submission or recognition of disease context. Overcome uncertainties are not expected to have a positive or negative impact on HTA outcomes.
Clinical Uncertainties Not Overcome (Total number)	X			Clinical uncertainties coded as not-overcome relate to all clinical issues that are not dismissed by HTA agencies. Uncertainties that are not-overcome are expected to have a negative impact on HTA outcomes.
Economic Uncertainties Overcome (Total number)		X		Economic uncertainties relate to issues raised by HTA agencies on modelling assumptions, modelling type, model inputs including costs, utilities and clinical evidence, cost-effectiveness estimates and sensitivity analysis. Uncertainties coded as overcome were raised by HTA agencies in decision reports, but dismissed based on supplemental data, patient submission, clinical expert submission or recognition of disease context

				or minimal impact on model outputs. Overcome uncertainties are not expected to have a positive or negative impact on HTA outcomes.
Economic Uncertainties Not Overcome (Total number)	X			Economic uncertainties coded as not-overcome relate to all economic issues that are not dismissed by HTA agencies. Uncertainties that are not-overcome are expected to have a negative impact on HTA outcomes.
D. Social Value Judgments[4]				
Disease Severity (not-raised=0, raised=1)			X	The HTA agency acknowledged the severity of disease during the appraisal of evidence. HTA agencies may show greater leniency or willingness to approve of products that address a serious, life-threatening or chronically debilitating disease, given higher levels of patient morbidity and mortality.
Unmet Need (not-raised=0, raised=1)			X	The HTA agency acknowledged there is an unmet clinical need for effective treatments in the therapeutic indication. HTA agencies may show greater leniency or willingness to approve products that address unmet clinical needs.
Administration Advantage (not-raised=0, raised=1)			X	The HTA agency acknowledged that the product under evaluation provides a benefit to patients in terms of the route of administration that is not captured by the clinical or economic evidence. This is expected to have a positive impact on HTA outcome.
Innovation (not-raised=0, raised=1)			X	The HTA agency acknowledges that the product has an innovative mechanism of action. The impact of innovation on decision making is ambiguous. It is beneficial for patients to have access to therapies with varied mechanisms of actions, particularly if they fail to respond to one treatment.
Quality of Life (not-raised=0, raised=1)			X	The HTA agency acknowledges that the product improves patient quality of life in ways not captured by the clinical evidence submitted. This is expected to have a positive impact on HTA outcome.
Special Demographics (not-raised=0, raised=1)		X		The HTA agency acknowledges that the product is to be used in a special patient demographic (e.g. pediatric patients or elderly patients). It is unclear if HTA agencies will prioritise special demographics differently during decision-making.

Source: The authors, adapted from [19]. Abbreviations: HTA – Health Technology Assessment

[1] Disease characteristics considered include therapeutic area and orphan status. Data on ATC code was collected for all drugs included in the sample. Given low sample size, therapeutic area was considered as a binary variable (cancer vs non-cancer indications). Data on orphan status was collected at EMA level, as no such designation exists in Canada.
[2] Pivotal trial characteristics considered include trial phase, comparator, and endpoint. Trial phase was considered as a binary variable (phase I/II vs Phase III) to provide an approximate measure of trial size and length. Comparator was considered in terms of whether an active comparator was present in the trial, in order to provide an indication of whether direct comparative evidence was available. Endpoint was considered in terms of whether the primary endpoint consisted of a surrogate or clinical endpoint.

[3] Uncertainties represent scientific value judgments raised by HTA agencies during the assessment of a product's clinical and economic evidence. A full taxonomy of uncertainties is available in Appendix B

[4] Social Value Judgments refer to dimensions of value identified by HTA agencies beyond clinical and economic evidence, and can relate to disease severity, unmet need, administration advantage, innovation, quality of life or special demographics

5.2.2 Data and sample selection

The scope of this study was limited to France, England, Scotland and Canada. Country selection was based on the following criteria: a) Implementation of a conditional approval pathway, b) requirement to pass through HTA, c) publicly available HTA reports, d) language of HTA reports (English and French). Marketing authorisation agencies considered include the European Medicines Agency (EMA - France, England, and Scotland) [83] and Health Canada (HC - Canada) [85]. HTA agencies considered include the National Institute of Health and Care Excellence (NICE – England) [129], the Scottish Medicines Consortium (SMC – Scotland) [130], the Haute Autorité de Santé (HAS – France) [131], the Canadian Agency for Drugs and Technology in Health (CADTH – Canada) [134] and the Institut National d'Excellence en Santé et en Services Sociaux (INESSS – Canada) [135]. An overview of marketing authorisation and HTA systems in these settings is provided in Appendix A.

The European Union Register of medicinal products [202] was screened to identify all new drug approvals between 01.01.2010 and 31.12.2017. The study period was set to provide sufficient time to track HTA approvals after marketing authorisation. A cut-off date of 31.12.2019 was applied for the identification of HTA reports. Indication extensions during the study period were identified through EMA annual summary reports and by screening EMA variation reports for individual drugs during the study period [83]. Veterinary products, generics, hybrids and biosimilars were excluded. Included drug indication-pairs were screened to identify drug-indication pairs with conditional marketing authorisation. Health Canada drugs with notice of compliance with conditions were identified via the Health Canada list of notice of compliance with conditions [5]. HTA agency websites across all included countries were then screened to identify matching HTA reports for the drug and therapeutic indication of interest [129-131, 134, 135]. Conditionally approved drugs without a minimum of one HTA report completed were excluded from the sample. Non-conditionally approved drug-

indications pairs (those with standard marketing authorisation) were then screened to identify a representative sample of standard approval drugs. Selection was based on 3 criteria: first, each drug in the sample had a minimum of one HTA recommendation across included HTA agencies; second, the total sample included a similar proportion of cancer vs non-cancer drugs relative to the conditional approval sample; finally, the total sample included a similar distribution over time (in terms of the marketing authorisation year) as the conditional approval sample. With the exception of therapeutic area and authorisation year, all details on drug-indication pairs were blinded in order to facilitate a random sampling. A flow chart, outlining the sample selection is provided in figure 1 of the results section.

HTA agency websites were screened again to identify all matching HTA reports for the final list of included drug-indication pairs. HTA reports with non-perfect matches in the therapeutic indication were screened by a second reviewer, with any disagreements on inclusion resolved by a third reviewer. In the event that an HTA agency split an indication into sub-indications, all sub-indications were included, provided separate reports were available for each sub-indication. An overview of the identification of HTA reports is provided in Appendix B.

5.2.3 Data collection

Several variables were considered as potential determinants of HTA outcomes through review of previous literature on HTA decision-making [17, 21, 39, 53-56, 188-191]. Positive HTA outcome were defined as unrestricted listing (L) or restricted listing (LWC) outcomes in NICE, SMC, CADTH and INESSS, and SMR ratings above insufficient in HAS. Negative HTA outcomes were defined as do not list (DNL) outcomes in NICE, SMC, CADTH, and INESSS, and an SMR rating of insufficient in HAS. Data on HTA outcome, HTA restrictions (population or economic), HTA date, previous submissions, clinical evidence, scientific value judgments (both clinical and economic uncertainties) and social value judgments (additional

dimensions of value beyond clinical and economic evidence) were collected from HTA reports. Clinical and economic uncertainties were double coded according to the type of uncertainty and the impact of the uncertainty on decision making. Uncertainties dismissed by the HTA agency due to patient submissions, clinical expert submission, supplemental data or disease context are categorised as "overcome". Uncertainties that are not dismissed are categorised as "not-overcome". The categorisation of clinical and economic uncertainties was reviewed and validated by a team of 4 researchers involved in WP7 of the IMPACT HTA Horizon 2020 project. A full taxonomy of clinical and economic uncertainties is provided in Appendix B.

Data on marketing authorisation approval (type of authorisation, date and conversion from conditional to standard approval) were collected from publicly available marketing authorisation reports.

5.2.4 Empirical methods

Data was extracted into Microsoft Excel and coded. Statistical analysis was performed using STATA SE Version 17.0. The unit of analysis was defined as a drug-indication-agency trio. A single HTA outcome is specific to both a therapeutic indication and HTA agency, meaning that HTA outcomes for different therapeutic indications of a single molecule are recorded as separate entries.

Maximum likelihood logistic regression models were constructed to assess the association of collected variables with a) type of marketing authorisation pathway and b) HTA outcome. Kaplan-meier survival curves were used to compare conditionally approved drugs with standard approval drugs for time from MA to HTA outcome.

First, univariate binomial logistic regression models were used to explore the association of collected variables with type of marketing authorisation pathway. The dependent variable for

univariate analysis ($Y_{1/0}$) was coded as 1 for drug-indication-agency trios with conditional approval and 0 for drug-indication-agency trios with standard approval:

$$Y_{1/0}\begin{pmatrix} Y = 1, & if\ conditional\ approval \\ Y = 0, & if\ standard\ approval \end{pmatrix} \quad (1)$$

Independent variables (x_i) included therapeutic area, orphan status, pivotal trial phase, pivotal trial comparator, pivotal trial endpoint, scientific value judgments raised by HTA agencies (clinical and economic uncertainties), social value judgments raised by HTA agencies, submission history and HTA outcome.

$$Logit\left(Y_{1/0}\,|X_1 = x_1\right) = \beta_o + x_1\beta_1 \quad (2)$$

Where x_i represents the independent variable, β_i represents the regression coefficient and β_o represents the intercept. Odds ratios, 95% confidence intervals and p-values are reported.

$$Odds\left(Y_{1/0}\,|X_1 = x_1\right) = \exp(\beta_o + x_1\beta_1) \quad (3)$$

Second, multivariate binary logistic regression models were used to explore the association of collected variables with HTA outcomes. The dependent variable for multivariate analysis ($Z_{1/0}$) was coded as 1 for a drug-indication-agency trios with an HTA outcome of List (L) or List with criteria (LWC) and 0 for drug-indication-agency trios with an HTA outcome of Do not List (DNL).

$$Logit\left(Z_{1/0}\,|X_1 = x_1\right) = \beta_o + x_1\beta_1 \quad (4)$$

Where x_i represents the independent variable, β_i represents the regression coefficient and β_o represents the intercept. Independent variables included type of marketing authorisation pathway, therapeutic area, orphan status, pivotal trial phase, pivotal trial comparator, pivotal

trial endpoint, scientific value judgments raised by HTA agencies (clinical and economic uncertainties), social value judgments raised by HTA agencies, submission history and HTA outcome. The general specification of the multivariate model was:

$$Logit\left(Z_{1/0}\,|X_{iat} = x_{iat}\right) = \beta_o + x_{iat}\beta' + d_i\gamma' + a_a\zeta' + t_t\eta' \qquad (5)$$

Where x_{iat} is a vector of HTA characteristics (submission history, clinical evidence, scientific value judgments, and social value judgments) for drug-indication "i", agency "a", and assessment year "t" and d_i is a vector of disease characteristics (therapeutic area and orphan status) that are agency-invariant. To control for heterogeneity across agencies and over time, we include agency fixed effects (a_a) and time fixed effects (t_t). β', γ', ζ', and η' represent the regression coefficients and β_o represents the intercept. Odds ratios and robust standard errors adjusted for clustering at molecule level are reported. We additionally calculate average marginal effects (ME) to examine inter-agency differences and the impact of interactions in the model. As a robustness check, additional analyses were performed on cost-effectiveness countries only (excluding France) and excluding time and agency fixed effects.

Third, survival analysis using Kaplan-Meier curves was performed to assess the association of marketing authorisation type with time from marketing authorisation to HTA approval. The "death" event was defined as a positive HTA outcome (List or List with condition). The time unit was defined as days between marketing authorisation approval and HTA outcome.

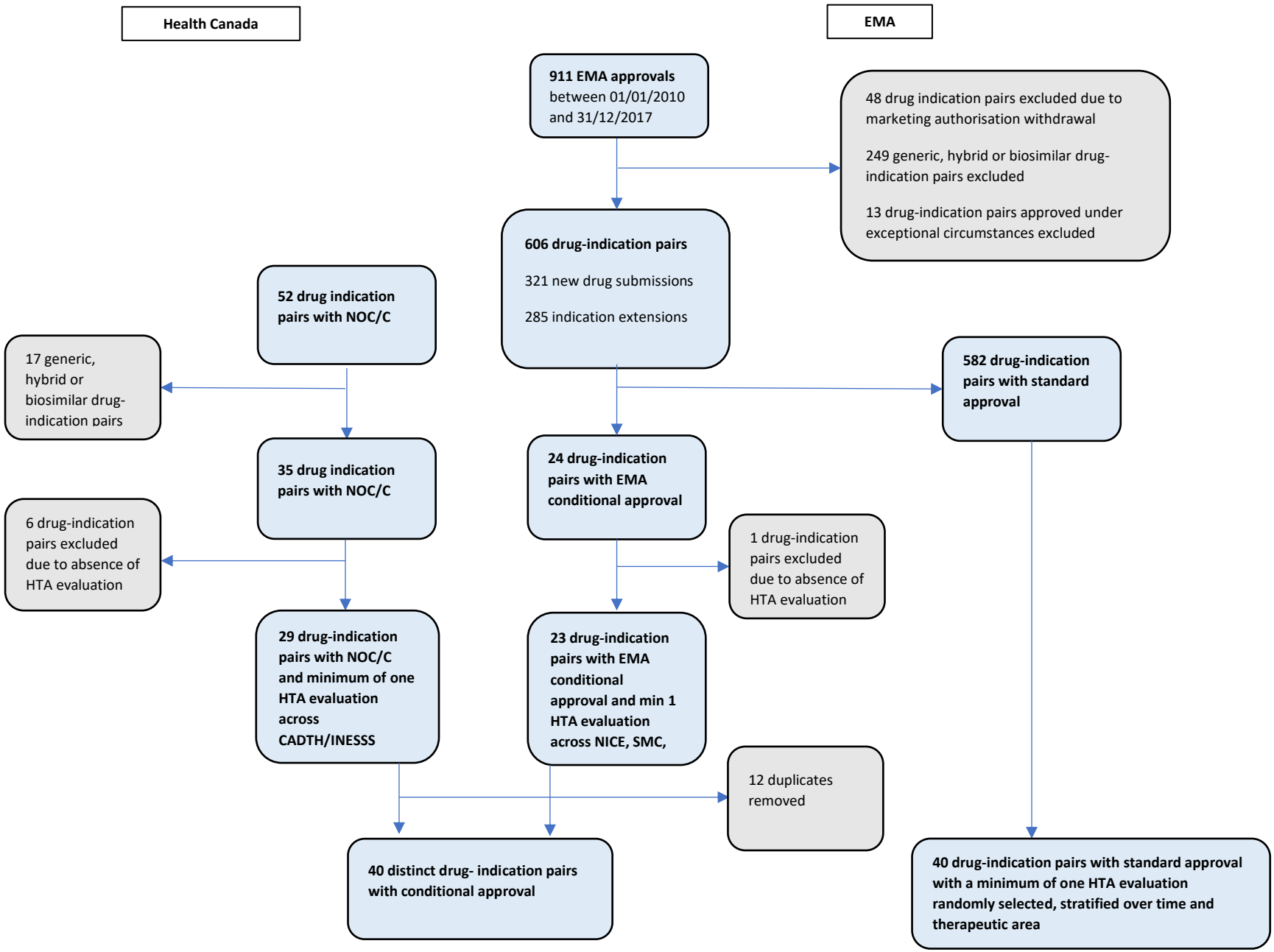
5.3 Results

A total of 339 drug-indication-agency trios were included in the analysis consisting of 40 unique conditionally approved drug-indication pairs and 40 standard approval drug-indication pairs [See **Figure 5.1**]. A full list of included drug-indication pairs is provided in Appendix C. A total of 58 HTA rejections (17.1%) and 281 HTA approvals (83.5%) were identified in the pooled sample. INESSS had the highest proportion of rejections (46.0% rejection vs 54.0% approval), followed by CADTH (16.4% vs 83.6%), SMC (12.1% vs 87.9%), NICE (10.6% vs 89.4%) and HAS (2.7% vs 97.3%) $\left(\chi^2_{(5\,|N=339)} = 48.3, p < 0.01\right)$. In 11 instances, conditional approval was converted to standard approval prior to publication of an HTA outcome.

5.3.1 Comparing HTA characteristics by marketing authorisation pathway

Conditional approval and standard approval drugs were compared regarding disease characteristics, pivotal trial characteristics, uncertainties, social value judgments, and HTA outcomes. Results of univariate analysis are presented in **Table 5.2**.

Significant differences across conditional approval and standard approval drug-indication-agency trios were identified in pivotal trial characteristics, uncertainties and social value judgments, and HTA outcomes. Relative to drug-indication-agency trios with standard approval, conditionally approved drug-indication-agency trios are less likely to be based on a phase III trial, include a clinical primary endpoint, or include a direct comparator. Results for uncertainties and social value judgments were mixed, with conditionally approved drug-indication-trios statistically more likely to have a higher number of clinical uncertainties not overcome and a higher number of economic uncertainties not overcome, and more likely to have HTA agencies recognise disease severity, unmet need, and special demographics.


Health Canada
EMA
911 EMA approvals between 01/01/2010 and 31/12/2017
48 drug indication pairs excluded due to marketing authorisation withdrawal
249 generic, hybrid or biosimilar drug-indication pairs excluded
13 drug-indication pairs approved under exceptional circumstances excluded
606 drug-indication pairs
321 new drug submissions
285 indication extensions
52 drug indication pairs with NOC/C
17 generic, hybrid or biosimilar drug-indication pairs
582 drug-indication pairs with standard approval
35 drug indication pairs with NOC/C
24 drug-indication pairs with EMA conditional approval
6 drug-indication pairs excluded due to absence of HTA evaluation
1 drug-indication pairs excluded due to absence of HTA evaluation
29 drug-indication pairs with NOC/C and minimum of one HTA evaluation across CADTH/INESSS
23 drug-indication pairs with EMA conditional approval and min 1 HTA evaluation across NICE, SMC,
12 duplicates removed
40 distinct drug- indication pairs with conditional approval
40 drug-indication pairs with standard approval with a minimum of one HTA evaluation randomly selected, stratified over time and therapeutic area

CADTH - Canadian Agency for Drugs and Technologies in Health; HAS – Haute Autorité de Santé; INESS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

Figure 5.1 - Flowchart Illustrating Identification of Conditionally Approved Drug-Indication Pairs and Selection of Standard Approval Drug-Indication Pairs Across Health Canada and the European Medicines Agency

The European union register of medicinal products website (https://ec.europa.eu/health/documents/community-register/html/) was screened to identify new drug approvals between 01/01/2010 and 31/12/2017. European Medicines Agency (EMA) annual reports and variation reports were subsequently screened to identify approvals of new therapeutic indications (indication extensions) between 01/01/2010 and 31/12/2017. Products with withdrawals, generic products, hybrid products, biosimilar products and products authorised under exceptional circumstances were excluded from the sample. Remaining drug-indication pairs were stratified according to type of marketing authorisation (standard approval vs conditional approval). EMA conditionally approved products without a matching HTA report in one of NICE, SMC or CADTH were excluded from the sample. The Health Canada Notice of Compliance with conditions (NOC/C) list (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html) was screened to identify drug-indication pairs with conditional approval in Canada between 01/01/2010 and 01/012017. Generic, hybrid and biosimilar products with conditional approval were excluded from the sample. Health Canada conditionally approved products without a matching HTA report in one of CADTH or INESSS were excluded from the sample. The therapeutic indications of conditionally approved products in Health Canada and EMA were compared to identify duplicates. Matching of drug-indication pairs was performed by two reviewers, with any disagreements resolved by a third reviewer. Please refer to the supplementary material for a breakdown of the number of matching HTA reports identified per agency.

Table 5.2 - Univariate Analysis Comparing HTA Assessment of Conditional Approval and Standard Approval Drugs

		Standard Approval Drug-Indication-Agency Trios		Conditional Approval Drug-Indication-Agency Trios		Univariate		
		No	**(%)**	**No**	**(%)**	**OR**	**[95% CI]**	**P-value**
A. Disease Characteristics								
Therapeutic Area	Cancer	164	(75.9%)	104	(83.2%)	1.57	[0.89-2.76]	0.116
	Non-Cancer	52	(24.1%)	21	(16.8%)	1.00	[Reference]	
Orphan Status	Orphan	52	(24.1%)	34	(27.2%)	1.18	[0.71-1.95]	0.52
	Non-Orphan	164	(75.9%)	91	(72.8%)	1.00	[Reference]	
B. Pivotal Trial Characteristics								
Trial Phase[1]	Phase III	182	(84.2%)	67	(53.6%)	0.22	[0.13-0.36]	**0.000**
	Phase I/II	34	(15.7%)	58	(46.4%)	1.00	[Reference]	
Endpoint[2]	Clinical	60	(27.8%)	13	(10.4%)	0.30	[0.16-0.56]	**0.000**
	Surrogate	156	(72.2%)	112	(89.6%)	1.00	[Reference]	
Comparator	Active	109	(50.5%)	49	(39.2%)	0.63	[0.40-0.99]	**0.045**
	Placebo/No comparator	107	(49.5%)	76	(60.8%)	1.00	[Reference]	
C. Uncertainties								
Clinical Uncertainties Overcome	Mean [95%CI]	2.33	[1.98-2.68]	2.77	[2.26-3.27]	1.06	[0.98-1.15]	0.151
Clinical Uncertainties Not Overcome	Mean [95%CI]	3.11	[2.73-3.48]	4.62	[4.06-5.19]	1.19	[1.10-1.28]	**0.000**
Economic Uncertainties Overcome[3]	Mean [95%CI]	1.37	[1.10-1.62]	1.40	[0.98-1.83]	1.01	[0.89-1.15]	0.871
Economic Uncertainties Not Overcome[3]	Mean [95%CI]	2.44	[2.14-2.73]	3.11	[2.67-3.56]	1.17	[1.04-1.33]	**0.011**
D. Social Value Judgments								
Disease Severity	Considered	108	(50.0%)	79	(68.1%)	2.14	[1.33-3.43]	**0.002**
	Not-considered	108	(50.0%)	37	(31.9%)	1.00	[Reference]	
Unmet Need	Considered	163	(75.5%)	101	(87.1%)	2.19	[1.17-4.09]	**0.014**
	Not-considered	53	(24.5%)	15	(12.9%)	1.00	[Reference]	
Administration Advantage	Considered	62	(28.7%)	43	(37.1%)	1.46	[0.91-2.36]	0.119
	Not-considered	154	(71.3%)	73	(62.9%)	1.00	[Reference]	
Innovation	Considered	72	(33.3%)	47	(41.2%)	1.40	[0.88-2.24]	0.156
	Not-considered	144	(66.7%)	64	(58.7%)	1.00	[Reference]	
Quality of Life	Considered	82	(38.1%)	60	(48.0%)	1.50	[0.96-2.34]	0.076
	Not-considered	133	(61.9%)	65	(52.0%)	1.00	[Reference]	
Special Demographics	Considered	10	(4.7%)	17	(13.6%)	3.22	[1.43-7.29]	**0.003**
	Not-considered	205	(95.3%)	108	(86.4%)	1.00	[Reference]	
E. HTA Outcomes								

Submission History	Prior-rejection	34	(15.7%)	27	(21.6%)	1.47	[0.84-2.59]	0.175
	First submission	182	(84.3%)	98	(78.4%)	1.00	[Reference]	
HTA Outcome[4]	L or LWC	186	(86.11%)	97	(77.6%)	0.56	[0.32-0.99]	**0.046**
	DNL	30	(13.9%)	28	(22.4%)	1.00	[Reference]	

Abbreviations: L – List; LWC - List with Conditions; DNL – Do not List;

HTA characteristics of conditional vs standard approval across NICE, SMC, HAS, CADTH and INESSS. Conditional approval status defined based receipt of a conditional marketing authorisation in EMA or notice of compliance with condition (NOC/C) in Health Canada. The dependent variable, type of marketing authorisation, is coded as 1 for conditionally approved drug-indication-agency trios, and 0 for standard approval drug-indication-agency trios. Odds ratios reflect the likelihood of differences in disease characteristics, pivotal trial characteristics, uncertainties, social value judgments and HTA outcomes across conditionally approved and standard approval drugs. Results are pooled across all agencies.

[1] Where multiple pivotal trials are available, highest phase is recorded
[2] According to primary endpoint in pivotal trial
[3] Statistical tests on economic uncertainties calculated excluding HAS
[4] In HAS, products with a medical service rendered (SMR) rating of insufficient are not reimbursed and are considered as DNL. All other SMR ratings are considered in the L/LWC category.

Conditionally approved drug-indication-agency trios were statistically more likely to receive a negative HTA outcome relative to standard approval drug-indication-agency trios. This result remains significant when removing HAS from analysis (CEA countries only). No statistically significant differences were identified for disease characteristics or submission history.

As a robustness check, the 11 drug-indication-agency trios with converted MA were reclassified as standard approval drugs and univariate analysis was repeated. Results were consistent with the original classification, with statistically significant differences identified for trial phase, endpoint, comparator, clinical uncertainties not overcome, economic uncertainties not overcome, disease severity, unmet need, special demographics and HTA outcome.

5.3.2 Multivariate regression examining drivers of HTA outcomes

In order to capture the impact of respective groups of variables on HTA outcomes, regression models were constructed in a step-wise manner. A baseline model (Model 0) included type of marketing authorisation pathway, with agency and time fixed-effects, to provide a benchmark. Type of marketing authorisation pathway was excluded from subsequent models given high collinearity with the other independent variables. Disease characteristics and submission history (Model 1), pivotal trial characteristics (Model 2), uncertainties (Model 3), and social value judgments (Model 4) were added sequentially. Model 5 presents results of cost-effectiveness countries only (excluding HAS). All models controlled for agency and time fixed effects. Results of the multivariate models are presented in **Table 5.3**. Additional models without fixed effects are presented in Appendix E.

Table 5.3 - Multivariate Logistic Regression Models Comparing Positive and Negative HTA Outcomes Across NICE, HAS, SMC, CADTH and INESSS.

	Model 0	Model 1	Model 2	Model 3	Model 4	Model 5
Dependent Variable: HTA Outcome (List or List with condition: 1, Do not list: 0)						
A) Regulatory Approval						
Conditional Approval	0.714 (0.256)					
B) Disease Characteristics						
Cancer		2.724** (1.107)	2.605** (1.034)	2.631** (1.219)	2.625* (1.363)	3.628** (2.061)
Orphan		2.323 (1.281)	3.452** (1.965)	4.019** (2.742)	6.217** (5.006)	9.119** (9.274)
C) Submission History						
Resubmission		3.921*** (1.953)	3.731*** (1.910)	10.567*** (8.570)	10.223*** (7.948)	10.634*** (8.401)
D) Pivotal Trial Characteristics						
Trial Phase			1.999 (0.876)	2.474* (1.283)	3.365** (2.064)	3.528* (2.384)
Endpoint			1.344 (0.673)	1.491 (0.799)	1.278 (0.748)	1.211 (0.743)
Comparator			1.305 (0.593)	1.657 (0.877)	1.306 (0.670)	1.097 (0.593)
E) Uncertainties						
Clinical Overcome				1.493*** (0.165)	1.504*** (0.199)	1.505*** (0.196)
Clinical Not-Overcome				0.780*** (0.062)	0.760*** (0.070)	0.760*** (0.072)
Economic Overcome				1.935*** (0.433)	2.431*** (0.570)	2.440*** (0.532)
Economic Not-Overcome				0.845* (0.084)	0.830* (0.094)	0.845 (0.104)
F) Social Value Judgments						

Disease Severity					1.102 (0.592)	1.275 (0.690
Unmet Need					0.489 (0.310)	0.337 (0.203)
Administration Advantage					2.052 (1.175)	2.153 (1.229)
Innovation					0.958 (0.567)	0.919 (0.574)
Quality of Life					1.588 (0.862)	1.437 (0.814)
Special Demographics					4.157 (3.794)	4.051 (3.935)
Number of Observations	339	339	339	339	339	256
Pseudo-R^2	0.178	0.221	0.252	0.408	0.448	0.435
AIC	282.9	273.5	270.1	220.9	216.9	199.9
Time FE	Yes	Yes	Yes	Yes	Yes	Yes
Agency FE	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; FE – Fixed Effects; HAS – Haute Autorité de Santé (HAS); NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

Model 0 is a reference case controlling only for type of marketing authorisation with country and time fixed effects. Disease characteristics and submission history (Model 1), pivotal trial characteristics (Model 2), Uncertainties (Model 3) and Social Value Judgments (Model 4) were added sequentially. Model 5 presents results for cost-effectiveness countries only (excluding France). Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies.

P-Values *p<0.1; **p<0.05; ***p<0.01

See supplementary material for regression models without time and agency fixed effects.

Disease Characteristics and Submission History

In the aggregate sample, HTA approval was marginally higher for oncology drugs (85.0%) vs non-oncology drugs (75.3%). This effect was significant in all multivariate models (1-5), although in model 4 significance was only achieved at a level of $p<0.1$ (OR 2.631, 95% CI [0.948-7.27]). HTA approvals were also higher for orphan drugs(94.1%) vs non-orphan drugs (79.2%). In the final model (model 4), this effect was statistically significant (OR 6.22, 95% CI [1.28 – 30.1], $p = 0.023$). Finally, HTA approvals are marginally more likely in drug-indication-agency trios with a previous rejection (85.3%) compared to drugs without previous rejection (82.5%). This effect was significant in all multivariate models (OR 10.223, 95% CI [2.27 – 46.9], $p = 0.001$). Interpretation of magnitude of effect (particularly for orphan status and resubmission status) is limited in later models (3-5), given high robust standard errors and wide confidence intervals.

Clinical Evidence

The association of pivotal trial characteristics and HTA approvals was mixed across multivariate models. In the aggregate sample, HTA approvals were a) slightly higher for drug-indication-agency trios supported by phase III trials (85.5%) vs phase I or II trials (76%), b) similar for drug-indication-agency trios supported by at least one clinical endpoint (86.3%) vs surrogate (82.1%), and c) slightly higher for drug-indication-agency trios supported with a trial including an active comparator (89.2%) vs placebo control (77.60%). Odds ratios in multi-variate models for pivotal trial characteristics are predominantly non-significant with the exception of trial phase, which achieved significance at $p<0.05$ in model 4 (OR 3.365, 95% CI [1.01 – 11.2]. Wide confidence intervals are present across all pivotal trial characteristic variables, and were largest in models 3, 4 and 5.

Scientific and Social Value Judgments

Uncertainties showed significant differences for clinical uncertainties overcome, clinical uncertainties not overcome, and economic uncertainties overcome. HTA approvals were more likely to have a higher number of clinical uncertainties overcome (OR 1.504, 95% CI [1.16 – 1.95], p=0.002), a lower number of clinical uncertainties not overcome (OR 0.760, 95% CI [0.63 – 0.91], p<0.003), and a high number of economic uncertainties overcome (OR 2.431, 95%CI [1.54 – 3.85], p<0.001). No significant differences (at p<0.05) were detected for number of economic uncertainties not overcome. Relative to other covariates, confidence intervals were narrower for clinical and economic uncertainties and effect sizes were relatively consistent across models. Results remain consistent in model 5, which assessed CEA countries only.

Sub-analysis according to type of clinical and economic uncertainty is provided in Appendix D. The positive association between the aggregate of clinical uncertainties overcome and HTA outcomes appears to be driven largely by uncertainties in clinical benefit, which showed a significantly positive effect across both models. Overcome uncertainties in clinical evidence also contribute positively, although high robust standard error on the odds ratios limit interpretation of results. Conversely, the negative association between the aggregate clinical uncertainties not overcome and HTA outcomes appears to be driven largely by unresolved uncertainties in clinical benefit, study design, and adverse events, which significantly lower the probability of a positive outcome across both models. The positive association between the aggregate of economic uncertainties overcome is largely driven by overcome uncertainties in modelling. Overcome uncertainties in utilities and cost-effectiveness also contribute positively, although high robust standard error on the odds ratios limit interpretation of results.

Social value judgments were not significantly associated with HTA outcomes. Most SVJs are raised with similar frequency in HTA approvals and rejections. HTA approvals are a) similar when severity is raised (85.6%) vs not raised (80.0%); b) similar when unmet need is raised (82.6%) vs not raised (85.3%); c) similar when administration advantage is raised (86.7%) vs not raised (81.5%); slightly higher when innovation is raised (89.1%) vs not raised (79.6%) and similar when special demographics are raised (83.8%) vs not raised (82.3%). Effects were insignificant in models 4 and 5 for all social value judgments. Widest confidence intervals were present for administration advantage (only raised in 32% of all HTA assessments) and special demographics (only raised in 8.6% of all HTA assessments).

Model Fit

Pseudo R^2 values suggest that disease characteristics and submission history account for 6.2% of the variation in HTA outcomes. Pivotal trial characteristics account for a further 3.1% of the variation. Scientific value judgments (uncertainties) increased the Pseudo R^2 by a further 15.6%. Social value judgments only accounted for 4.0% of variation and did not contribute substantially to model fit, as shown by only a marginal decrease in the AIC when this group of variables was added. Agency and fixed effects account for approximately 15% of variation (see Appendix E).

5.3.3 Inter-agency effects

The interaction of a set number of predictors with agency dummies is presented in **Table 5.4**. Conditional approval appears to reduce the probability of approval across each agency, although no effects were statistically significant. All agencies also appear to favour oncology drugs, although only INESSS showed significance (at $p<0.1$). CADTH, INESSS, SMC and NICE appear to favour orphan drugs in HTA approvals over non-orphan drugs. The effect of uncertainties is consistent across most agencies with clinical and economic uncertainties

overcome increasing the probability of approval, clinical uncertainties not overcome reducing the probability of approval, and no effect shown for economic uncertainties not overcome. The exception was HAS, where no significance was seen for uncertainties.

5.3.4 Survival analysis of time from marketing authorisation to positive HTA outcome

Results from survival analysis for the pooled sample and agency specific models are presented in **Figure 5.2**. Within the pooled sample, and in each of the agency-specific models, conditionally approved drugs have a longer median time to HTA approval than standard approval drugs. The difference was statistically significant in the pooled sample (median time from MA to HTA approval of 458 days (conditional) vs 265 days (standard), $p < 0.001$), in CADTH (median time from MA to HTA approval of 391 days (conditional) vs 144 days (standard), $p=0.01$) and HAS (median time from MA to HTA approval of 338 days (conditional) vs 229 days (standard), $p=0.01$). Differences were non-significant in INESSS (605 days (conditional) vs 511 days (standard)), NICE (583 days (conditional) vs 385 days (standard)), and SMC (323 days (conditional) vs 263 days (standard).

Table 5.4 - Average Marginal Effects of Selected Predictor Variables Interacting with Agency Dummies

Average Marginal Effects (dydx) – Interaction of Predictors with Agency									
	Type of MA	**Cancer**	**Orphan**	**Trial Phase**	**Comparator**	**Clinical Uncertainties**		**Economic Uncertainties**	
						Overcome	**Not-overcome**	**Overcome**	**Not-overcome**
CADTH	-0.044 (0.048)	0.104 (0.067)	0.118*** (0.038)	0.136* (0.078)	0.018 (0.035)	0.040*** (0.014)	- 0.027*** (0.009)	0.088*** (0.121)	- 0.017 (0.012)
INESSS	-0.079 (0.085)	0.130* (0.071)	0.217*** (0.082)	0.167** (0.083)	0.037 (0.070)	0.055*** (0.015)	- 0.037*** (0.011)	0.121*** (0.029)	- 0.023 (0.017)
HAS	-0.009 (0.012)	0.032 (0.025)	0.028 (0.023)	0.042 (0.035)	0.007 (0.014)	0.011 (0.007)	- 0.007 (0.005)	-	-
SMC	-0.038 (0.045)	0.077 (0.050)	0.111** (0.049)	0.097 (0.060)	0.018 (0.035)	0.028** (0.012)	- 0.019** (0.007)	0.060*** (0.021)	- 0.011 (0.008)
NICE	-0.033 (0.038)	0.060 (0.037)	0.094** (0.046)	0.077* (0.042)	0.015 (0.029)	0.022*** (0.008)	- 0.015*** (0.005)	0.050*** (0.013)	- 0.009 (0.007)
Number of observations	323	323	323	323	323	323	323	256	256

Abbreviations – MA – Marketing authorisation

Average marginal effects of type of marketing authorisation after interacting with agency dummies, controlling only for agency and time fixed effects. Average marginal effects of Cancer, Orphan, Trial Phase, Comparator, Clinical Uncertainties, and Economic Uncertainties after interacting with agency dummies, controlling for covariates specified in model [4].

P-Values *p<0.1; **p<0.05; ***p<0.01

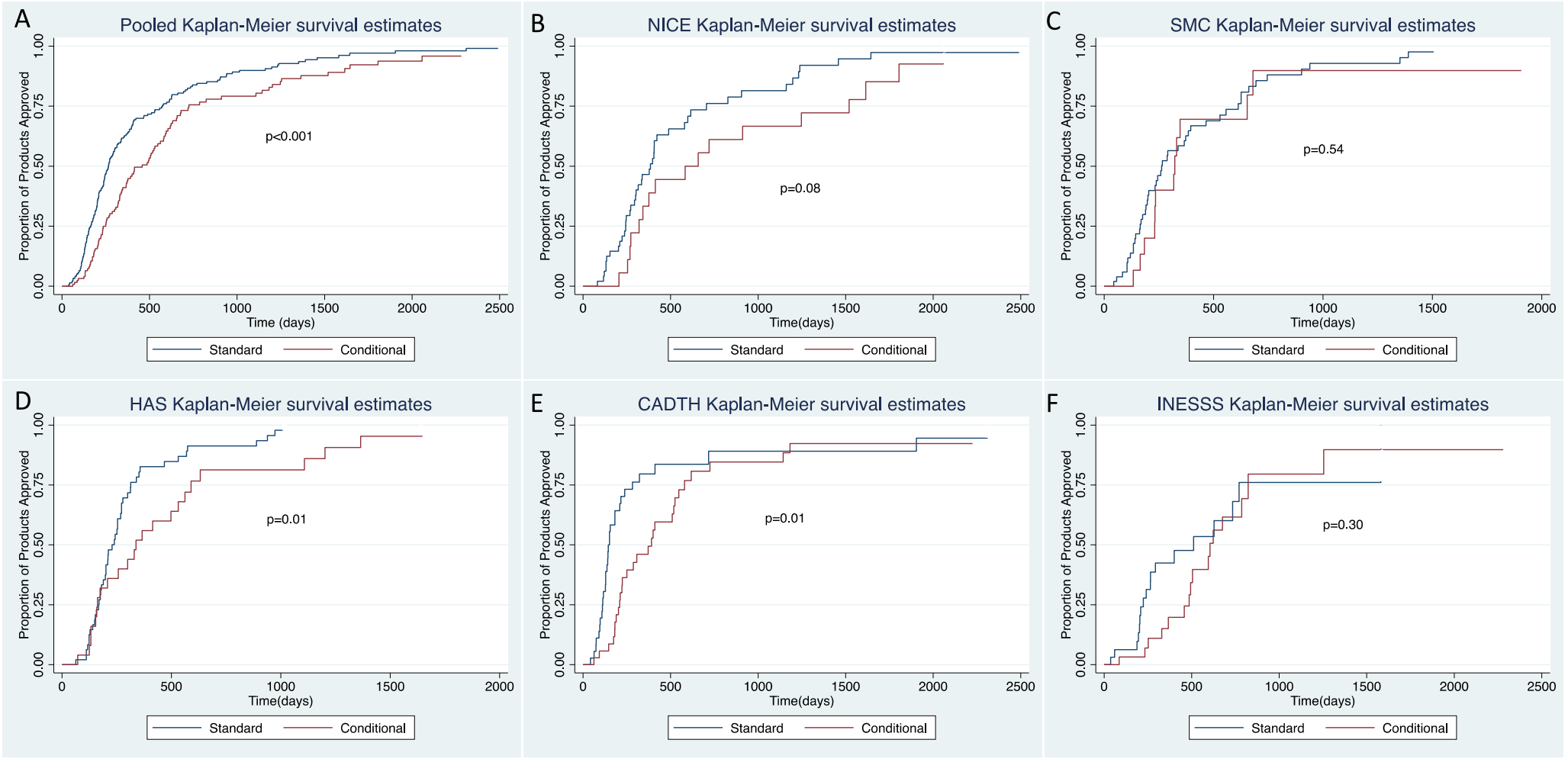


Figure 5.2 - Kaplan Meier Plots of HTA Approval Time Conditional Approval and Standard Approval Drug-Indication-Agency Trios, Defined as Time from Marketing Authorisation to HTA Approval.

HTA approval time of conditional vs standard approval products in pooled sample. B – HTA approval time of conditional vs standard approval products in NICE, C – HTA approval time of conditional vs standard approval products in SMC. D – HTA approval time of conditional vs standard approval products in HAS. E – HTA approval time of conditional vs standard approval products in CADTH. F – HTA approval time of conditional vs standard approval products in INESSS. Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health, HAS – Haute Autorité de Santé (HAS), NICE – National Institute of Health and Care Excellence, SMC – Scottish Medicines Consortium.

5.4 Discussion

Availability of innovative medicines across settings remains extremely fragmented [14]. With a rising number of targeted therapies, personalised medicines, immunotherapies and cell and gene therapies under development, policy makers must take appropriate steps to ensure that patients do not face unnecessary delays in access to life-saving treatments [26]. At the same time, financing of healthcare must be sustainable and health insurers must make coverage decisions with confidence that they are allocating resources in an optimal way [5]. Conditional approval pathways provide an excellent case study for exploring this trade-off, requiring HTA agencies to contend with higher levels of uncertainty in their decision-making.

This paper provided a meta-analysis of HTA coverage decisions for 80 drug-indication pairs, 40 of which received conditional marketing authorisation, and 40 which received standard marketing authorisation, across five HTA agencies. Our empirical approach to analysing HTA outcomes provides an important preliminary contribution to our understanding of how scientific and social value judgments shape HTA decision-making, which will benefit from further validation across other settings and larger cohorts of drug-indication pairs. Further, our multi-country approach validates previous findings that agencies vary systematically in their interpretation and assessment of health technologies. There are a number of important take-aways from our results.

HTA agencies raise uncertainties more frequently for conditionally approved drugs

First, conditionally approved drugs in our sample had a higher average number of unresolved clinical and economic uncertainties raised relative to standard approval drugs. A wide range of clinical issues or uncertainties are raised during HTA, including but not limited to uncertainty in magnitude of clinical benefit, absence of clinical evidence, inadequate study design, limitations in indirect comparisons, and issue in generalisability of trial results. In an attempt

to measure the extent to which this weaker evidence base translates into a higher level of uncertainty during HTA, decision text was qualitatively analysed to identify different types of clinical and economic uncertainties. This enables us to a) examine the frequency with which different clinical and economic are raised, and b) explore the association between uncertainties and HTA outcomes. While we are not able to assign specific weights of individual uncertainties on decision-making, our findings that conditionally approved drugs have a higher average number of unresolved clinical uncertainties are consistent with the differences seen in pivotal trial characteristics.

Fundamentally, conditionally approved drugs are expected to have weaker evidence bases than standard approval drugs, given the respective regulatory requirements [101, 153]. Our univariate analysis provides validation of previous literature on the extent of the evidence gap [30, 137, 194, 195] showing that conditionally approved drugs are less likely to have a phase III trial design, less likely to utilise a clinical endpoint and less likely to include a direct comparator. The potential impact of this difference in clinical evidence, both in terms of development time and cost, is significant, ranging from US$ 1.4 to US$ 6.6 million for phase 1 trials, US$ 7.0 to US$ 19.6 million for phase II trials and US$ 11.5 to US$ 52.9 million depending on therapeutic area [203]. Inclusion of clinical endpoints, such as overall survival, can dramatically increase the length, and cost of a trial [204]. In the absence of HTA (i.e. in the USA), conditional approval, when paired with other accelerated marketing authorisation pathways such as priority review, reduces clinical development time by an average of nearly two years [29].

HTA barriers for conditionally approved drugs?

Second, our results indicate that conditional approval drugs likely face increased barriers at HTA level relative to standard approval drugs, although interpretation of the size of effect is

limited by study sample size and frequency of HTA rejections (only 17.1% of evaluations). HTA barriers were measured in two ways: first, whether conditionally approved drugs have an increased probability of rejection at HTA level; and second, whether conditionally approved drugs face delays in receiving HTA approval. Based on the conceptual framework and results of the univariate analysis, conditionally approved drugs were predicted to have characteristics that both improved probability of approval (unmet need and disease severity) and reduced probability of approval (orphan status, pivotal trial characteristics, number of clinical uncertainties not overcome).

The alignment of our empirical results with the conceptual framework informing this study was mixed. Pivotal trial characteristics, which were expected to have a positive impact on HTA outcomes predominantly did not exhibit a significant effect in multi-variate models and only account for a marginal part of the variation in the sequential models. There are some indications that trial phase contributes positively towards HTA approval, however there is considerable uncertainty in the magnitude of effect (given high standard error and wide confidence intervals). A marginal or limited impact of pivotal trial characteristics is consistent with findings from previous single-setting studies of HTA outcomes in France and England [17, 53].

The impact of scientific value judgments on HTA outcomes was more closely aligned with hypothesised effects. Drugs with higher unresolved clinical uncertainty, particularly surrounding clinical benefit, study design and adverse events, face a significantly lower probability of HTA approval, an effect which holds in each HTA agency apart from HAS. However analysis of marginal effects in the HAS is likely limited by a small number of rejections in the sample (n=2). Meanwhile, uncertainties that were dismissed by HTA agencies (clinical and economic overcome) had a positive impact on probability of HTA approval, an effect which again holds in each HTA agency apart from HAS. Overall, the strength of

evidence was highest for this group of variables, given the total proportion of variance explained and relatively low robust standard errors.

These findings suggest that the interpretation of evidence, rather than the evidence itself drives decision-making at HTA level (i.e. a phase II single arm trial may or may not be acceptable depending on the disease context). This narrative is aligned with a recent study which found a positive correlation between HTA outcomes and implementation of managed entry agreements (tools which help to mitigate clinical and economic uncertainty) [193]. Health systems have a wide range of managed-entry tools available to them to help mitigate clinical and economic uncertainties, including outcome-based payment, price-volume-caps, and coverage with evidence development [205, 206]. In theory, one might expect that managed entry agreement implementation would occur more frequently with conditionally approved drugs to mitigate higher levels of uncertainty. Within our sample, the presence of managed entry agreement (patient access scheme or commercial access agreement) was recorded for NICE and SMC (CADTH and INESSS are advisory bodies without direct links to healthcare payers, while HAS evaluations are issued independently of managed entry agreements). The vast majority of positive HTA outcomes in NICE and SMC included a patient access scheme (98% and 91% respectively). While all conditionally approved drugs had managed entry agreements, the high frequency of application in the standard approval cohort prevents us from drawing meaningful conclusions about their differential application across type of marketing authorisation. Further, the terms of managed entry agreements in both settings are commercial in confidence, limiting our ability to fully assess how these tools can mitigate additional uncertainty present in conditionally approved drugs.

Surprisingly, no association was detected between social value judgments and HTA outcome. Unmet need and disease severity, key eligibility criteria for conditional approval pathways,

were predicted to have a positive impact on the probability of HTA approval. These findings contrast with previous case study analysis which indicate that social value judgments render clinical and economic certainties more acceptable [207]. Indeed, supplementary analysis (Appendix D) exploring the association of SVJs and uncertainties indicate that disease severity, unmet need, innovation and quality of life are positively associated with the total number of clinical uncertainties overcome. The absence of effect on HTA outcomes could partially be explained by imprecision in the model estimates, which consider social value judgments as a binary variable, while the true effect of these parameters may be variable or weighted. Alternatively, this could reflect a lack of statistical power to detect significant effects.

Univariate analysis indicates that conditional approval is associated with a reduced probability of HTA approval across the aggregate sample. Interestingly, the effect lost significance in the multi-variate model after adding country and fixed effects, signalling that effect size is likely small and that the model may be underpowered to detect positive associations of existing variables. Analysis of average marginal effects suggest a tendency for each agency to be biased against conditionally approved drugs, although no significance was reached. This highlights the need to validate findings in larger cohorts of drugs and other settings.

Finally, conditionally approved drugs face marginal delays (on average 6 months longer) in receiving HTA approval relative to standard marketing authorisation drugs. In theory, delays from receipt of marketing authorisation to receival of HTA approval can occur through three broad mechanisms: 1) initial rejection requiring resubmission for HTA approval, 2) delays in HTA review and 3) delays in manufacturer submission.

Evidence from our dataset does not provide strong support of the first mechanism, given only marginal and non-statistically significant increases in the number resubmissions for conditionally approved drugs vs standard approval (21.6% of conditionally approved drugs had

multiple submissions vs 15.7% of standard approval). It is possible that review timelines are longer for drugs with conditional approval. Despite published target timelines for HTA review across each of the included HTA agencies, a number of factors can delay the HTA process including requirements for supplemental data, requirements for revisions to economic modelling, and clinical expert and patient consultation [208].

Launch times for pharmaceuticals have been shown to relate to market size [59, 71], firm size [72] firm location [60, 69] and price controls (external reference pricing) [71][59]. While these factors may help to explain inter-agency differences in average time from MA to HTA, they do not offer an explanation for differences in HTA approval timelines of conditional drugs vs standard approval drugs. Perceived institutional barriers to entry at HTA level may result in submission delays, as manufacturers seek to avoid initial rejections and resubmissions. Manufacturers with immature clinical evidence, provided there is transparency and awareness of HTA evidence requirements, may elect to delay submission until more mature clinical evidence is available. Greater involvement of HTA agencies earlier in clinical development pathways through the use of joint-early dialogue and scientific advice may help to clarify evidence requirements and avoid unnecessary delays in HTA approval [154].

Strengths and limitations

This study relies on a meta-analysis of 339 HTA decisions, spanning 5 HTA agencies and 80 drug-indication pairs. The mixed-methods approach enabled collection of an extensive set of variables relating to scientific and social value judgments, providing novel insights on determinants of HTA decision-making. To the best of our knowledge this is the first empirical study that examines health technology assessment of conditionally approved drugs in comparison to a cohort of standard approval medicines. Our study a) provides important

insights to health regulators, insurers, policy makers, and pharmaceutical companies; and b) offers a methodological approach towards future research on health technology assessment.

The present study is not without limitations. Unavoidably, the small number of conditionally approved drugs present across Europe and Canada limits our sample size. There was a low frequency of HTA rejections within the sample, which places limitations on the precision of model estimates and statistical power. This is evident in the later multivariate models where some covariates have high odd ratios and wide confidence intervals. While the effect of variable groups on explaining variance in HTA outcome are still informative, individual effect sizes in the multivariate model must be interpreted with caution and model power may not have been sufficient to detect all relevant effects. The external validity of findings may be limited by sample selection of standard approval drugs (matching according to therapeutic area and over time) and agency selection. Inclusion of all standard approval drug-indication pairs was not feasible given the extent of data that is collected for each HTA evaluation. Further research including other settings and a more recent sample of drugs would help to validate findings. Finally, exclusion of conditionally approved drugs without HTA assessments (and therefore without HTA data) may bias findings on the extent to which conditionally approved drugs face barriers at HTA level. Manufacturers may elect not to submit drugs that are unlikely to receive HTA approval. Further research is needed to investigate the characteristics of non-submitted conditionally approved drugs.

5.5 Conclusion

Our empirical results indicate that conditionally approved drugs likely face increased barriers at HTA level relative to drugs with standard marketing authorisation, both in terms of HTA outcomes and time to HTA approval. Conditionally approved drugs tend to have lower levels of clinical evidence than drugs with standard marketing authorisation, which likely translates

into a higher level of clinical and economic uncertainties at HTA level and reduced probability of HTA approval. Delays in HTA approval may offset some of the reductions in clinical development time facilitated by the conditional approval pathway. Greater and earlier involvement of HTA agencies in scientific advice processes should be explored as an option to clarify evidence requirements and help to mitigate delays in HTA approval.

5.6 Appendices

Appendix A – Overview of regulatory and HTA systems

Table 5.5 - Comparison of Marketing Authorisation and HTA Systems Across England, Scotland, France, and Canada

	England	Scotland	France	Canada (Ontario)	Canada (Quebec)
A. Regulatory System					
Agency	European Medicines Agency (EMA)			Health Canada	
Conditional Approval Pathway	Conditional Marketing Authorisation (CMA)			Notice of Compliance with Conditions (NOC/C)	
Conditional Approval Criteria	1. Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases; 2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC; or 3. medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.			Promising new drug therapies intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions for which a) there is no alternative therapy available on the Canadian market or, b) where the new product represents a significant improvement in the benefit/risk profile over existing products.	
B. HTA System					
Agency	NICE	SMC	HAS	CADTH	INESSS
Products selection	By submission	By submission	All authorised products	By submission	By submission
Publicly available decision reports (language)	Yes (English)	Yes (English)	Yes (French)	Yes (English)	Yes (French)
Clinical evaluation	Yes	Yes	Yes	Yes	Yes
Economic evaluation	Yes	Yes	No[1]	Yes	Yes[2]

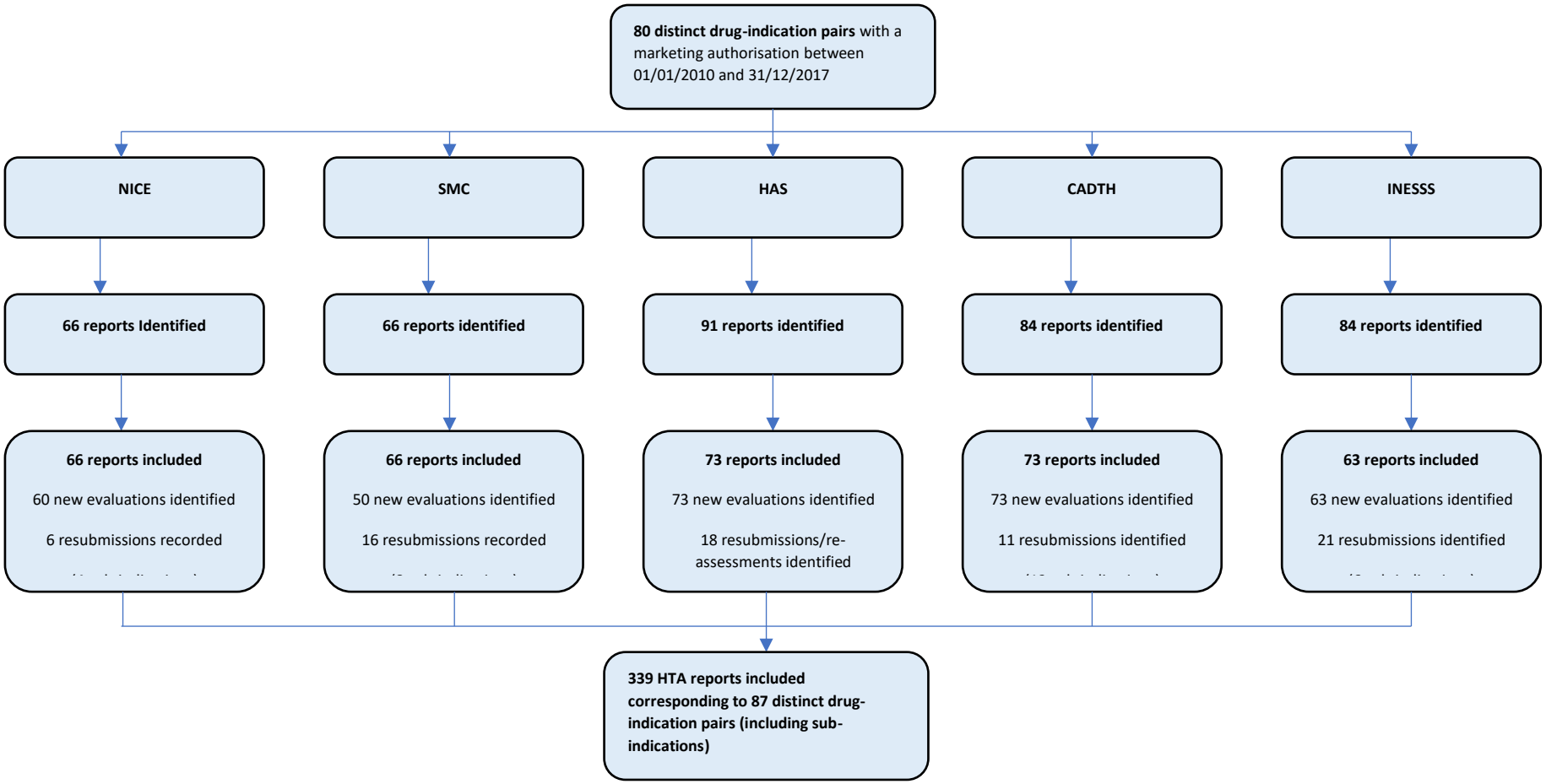
Type of decision	Binding[3]	Binding[4]	Advisory[5]	Advisory[6]	Advisory[7]
Target review time	12 months	6 months	3 months	6 months	6 months
Parallel review available	Yes	No	No	Yes	Yes

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; EC- European Commission; HAS – Haute Autorité de Santé; INESS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium.

Source: The authors, based on a review of regulatory and HTA websites across France, England, Scotland, and Canada.

[1] Cost-effectiveness is not considered as a key criterion during HTA evaluation by the HAS. Products claiming an ASMR (Improvement in medical service rendered) of III or higher must submit an economic dossier which may be used to inform price negotiations following completion of HTA.
[2] Economic evaluation is only appraised by INESSS if the agency determines there is clinically meaningful benefit.
[3] Positively recommended products must be made available to patients by the NHS within 3 months of the decision.
[4] SMC informs NHS boards of positively recommended products four weeks before publishing a decision in order to provide preparation time for introduction of a new medicine in health boards.
[5] The Ministry of Health makes final decisions on reimbursement of a new medicine, according to recommendations from the Transparency committee with HAS and pricing negotiations with the Economic Committee of Healthcare Products (CEPS).
[6] Pricing and reimbursement decisions are made at provincial level. Provinces in Canada (excluding Quebec) use CADTH recommendations to inform decision-making.
[7] The Ministry of Health and Social Services in Quebec makes final pricing and reimbursement decisions based on recommendations from INESSS.

Appendix B - Identification of HTA reports



CADTH - Canadian Agency for Drugs and Technologies in Health; HAS – Haute Autorité de Santé; INESS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

Figure 5.3 - Identification of Matching HTA Reports in NICE, SMC, HAS, CADTH and INESSS.

NICE, SMC, HAS, CADTH, and INESSS websites were screened to identify all matching reports for the 80 included drug-indication pairs between 01/01/2010 and 31/12/2019. Identification and selection of matching reports was performed by two separate reviewers, with any disagreements resolved by a third reviewer. In the event an HTA agency split an indication into multiple sub-indications and conducted separate evaluations on the distinct sub-indications, both reports were included. In the event of a resubmission following an initial rejection, only the most recent evaluation is included. Minor re-assessments following initial positive recommendation are excluded (E.g. for a new dosage form or a re-evaluation of ASMR in the HAS).

Table 5.6 - Breakdown of HTA Recommendations for Included Drug-Indication-Agency Trios

NICE			**SMC**			**CADTH**			**INESSS**		
HTA rejection	HTA approval		HTA rejection	HTA approval		HTA rejection	HTA approval		HTA rejection	HTA approval	
DNL **7**	LWC **58**	L **1**	DNL **8**	LWC **53**	L **5**	DNL **12**	LWC **61**	L **0**	DNL **30**	LWC **33**	L **0**
HAS[1]											
HTA rejection SMR Insufficient	HTA approval SMR Low					HTA approval SMR Moderate			HTA approval SMR Important		
2	ASMR I	0				ASMR I	0		ASMR I	0	
	ASMR II	0				ASMR II	0		ASMR II	4	
	ASMR III	0				ASMR III	0		ASMR III	19	
	ASMR IV	0				ASMR IV	3		ASMR IV	26	
	ASMR V	7				ASMR V	0		ASMR V	12	

ASMR – Added Medical Service Rendered; CADTH - Canadian Agency for Drugs and Technologies in Health; HAS – Haute Autorité de Santé; INESS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium**;** SMR – Medical Service Rendered.

[1] The HAS issues an SMR rating, which determines the reimbursement level and an ASMR rating which determines level of added benefit. There are four possible SMR values: insufficient (0% reimbursement), Low (15% reimbursement), Moderate (30% reimbursement), Important (65% reimbursement). There are five levels of ASMR: ASMR I, II, III (eligible for price negotiations), ASMR IV (price parity to standard of care), ASMR V (priced lower than standard of care).

Appendix C - List of included drug indication pairs

Table 5.7 - Full List of Included Drug Indication Pairs

Conditionally Approved Drug Indication Pairs		
Molecule name	**Brand name**	**Indication**
Alectinib	Alecensaro	As monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK) positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
Asfotase alfa	Strensiq	As long-term enzyme therapy in patients with hypophosphatasia in the childhood and adolescent age to treat the bone manifestations of the disease.
Ataluren	Translarna	For the treatment of Duchenne muscle dystrophy, resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients 5 years of age or more
Avelumab	Bavencio	As monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).
Bedaquiline	Sirturo	For use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.
Blinatumomab	Blincyto	For previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia
Bosutinib	Bosulif	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
Brentuximab Vedotin	Adcetris	For the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.
Brentuximab Vedotin	Adcetris	For the treatment of adult patients with relapse or refractory systemic large cell anaplastic lymphoma (sALCL).
Cabozantinib	Cometriq	For the treatment of medullary thyroid carcinoma in adult patients with progressive, non-resectable, locally advanced or metastatic disease.
Ceritinib	Zykadia	For treating adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib
Crizotinib	Xalkori	For the treatment of advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kynase (ALK+) for adult patients previously treated with at least one other lung cancer treatment
Daclatasvir	Daklinza	In combination with sofosbuvir (SOF), be reimbursed for the treatment of patients with genotype 3 chronic hepatitis C (CHC)
Daratumumab	Darzalex	As a monotherapy for the treatment of adult patients with recurrent and refractory multiple myeloma who have already been treated with a proteasome inhibitor and an immune modulator and have shown a disease progression during the last therapy.
Delamanid	Deltyba	for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

eculizumab	Soliris	For the treatment of patients with atypical hemolytic uremic syndrome (atypical HUS) to inhibit complement-mediated thrombotic microangiopathy
Everolimus	Votubia	For the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.
ex vivo expanded autologous human corneal epithelial cells containing stem cells	Holoclar	Treatment of patients with moderate-severe (superficial corneal neovascularisation in at least two quadrants) limbal stem cell deficiency, unilateral or bilateral with a minimum of 1-2 mm2 of undamaged limbus, due to ocular burns.
Fampridine	Fampyra	For the improvement of walking ability of adult patients with multiple sclerosis (MS) with walking impairment (EDSS 4-7).
Ibrutinib	Imbruvica	For the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL)
Idelalisib	Zydelig	For the treatment of relapsed/refractory follicular lymphoma (FL) that has progressed despite prior treatment with rituximab and an alkylating agent.
Nivolumab	Opdivo	For the treatment of adult patients with classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after: autologous stem cell transplantation (ASCT) and brentuximab vedotin, or 3 or more lines of systemic therapy including ASCT,
Nivolumab	Opdivo	As a monotherapy or in combination with Yervoy in adults for the treatment of advanced (non-resectable or metastatic) melanoma.
Obeticholic Acid	Ocaliva	For treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.
Ofatumumab	Arzerra	To treat, in combination with chlorambucil or bendamustine, patients with CLS who have not received prior treatment and who are not suitable for fludarabine-based treatment (a type of cellular toxicity)
Olaparib	Lynparza	As a monotherapy (alone) for maintenance therapy for ovarian cancer recurrence in patients with a specific mutation, BRCA
Olaratumab	Lartruvo	In combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin
Osimertinib	Tagrisso	For the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy
Palbociclib	Ibrance	Used in patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer
parathyroid hormone	Natpar	For adjuvant therapy in adult patients with chronic hypoparathyroidism which cannot be adequately controlled by conventional treatment alone.
Pazopanib	Votrient	In adults for the first-line treatment of advanced renal-cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.
Pembrolizumab	Keytruda	As a monotherapy for the treatment of advanced (non-resectable or metastasizing) melanoma in adults.
Pembrolizumab	Keytruda	For the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with PD-L1 expressing tumours after prior chemotherapy in adults. Patients with EGFR- or ALK-positive tumour mutations should already have received a therapy approved for these mutations prior to therapy with KEYTRUDA.

Pixantrone	Pixuvri	As monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non Hodgkin B cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy.
Ponatinib	Iclusig	For the treatment of two types of blood cancer, chronic myeloid leukemia (KML) and Philadelphia chromosomal acute lymphocytic leukemia (Ph + ALL)
Romidepsin	Istodax	For the treatment of recurrent peripheral T lymphoma orrefractory, in people:•who are not eligible for a hematopoietic stem cell transplant attime of initiation of treatment;and•whose performance status according to ECOG is 0 to 2
Sebelipase alfa	Kanuma	For the treatment of infants, children, and adults diagnosed with LAL deficiency.
Vandetanib	Caprelsa	For the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease
Venetoclax	Venclexta	For the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy, or patients with CLL without 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options.
Vismodegib	Erivedge	Erivedge is indicated for the treatment of adult patients with: - symptomatic metastatic basal cell carcinoma or - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy

Standard Approval Drug Indication Pairs

Molecule name	Brand name	Indication
Afatinib	Giotrif	For treatment of locally advanced or metastatic non-small cell lung cancer with mutations of epidermal growth factor receptor (EGFR) previously untreated with other EGFR tyrosine kinase inhibitors
Atezolizumab	Tecentriq	For the treatment of adult patients with locally advanced or metastatic non small cell lung cancer (NSCLC) after prior chemotherapy.
Axitinib	Inlyta	Treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine
Bevacizumab	Avastin	In combination with carboplatin and paclitaxel for 'the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer
Bevacizumab	Avastin	In combination with carboplatin and gemcitabine for 'treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents
Bortezomib	Velcade	In combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation
Brentuximab Vedotin	Adcetris	the treatment of adult patients with Hodgkin Lymphona (HL) at increased risk of relapse or progression following autologous stem cell transplantation (ASCT).
Cabozantinib	Cabometyx	For the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy
Carfilzomib	Kyprolis	In combination with dexamethasone alone in the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy

Cobimetinib	Cotellic	In combination vermurafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation
Ceritinib -2	Zykadia	The first-line treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC,
Dabrafenib	Tafinlar	As monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Elosulfase alfa	Vimizim	For the treatment of mucopolysaccharidosis type IVA (MPS IVA)
Eltrombopag	Revolade	For the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in patients who have had a splenectomy and whose condition is refractory to other treatments (for example, corticosteroids or intravenous immunoglobulins), and as a second-line treatment for patients who have not had a splenectomy because surgery is contraindicated
Enzalutamide	Xtandi	For the treatment of adult men with metastatic castration-resistant prostate cancer whose disease progresses during or after chemotherapy with docetaxel.
Everolimus	Afinitor	For treatment of post menopausal women with hormone receptor-positive advanced breast cancer in combination with exemestane, after progression or recurrence (failure) on NSAI therapy.
Ibrutinib	Imbruvica	For previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation
Idelalisib	Zydelig	In combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy
Linaclotide	Constella	For the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (RDS-O) in adults.
Lisdexamfetamine Dimesilate	Elvanse	As part of an overall therapeutic strategy for the treatment of attention deficit Hyperactivity Disorders (ADHD) in children aged six years of age if the response to a previously obtained treatment with methylphenidate is considered clinically unsatisfactory.
Midostaurin	Rydapt	In combination with standard induction and consolidation chemotherapy followed by Rydapt single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are Fms-like tyrosine kinase receptor-3 (FLT3) mutation-positive;
Migalastat	Galafold	For the sustained treatment of adults and adolescents from 16 years of age and older with confirmed Fabry's disease (α-galactosidase A deficiency), which have a mutation responsive to the treatment
Nintedanib	Ofev	For the treatment of idiopathic pulmonary fibrosis (IPF)
Nintedanib	Vargatef	In combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small-cell lung carcinoma (NSCLC) with adenocarcinoma histology after first-line chemotherapy.
Nivolumab	Opdivo	In adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy.
Nivolumab	Opdivo	As monotherapy in adults for the treatment of advanced renal cell carcinoma after pretreatment.
Nivolumab	Opdivo	Treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy
Nivolumab	Opdivo	for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Obinutuzumab	Gazyvaro	In combination with chlorambucil for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them
Obinutuzumab	Gazyvaro	for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen
Pembrolizumab	Keytruda	First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) without activating EGFR or ALK mutations in adults
Propranolol	Hemangiol	For the treatment of proliferative infantile hemangiomas requiring systemic therapy: - Life- or functional hemangioma - Ulcerated hemangioma which causes pain and / or does not respond to simple wound care measures - Hemangioma, Scars or distortion
Regorafenib	Stivarga	For the treatment of a type of gastrointestinal cancer called gastrointestinal stromal cell tumours (GIST)
Ramucirumab	Cyramza	For advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy.
Sarilumab	Kevzara	For the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more biologic or nonbiologic disease-modifying antirheumatic drug (DMARD), as monotherapy or in combination with methotrexate (MTX) or another non-biologic DMARD
Saxagliptin/Metformin	Onglyza	For adult patients aged 18 years and older with type 2 diabetes mellitus to improve blood glucose control: as an oral double therapy and oral triple therapy.
Selexipag	Uptravi	For the long-term treatment of pulmonary arterial hypertension (PAH) in adult WHO-FC patients II to III, either as a combination therapy in patients whose disease is associated with an endothelin receptor antagonist (ERA) and / or a phosphodiesterase- 5 (PDE-5) inhibitor is inadequately controlled or as a monotherapy in patients who are not eligible for these therapies.
Tolvaptan	Jinarc	To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.
Trametinib	Mekinist	For treatment in combination with dabrafenib (Tafinlar) in malignant melanoma.
Trifluridine–tipiracil	Lonsurf	Lonsurf is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents.

Table 5.8 - Taxonomy of Clinical and Economic Uncertainties

Type of Uncertainty	Type of Variable	Description
		Clinical uncertainties
Size of clinical benefit[1]	Continuous	Number of uncertainties raised around the size of clinical benefit extrapolated from the evidence submitted. Coded as overcome or not-overcome.
Generalisability[2]	Continuous	Number of uncertainties raised related to generalisability to the country's population. Coded as overcome or not-overcome.
Study Design[3]	Continuous	Number of uncertainties raised related to clinical trial study design. Coded as overcome or not-overcome.
Indirect Comparison[4]	Continuous	Number of uncertainties raised related to suitability of indirect comparisons. Coded as overcome or not-overcome.
Clinical evidence[5]	Continuous	Number of uncertainties raised related to the availability of clinical evidence. Coded as overcome or not-overcome.
Clinical Practice[6]	Continuous	Number of uncertainties raised related to generalisability to the country's local clinical practice. Coded as overcome or not-overcome.
Comparator Used[7]	Continuous	Number of uncertainties raised related to the compactor in the clinical trial. Coded as overcome or not-overcome.
Adverse event[8]	Continuous	Number of uncertainties raised around the adverse event profile. Coded as overcome or not-overcome.
		Economic uncertainties
Modelling[9]	Continuous	Number of uncertainties raised related to the economic model structure and assumptions. Coded as overcome or not-overcome.
Model Type[10]	Continuous	Number of uncertainties raised related to the appropriateness of the type of model employed. Coded as overcome or not-overcome.
Comparator[11]	Continuous	Number of uncertainties raised related to the compactor employed in the economic model. Coded as overcome or not-overcome.
Cost[12]	Continuous	Number of uncertainties raised related to the cost estimates used in the economic model. Coded as overcome or not-overcome.
Utilities[13]	Continuous	Number of uncertainties raised related to the utilities estimates used in the economic model. Coded as overcome or not-overcome.
Cost-effectiveness[14]	Continuous	Number of uncertainties raised related to the cost-effectiveness estimate in the model. Coded as overcome or not-overcome.
Sensitivity analysis[16]	Continuous	Number of uncertainties raised related to the sensitivity analysis performed. Coded as overcome or not-overcome.

1 Concerns raised around the magnitude of clinical benefit (e.g. is too little or confounded by other factors that are not related to the clinical design) may comprise but are not limited to: (1) Modest or low clinical benefit from trial; (2) The response of the pharmaceutical varied from study to study; (3) The response of the pharmaceutical is effective only in a sub-population; (4) The response of the pharmaceutical is not statistically significant compared with the comparator.

2 Concerns raised around the **generalisability of the population** used in the clinical evidence to the country of the HTA body may comprise but are not limited to: (1) the trial population is not generalisable to the country population due to ethnicity/ baseline characteristics and prevalence; (2) The trial population is not included/underrepresented the population of the indication under review; (3) Only a subgroup of the trial is considered suitable for the indication.

[3] Concerns raised across the design of the trials (blinding, phase and clinical or surrogate endpoints, length, sample size, outcome measure, low patient numbers, study duration). It may comprise but it's not limited to: 1) Limitation in trial design leading to confounding in the clinical benefit (e.g. cross-over) 2) Study blinding unsuitable 3) Sample size (too small) 4) Use of surrogate endpoints vs clinical endpoints.
[4] Concerns raised around the type of indirect comparison, adjustment methods, or studies included in indirect comparison. It may comprise but it's not limited to: 1) indirect comparison not well designed 2) population across different studies non comparable 3) Statistical analysis performed not suitable (e.g. butcher vs Bayesian model)
[5] Concerns raised around lack of comparative clinical evidence, lack of evidence on a subgroup, or lack of long-term clinical evidence. It may comprise but it's not limited to: 1) Lack of comparative clinical data 2) Unsuitable data 3) Lack of long-term evidence 4) Lack of safety data
[6] Concerns raised around **generalisability of the clinical practice** of the clinical trials submitted by the manufacturer (e.g. administration route or pre- and concomitant medication or a different use of the resource of the health system) may comprise but are not limited to: (1) differences in the pathway in the clinical practice of the country; (2) differences in the administration and dose in comparison with the standard of care; (3) When the treatment criteria (e.g. baseline of the patients for starting the treatment) differed between the study and clinical practice; (4) A pharmaceutical may have limited use in the study country (e.g. PBAC clinical pathways).
[7] Comprises all the concerns raised across the comparator(s) such as use of placebo or the use of a comparator different from the one preferred by the HTA bodies or used routinely in the clinical practice. Comparator used in clinical trial was inappropriate. It may comprise but it's not limited to: 1) comparator not marketed in the country 2) comparator not suitable because not used in the clinical practice 3) comparator is not the standard of care in the country 4) Placebo-controlled trial
[8] Concerns around the safety profile of the medicine under evaluation stemmed from the clinical benefit evidence or the EPAR. It may comprise but is not limited to: (1) Substantial number of patients discontinuing the therapies due to adverse events; (2) EPAR with too many safety issues in comparison with current treatment used; and (3) There are notable adverse events that would lead to specific monitoring.
[9] Concerns around the modelling used (e.g. in Markov/ partitioned survival model), or the extrapolation technique used for the clinical data may comprise but is not limited to: (1) the modelling used is not suitable; (2) the use of curves is not appropriate; (3) extrapolations method is not appropriate; (4) misrepresentation of the population under review or of some specific subgroup; (5) any computational errors.
[10] Concerns around the use of a certain model (cost-minimisation or cost-utility etc) in that may not be suitable for the analysis.
[11] Concerns around the appropriate comparator used within an economic model. It may comprise but it's not limited to: 1) comparator used in the economic model is not marketed in the country 2) comparator used in the economic model is not suitable because not used in the clinical practice 3) comparator used in the economic model is not the standard of care in the country.
[12.] Concerns around the **cost data** used to build the model leading to over- or under-estimation of the ICER may comprise but is not limited to: (1) some costs included in the model are too low or too high; (2) the model does not include specific cost that would lead to an over-estimation or under-estimation of the cost-effectiveness such as administration cost or wastage.
[13] Concerns around the **utility data** used to build the model leading to over- or under-estimation of the ICER may comprise but are not limited to: (1) the utility values used in the model are not suitable leading to over-estimation or under-estimation of the ICER; (2) the utility source is not suitable/ or the measured was not appropriate.
[14] Concerns around the magnitude of ICER to high or too much uncertainty in ICER estimate. It may comprise but it's not limited to: 1) cost-effectiveness over the threshold 2) ICER too high even after testing with sensitivity analysis or re-evaluation carried out by manufacturer/HTA body/ external reviewers
[15] Concerns around the clinical evidence used in the economic model. It may comprise but it's not limited to: 1) the clinical evidence used in the economic model is not suitable due to limitations such as sample size, poor trial design etc. 2) there is a lack of evidence following the nature progression of the disease (e.g. lack of long-term evidence) 3) the indirect comparison used to populate the clinical input of the model is poorly design/with an unsuitable design
[16] Sensitivity analysis performed to demonstrate robustness of model inappropriate or missing. It may comprise but it's not limited to: any issues around the sensitivity analysis performed by the manufacturer or by the HTA body experts. The sensitivity analysis produced cost-effectiveness ratios outside of acceptable levels The sensitivity analysis did test the deterministic sensitivity of a key variable or assumption.

Source: The authors, adapted from [19].

Table 5.9 - Multivariate Logistic Regression of HTA Outcomes Across France, England, Scotland, Canada, Controlling for Clinical Uncertainties

		Model 0	Model 4
Clinical Benefit	Overcome	3.051*** (0.958)	9.071*** (4.618)
	Not-overcome	0.557** (0.142)	0.331*** (0.1239)
Clinical Evidence	Overcome	5.588 (6.229)	12.582* (19.26)
	Not-overcome	0.961 (0.236)	1.754 (0.685)
Study Design	Overcome	1.297 (0.402)	1.440 (1.397)
	Not-overcome	0.559*** (0.101)	0.132*** (0.055)
Indirect Comparison	Overcome	1.197 (1.139)	0.238 (0.279)
	Not-overcome	1.631 (0.764)	4.090** (2.487)
Comparator	Overcome	2.077 (1.158)	0.796 (0.824)
	Not-overcome	4.972** (3.689)	155.43*** (197.59)
Generalisability	Overcome	0.660 (0.372)	2.367 (3.302)
	Not-overcome	1.019 (0.407)	0.853 (0.398)
Clinical Practice	Overcome	12.276 (0.713)	1.712 (1.607)
	Not-overcome	0.817 (0.320)	1.712 (1.670)
Adverse Events	Overcome	0.732 (0.368)	0.808** (0.564)
	Not-overcome	0.275** (0.142)	0.036*** (0.045)
Number of Observations		326	326
Pseudo-R^2		0.436	0.656
AIC		233.2	184.3
Time FE		Yes	Yes
Agency FE		Yes	Yes

Association between clinical uncertainties and HTA outcomes without controlling for covariates (Model 0) and controlling for covariates specified in model 4. Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies. Only coefficients for clinical uncertainties are reported.

P-Values *p<0.1; **p<0.05; ***p<0.01

Table 5.10 - Multivariate Logistic Regression of HTA Outcomes Across England, Scotland, Canada, Controlling for Economic Uncertainties

		Model 0	Model 4
Modelling	Overcome	3.900*** (2.027)	5.166** (3.591)
	Not-overcome	1.047 (0.178	1.112 (0.212)
Model Type	Overcome	1.222 (1.659)	0.948 (0.990)
	Not-overcome	1.410 (1.384)	1.006 (1.22)
Comparator	Overcome	3.971 (3.544)	2.421 (2.482)
	Not-overcome	0.769 (0.405)	0.676 (0.388)
Costs	Overcome	1.913 (1.759)	0.673 (0.271)
	Not-overcome	0.743 (0.219)	7.481 (5.819)
Utilities	Overcome	5.396 (6.181)	7.481*** (5.819)
	Not-overcome	0.412 (0.148)	0.346** (0.164)
Cost-effectiveness	Overcome	3.010* (1.802)	2.431 (1.672)
	Not-overcome	1.272 (0.320)	1.11 (0.283)
Sensitivity Analysis	Overcome	-	-
	Not-overcome	1.101 (1.302)	-
Number of Observations		326	326
Pseudo-R^2		0.304	0.421
AIC		264.4	241.9
Time FE		Yes	Yes
Agency FE		Yes	Yes

Association between economic uncertainties and HTA outcomes without controlling for covariates (Model 0) and controlling for covariates specified in model 4. Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies. Only coefficients for economic uncertainties are reported.

P-Values *p<0.1; **p<0.05; ***p<0.01

Table 5.11 - Linear Regression Models Exploring Association of SVJs and Uncertainties

	Model 1	Model 2	Model 3	Model 4
Dependent Variable: Total number of uncertainties raised				
Disease Severity	0.68** (0.296)	1.274*** (0.313)	-0.085 (0.245)	-0.014 (0.197)
Unmet Need	0.507* (0.291)	0.461 (0.419)	-0.091 (0.304)	0.662** (0.302)
Administration Advantage	-0.127 (0.349)	-0.119 (0.368)	-0.542*** (0.172)	-0.033 (0.227)
Innovation	1.500*** (0.280)	-0.197 (0.348)	1.484***u (0.204)	0.060 (0.230)
Quality of Life	0.689** (0.337)	0.483 (0.406)	-0.061 (0.189)	1.174*** (0.279)
Demographics	-0.125 (0.580)	0.659 (0.420)	-0.550** (0.215)	0.344 (0.398)

Linear regressions exploring the association SVJs with total clinical uncertainties overcome (Model 1), total clinical uncertainties not overcome (Model 2), total economic uncertainties overcome (Model 3) and total economic uncertainties not overcome (Model 4). Coefficients and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies

P-Values *p<0.1; **p<0.05; ***p<0.01

Table 5.12 - Multivariate Logistic Regression Models Without Fixed Effects Comparing Positive and Negative HTA Outcomes Across NICE, HAS, SMC, CADTH and INESSS.

	Model E0	Model E1	Model E2	Model E3	Model E4	Model E5
Dependent Variable: HTA Outcome (List or List with condition: 1, Do not list: 0)						
A) Regulatory Approval						
Conditional Approval	0.558** (0.162)					
B) Disease Characteristics						
Cancer		2.399** (0.872)	2.181** (0.767)	1.755 (0.671)	1.745 (0.737)	2.057 (0.925)
Orphan		5.257*** (2.313)	7.154*** (3.217)	5.921*** (2.911)	7.596*** (4.329)	6.243*** (4.462)
C) Submission History						
Resubmission		1.529 (0.667)	1.488 (0.647)	1.654 (0.736)	1.821 (0.851)	2.421 (1.403)
D) Pivotal Trial Characteristics						
Trial Phase			2.025* (0.757)	1.974 (0.849)	2.894** (1.432)	2.315 (1.184)
Endpoint			1.268 (0.514)	1.153 (0.485)	1.092 (0.495)	1.097 (0.525)
Comparator			2.173** (0.727)	1.769 (0.686)	1.459 (0.626)	1.296 (0.560)
E) Uncertainties						
Clinical Overcome				1.135 (0.097)	1.118 (0.100)	1.196* (0.125)
Clinical Not-Overcome				0.813***	0.789***	0.756***

				(0.048)	(0.053)	(0.058)
Economic Overcome				1.420*** (0.165)	1.904*** (0.292)	2.258*** (0.421)
Economic Not-Overcome				0.817*** (0.059)	0.786*** (0.065)	0.940 (0.098)
F) Social Value Judgments						
Disease Severity					2.267* (1.032)	1.365 (0.686)
Unmet Need					0.698 (0.371)	0.429 (0.252)
Administration Advantage					2.040 (1.057)	3.074** (1.569)
Innovation					0.867 (0.415)	0.775 (0.379)
Quality of Life					1.282 (0.464)	1.880* (0.682)
Special Demographics					3.208 (2.515)	4.771 (3.360)
Number of Observations	339	339	339	339	339	256
Pseudo-R^2	0.127	0.062	0.108	0.224	0.287	0.334
AIC	311.1	299.66	291.4	262.7	247.6	210.5
Time FE	No	No	No	No	No	No
Agency FE	No	No	No	No	No	No

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; FE – Fixed Effects; HAS – Haute Autorité de Santé (HAS); NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

Model E0 is a reference case controlling only for type of marketing authorisation. Disease characteristics and submission history (Model E1), pivotal trial characteristics (Model E2), Uncertainties (Model E3) and Social Value Judgments (Model E4) were added sequentially. Model E5 presents results for cost-effectiveness countries only (excluding France). Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies. No time or agency fixed effects are included in any model.

P-Values *p<0.1; **p<0.05; ***p<0.01

6. CONCLUSION

6.1 General overview

The nature of pharmaceutical development has changed drastically over the past 20 years, highlighted by a shift from small molecules to complex targeted and specialised therapies [209]. This has been largely driven by advancements in molecular genetics, biochemistry and our understanding of disease pathology [210]. Over this period, we have seen the first cell and gene therapy approved, a wide range of new orphan products, and the development of tumour agnostic therapies that target specific disease pathways involved in tumour pathogenesis across several different types of cancers [211]. While these therapies have tremendous potential to improve outcomes for patients across wide range of diseases, they also present unique challenges to healthcare systems which increasingly face pressure to make regulatory and funding decisions on high-cost therapies based on limited clinical data [212].

Given the dynamic nature of the pharmaceutical market it is imperative that regulatory policy and HTA policy adequately respond to the pace of innovation and new challenges presented by innovative therapies. This thesis explored the relationship between regulatory approval and HTA, and the associated implications on patient access to innovative therapies in two contexts that are increasingly relevant given current trends in pharmaceutical R&D: a) conditional marketing authorisation and b) approval of medicines with multiple therapeutic indications.

Three broad research questions were considered across four papers:

I) To what extent do conditional approval pathways accelerate firm entry in the pharmaceutical market, given HTA evidence requirements for reimbursement?

II) To what extent do differences in criteria applied, interpretation of evidence and use of social value judgments help explain the heterogeneity seen across settings in availability of medicines?

III) To what extent and on what basis do firms sequence the development and launch of multi-indication medicines?

Paper 1 presented a cohort analysis of 40 innovative medicines that have received conditional approval in Europe or in Canada, based on a comprehensive dataset obtained through a meta-analysis of publicly-available regulatory reports and HTA reports. This paper included an examination of the conditions of marketing authorisation, and analysis of the evidence gap between regulatory agencies and HTA agencies, a comparison across settings of HTA outcomes for conditionally approved medicines and a descriptive analysis of how HTA agencies interpret and appraise clinical and economic evidence for conditionally approved medicines.

Paper 2 provided a cohort analysis of 31 innovative oncology medicines with multiple approved therapeutic indications across England, Scotland, France, Germany, the USA, Canada and Australia, based on meta-analysis of regulatory approvals and HTA outcomes for 118 therapeutic indications. This study includes a mapping of regulatory approval and HTA recommendation sequence to identify instances of launch sequencing. Further, the characteristics of first vs subsequent indications are compared with the aim of understanding how pharmaceutical firms prioritise the development and launch of indications.

Paper 3 presented insights from current and former healthcare payers across nine OECD countries on pricing policy for medicines with multiple approved therapeutic indications. This

paper includes primary data from semi-structured interviews on current practices of price-setting for medicines with multiple distinct indications, on healthcare payer perspectives on how pricing practices impact the launch of multi-indications, and on the barriers and opportunities for implementing a formalised price discrimination system.

Paper 4 provided an econometric analysis of HTA barriers for conditional approval medicines. This paper relies on a meta-analysis of HTA recommendations for 40 conditionally approved drug-indication pairs and 40 standard approval drug-indication pairs across England, Scotland, France, and Canada. This paper includes a comparison of HTA for conditionally approved and standard approval medicines in terms of clinical evidence, scientific value judgments, social value judgments, HTA outcomes and time from marketing authorisation to HTA approval. It also provides an analysis of how clinical evidence, scientific value judgments, and social value judgments influence HTA outcomes.

This concluding chapter provides a summary of the key findings and contributions to literature of papers I-IV, a discussion on policy implications, a summary of the key limitations and ideas for future research.

6.2 Summary of key findings and contributions to literature

Study 1 – How do HTA Agencies Perceive Conditional Approval of Medicines? Evidence from England, Scotland, France, and Canada

Key Messages

1. **A significant proportion of conditionally approved medicines face rejection at HTA level, although the rate of rejection varies across settings.**
2. **In the majority of cases, evidence from confirmatory trials is not available at the time of HTA.**
3. **Rejected conditionally approved medicines were more likely to have unresolved uncertainties related to the magnitude of clinical benefit, study design, and issues in economic modelling**

This study found substantial variability across HTA agencies in the rate of rejection of conditionally approved medicines. INESSS in Quebec had the highest proportion of rejections (50% of conditionally approved products evaluated), followed by the SMC in Scotland (25%), CADTH in Canada (21%), NICE in England (6.7%) and HAS in France (4.7%). Across the aggregate sample, consideration of rarity as a social value judgment positively influenced HTA outcomes, while clinical issues in study design, and economic issues related to cost-effectiveness had a negative impact.

Over half of conditional approvals in both the EMA and Health Canada were based on non-randomised clinical evidence. The most common pivotal trial design for conditionally approved medicines was single arm phase II trials. Three types of conditions were imposed by regulators for conditional approvals: a) submission of follow-up data from the pivotal clinical trial; b) completion of a confirmatory phase II trial; or c) completion of a confirmatory phase III trial. Across all agencies, confirmatory trials were not available at the time of HTA for majority of assessments and HTA agencies relied on the same trial used to support regulatory approval. Evidence from confirmatory trials was available in 38% of HAS submissions, 40%

of NICE submissions, 33% of SMC submissions, 43% of CADTH submissions, and 43% of INESSS submissions.

HTA agencies do not rely on a single metric or criteria to arrive at an assessment outcome. A range of scientific and social value judgments were raised by HTA agencies during the evaluation of conditionally approved medicines. There were notable variations across settings in the frequency and types of uncertainties and SVJs raised. In the HAS in France, issues relating to the magnitude of clinical benefit or study design and consideration of disease rarity and unmet need were key in differentiating ASMR ratings. Within NICE, issues relating to the magnitude of clinical benefit, lack of clinical evidence, cost estimates and utility estimates contributed to their lone rejection of a conditionally approved medicine. Within the SMC, key parameters associated with HTA outcomes included issues in magnitude of clinical benefit, study design, trial generalisability, cost estimates and utility estimates, along with consideration of disease rarity and administration advantage. Within Canada, key parameters raised within CADTH included issues in study design, trial generalisability, economic modelling, and consideration of unmet need. Within INESSS, key parameters included issues in magnitude of clinical benefit, study design, cost estimates and consideration of mechanism of action and administration advantage.

At the time of this study, only a very limited body of literature addressing HTA for conditionally approved medicines was available including two studies which present single-setting analysis [198, 199], one study which provides preliminary descriptive data on HTA outcomes and timelines for oncology conditionally approved medicines in Europe [14], and one study which examines the role of trial controls on HTA outcomes in Europe [142].

This study provides three notable contributions to the literature and to our understanding of HTA on conditionally approved medicines. First and foremost, a meta-analysis and detailed

analysis of HTA outcomes across settings for conditionally approved medicines was lacking. The mixed-methods approach employed in study 1 enabled the creation of a comprehensive dataset on the parameters considered during HTA of conditionally approved medicines, on the interpretation of evidence and on the consideration of additional dimensions of value beyond clinical and economic evidence. A total of 49 marketing authorisation reports and 102 HTA reports were included in the analysis. In particular, inclusion of scientific and social value judgments in the analysis of HTA outcomes for conditionally approved medicines represents a novelty in the field. In doing so, this study provides important empirical evidence on the key issues HTA agencies consider when evaluating conditionally approved medicines and the extent to which social values such as unmet need, disease severity, and disease rarity can compensate for high levels of uncertainty.

Secondly, this study contributes to our understanding of the interaction between the dynamic nature of evidence generation for conditionally approved medicines and HTA. By nature, conditional approval shifts evidence generation from pre-approval to post-approval through conditions to complete confirmatory trials. This study includes a comparison of the evidence considered by regulatory agencies and HTA agencies and data on the extent to which evidence from confirmatory studies was available at the time of HTA.

Finally, this study provides international comparative data on Health Canada's NOC/C pathway and EMA's conditional marketing authorisation pathway. Despite similar eligibility criteria (both pathways require that an unmet need is addressed and are restricted to serious, life threatening, or chronically debilitating diseases), concordance in conditionally approved drug-indication pairs is low, highlighting either a difference in the commercial strategy of pharmaceutical firms across settings or a difference in how these agencies apply these criteria. Concordance was also low across all HTA agencies (only 38 % of EMA conditionally approved

medicines had positive outcomes across each of NICE, HAS and SMC, while only 46% of NOC/C approvals had positive recommendations in both CADTH and INESSS.

Study 2 – Launch Sequencing of Pharmaceuticals with Multiple Therapeutic Indications: Evidence from Seven Countries

Key Messages

1. **Pharmaceutical firms frequently sequence or withhold the launch of therapeutic indications for multi-indication products.**
2. **Pharmaceutical firms show a tendency to prioritise the launch of niche indications which address an unmet need.**

This study found substantial heterogeneity in global launch sequence, national regulatory approval sequence, and HTA approval sequence of multi-indication oncology medicines. No multi-indication medicine had a positive HTA coverage recommendation for all globally launched indications. The first indication launched for a medicine had a higher frequency of positive HTA recommendations relative to subsequent indications, ranging from 91% in the GBA to 72% in CADTH, with 88%, 84%, 81%, and 78% of first indications receiving positive recommendations in HAS, NICE, SMC and PBAC respectively. The frequency of positive HTA recommendations of subsequent indications ranged from 70% by the HAS to 56% by NICE, with 67%, 59%, 58%, and 58% of subsequent indications receiving positive recommendations in G-BA, CADTH, PBAC, and SMC respectively.

Relative to subsequent indications, the first indication launched for a medicine was more likely to receive conditional marketing authorisation, have an orphan designation, have a weaker study design and have a lower MCBS score. Within Germany and France, MCBS scores are significantly associated with HTA outcome. Products with an MCBS score of 1,2 or 3 were more likely to receive a rating of no added benefit or an SMR of insufficient. No significant differences in HTA outcome vs MCBS score were identified in NICE, SMC, CADTH or

PBAC, indicating greater flexibility in the acceptability of surrogate outcomes and weaker study designs.

Pharmaceutical firms can engage in sequencing both during development, in terms of which therapeutic indication they prioritise during R&D, and post-development, in terms of whether they launch a therapeutic indication in a market and the order in which they launch that indication. The results of this study suggest that post-development sequencing occurs mainly via withholding the launch of an indication, rather than delaying launch of an indication. No significant differences were identified in time from pivotal trial initiation to regulatory approval for first vs subsequent indications. Median clinical development time was fastest in the USA, followed by Europe, Australia, and Canada. In terms of HTA coverage recommendation timelines, first indications required significantly longer to receive approval than subsequent indication in England and Canada. This could partly be explained by the lower quality of evidence and increased proportion of conditional approvals in the first indication cohort. Within France, first indications received recommendations marginally faster than subsequent indications. No significant differences were identified for Australia, Germany, or Scotland across first vs subsequent indications for HTA coverage recommendation timelines.

At the time of this study, literature on pricing practices for multi-indication products was limited to papers on the economic theory of price discrimination and indication-based pricing [61-64], a simulation exploring the impact of indication-based pricing [63], an economic evaluation on an individual multi-indication medicine [158] or literature reviews [66, 159] [10,11]. Further, while the current body of empirical literature on firm entry and diffusion of medicines [59, 69, 71-73] has identified a number of pertinent factors associated with the launch of a medicine (including market size, competition, and firm size), the launch of a previously approved indication has not been considered.

This study provides three notable contributions to the literature. First, a meta-analysis and mapping of the launch and diffusion of multi-indication products was lacking. In many settings, countries have implemented indirect methods of price discrimination, either through weighted pricing models or differential discounting. In the absence of empirical evidence on the launch and assessment of multi-indication pricing, it was unclear whether or not these indirect approaches adequately captured the incremental value of indications and facilitated access to newly launched therapeutic indications or if perverse incentives still remain for firms to sequence or withhold the launch of therapeutic indications. This study provides empirical evidence that pharmaceutical manufacturers frequently withhold the launch of therapeutic indications or receive a negative HTA recommendation (indicating a disconnect between agency and firm on the value of a product in a therapeutic indication). Notably, this occurs more frequently for subsequent indications than first indications, supporting the notion that current indirect approaches of price discrimination still generate incentives to engage in launch sequencing.

Second, this study provides an interesting conceptual framework to analyze the launch of multi-indication products, which distinguished between pre-development sequencing and post-development sequencing. The development and launch of a pharmaceutical is a multi-faceted process involving a series of decision points. Decisions to develop a product or to launch a product in a specific market are dynamic and may change as new data or information becomes available. Through a comparison of the characteristics of first vs subsequent indications, this study shows the pre-development sequencing likely results in the prioritisation of developing indications in rare populations where there is high unmet need. On the other hand, post-development sequencing occurs through the withholding of indication launch and discordance in the global launch sequence, national regulatory launch sequence and HTA recommendation sequence.

Finally, this study provides international comparative evidence on the diffusion of multi-indication medicines through an analysis of clinical development time and time to HTA approval. Empirical evidence is provided on average time from pivotal trial initiation to regulatory approval, the extent to which this varies across regulatory bodies, and the extent to which these timelines are impacted by the launch of a previous indication. The same is also shown for time from regulatory approval to HTA.

Study 3 – Healthcare Payer Perspectives on the Assessment and Pricing of Oncology Multi-Indication Products: Evidence From Nine OECD Countries

Key Messages

1. **There are five different approaches to pricing of multi-indication products: weighted pricing, differential discounting, mandatory discount, price anchoring, and free pricing.**
2. **Healthcare payers indicated that pharmaceutical firms show a tendency to launch first in niche indications with high unmet need in order to achieve a high price in the first indication.**
3. **Despite evidence that manufacturers may withhold the launch of indications, healthcare payers generally consider their current pricing approaches fit-for-purpose and express concern over the administrative burden of a formal indication-based pricing system.**

This study identified a number of different approaches to the assessment and pricing of multi-indication products. England, Spain, Italy, France, Belgium, Switzerland, and Canada all employ HTA as a key tool for informing pricing and reimbursement and require full assessments for each indication for a given molecule. France, Spain, Belgium and Canada employ a weighted pricing approach for multi-indication products, whereby the reimbursement price for a molecule is renegotiated upon launch of a new indication. Within England and

Switzerland, it is possible for different indications to have different discount rates, although in both settings uniform discounting is preferred, and application of differential discounting is reserved for extreme cases where there are significant deviations in the value of two indications. Italy has begun to transition away from a model which facilitate individual managed entry schemes at indication level towards simple discounting. The launch of a new indication triggers a mandatory discount proportional to the increase in budget impact. The discount rate is determined through a deliberative process which accounts for quality of evidence, unmet need and added benefit. In Turkey the price is anchored according to the price of the first indication launched. Finally in the USA, free pricing applies, although individual PBMs may renegotiate discounts upon launch of a subsequent indication. Apart from the USA, no interview respondents could identify an example of price increases following launch of a new indication.

Healthcare systems vary in their capacity to track product use at indication level. Italy, Spain, Belgium, Switzerland, and Canada all have high capacity to track product use at indication level, while limitations in monitoring capacity were identified in England, France, Turkey and the USA.

Healthcare payers were asked to provide observations on the characteristics of first indications and on the priorities of pharmaceutical firms when launching multi-indication products. Across all settings, payers indicated that pharmaceutical firms prioritise achieving a highest first price for the first-indication launched across all healthcare systems. It is unclear whether this is a natural product of R&D considerations (given the cost of R&D it follows that firms would prioritise development of therapeutic indications with the highest market potential) or reflects the need to set a high first price, given expected price erosion upon launch of subsequent indications. This is further complicated by the presence of external reference pricing which further incentivises firms to achieve and maintain high prices, regardless of the number of uses

of a product. Other common priorities that were identified by healthcare payers include small populations and high unmet need.

Expectations were low for adoption of a formal indication-based pricing system. All healthcare payers identified administrative complexity as a key barrier towards implementation of formal indication-based pricing. Other barriers to implementation of indication-based pricing included monitoring capacity (England, France, and USA), supply chain issues (England, France, Spain, Italy, Belgium, USA, Canada) and regulatory/legal structure (England, Turkey, USA). Generally there is low political interest in adopting this type of system and the majority of healthcare payers consider their current system fit-for-purpose for the pricing and reimbursement of multi-indication products. Within France, Italy and Belgium, healthcare payers acknowledge that manufacturers may withhold the launch of therapeutic indications, however expressed confidence that this would typically only occur if therapeutic alternatives were available.

As noted above, while the number of publications relating to pricing of multi-indication products is increasing, overall evidence on pricing and access to multi-indication medicines remains scarce [179]. Further, many of the conceptual papers advocating for formal indication-based pricing [64, 157, 176, 177], do not accurately reflect current practices in pricing of multi-indication products. Indication-based pricing models may maximise social welfare relative to single-pricing models, however the social welfare implications of weighted pricing or differential discounting models have not been explored.

This study provides three notable contributions to the literature. First and foremost, it helps to validate and contextualise the empirical evidence presented in study 2, along with two additional recently published studies relating multi-indication oncology products [180, 181], which showed evidence that manufacturers sequence the development and launch of multi-

indication medicines. Healthcare payer perspectives on how pharmaceutical firms sequence development and launch of multi-indication medicines were generally consistent with the results of empirical analysis. However, many healthcare payers remain unconvinced that this occurs to the detriment of patients, and express confidence that current pricing practices adequately safeguard patient interests and would facilitate access to medicines in cases where a true unmet need is addressed.

Second, this study provides important primary evidence on the practicalities of implementing a formalised indication-based pricing system. Healthcare payers, by nature, are likely in the best position to comment on the challenges in administering payment models and the feasibility of adopting pricing reforms. Low willingness to implement a formal indication-based pricing approach and strong preferences towards administrative simplicity represent key barriers to future policy reform in this area. In particular, the finding that Italy has transitioned towards simple discounts, following their experience implementing complex agreements at indication level is highly relevant.

Finally, the review of assessment practices, price setting practices, and monitoring capacity provides new evidence, validation, much needed granularity on processes and important updates (for Italy and UK) to existing literature on pricing practices for multi-indication products [179].

Study 4 – HTA Barriers for Conditional Approval Drugs

Key Messages

1. **The ability of conditional marketing authorisation pathways to expedite patient access to innovative therapies is offset by barriers at HTA level. Relative to medicines with standard approval, conditionally approved medicines have a marginally increased probability of rejection and face delays in receiving HTA approval.**
2. **Conditionally approved medicines have lower quality of evidence, leading to higher frequency of clinical and economic issues raised at HTA level.**
3. **Scientific value judgments on clinical and economic evidence had the largest impact on explaining variations in HTA outcomes. No significant effects were identified for social value judgments.**

This study found a number of significant differences in characteristics of conditionally approved medicines and medicines with standard approval. Notably, conditionally approved medicines were more likely to have a lower trial phase, less likely to include a clinical endpoint, and less likely to include an active comparator. By extension, HTA agencies are more likely to raise unresolved clinical and economic uncertainties for conditionally approved medicines. Unsurprisingly, HTA agencies are also more likely consider disease severity and unmet need during their appraisal of conditionally approved medicines. Overall, the rate of HTA rejection was marginally higher for conditionally approved medicines relative to standard approval medicines.

Fixed-effects multi-variate models explored the association between disease characteristics, pivotal trial characteristics, scientific value judgments (uncertainties), and social value judgments with HTA outcomes. Scientific value judgments had the largest effect on HTA outcomes. Clinical and economic uncertainties that are addressed through submission of supplemental data, patient submissions or clinical expert submissions improved the likelihood of a positive HTA outcome, while unresolved uncertainties decreased the likelihood of HTA outcomes. Supplementary analysis indicated that the clinical uncertainty effect is driven by

issues in the magnitude of clinical benefit and design, although interpretation of results is limited by study sample size. Issues in modelling appear to predominantly drive the economic uncertainty effect, although again interpretation of results is limited by study sample size. Disease characteristics had a positive effect on HTA outcomes; orphan drugs and cancer drugs are more likely to receive a positive HTA outcome. Products with a previous submission were also more likely to receive a positive HTA outcome. This finding is intuitive as resubmissions provide pharmaceuticals with opportunities to address issues in the original submission. Interestingly, no social value judgments had a significant effect on HTA outcomes.

Survival analysis indicates that conditionally approved medicines face longer delays in receiving HTA approval than standard approval medicines. Median time from marketing authorisation to HTA approval was 6 months longer in the conditionally approved medicine cohort.

As noted above, a small number of studies have begun to examine HTA on conditionally approved medicines. This includes single HTA setting evaluations of conditionally approved medicines [198, 199], a descriptive analysis of HTA timelines and outcomes [14], and two descriptive studies which examine the impact of study design and post-approval studies on HTA outcomes in Europe [187, 200].

This study provides four notable contributions to the literature. First, the existing body of literature is restricted in scope to examination of HTA on conditionally medicines only, limiting our understanding of whether these medicines face barriers at HTA level over and above drugs with standard authorisation. This comparison is critical as it enabled us to determine whether the negative outcomes for conditionally approved medicines are driven by higher levels of uncertainty or if HTA agencies simply have high rates of negative outcomes generally.

Second, this study provides a meaningful empirical contribution to our understanding of the broader HTA landscape and factors that influence firm entry and availability of medicines. Importantly, pharmaceutical firms are unlikely to consider an individual HTA agency's requirements in silo in order to inform their evidence generation activities. Rather, firms will likely reflect on the totality of evidence requirements across agencies, weighted according to the importance of accessing a specific market. While single-setting analysis is useful to understand the factors associated with a particular agency's decision-making, it does not necessarily enable a meaningful understanding of the broader conditions, barriers and incentives of firm entry and availability of medicines. By aggregating outcomes through a multivariate model, this study explores these factors in a more substantive way. This approach also enables an exploration of the extent to which country specific differences contribute to HTA outcomes (controlling for agency and time fixed-effects accounts for over 15% of variation in our model).

Third, data collection presents a key challenge in research on HTA processes and decision-making. Existing studies examining HTA for conditionally approved medicines are largely limited to single-setting analysis and a small number of variables. The data collection process in the present study was extremely comprehensive and intensive given the mixed-methods approach adopted (extraction of a wide-range of parameters for each HTA evaluation through qualitative analysis of decision text). This enabled creation of a comprehensive dataset of HTA outcomes spanning 80 drug-indication pairs and a total of 339 HTA reports. As a result, this study was in a unique position to undertake quantitative analysis and assessment of HTA outcomes across a wide-range of variables that potentially influence HTA decision-making.

Finally, existing literature on firm entry and diffusion of medicines [68, 69, 71-73] has predominantly focused on the role of market characteristics, firm characteristics and competition on diffusion of medicines. The findings of this study highlight the importance of considering the impact of drug characteristics on firm entry to pharmaceutical markets. Survival analysis showed differences between conditionally approved medicines and standard approval medicines in time to HTA approval, suggesting that the quality of evidence of a product and by extension to level of uncertainty in clinical evidence has an influence the rate of adoption of a new medicine. To the extent that challenges in data collection can be overcome, these factors should be considered in future research on medicine diffusion.

6.3 Policy implications

Greater alignment is needed between regulatory agencies and HTA agencies on evidence requirements for conditionally approved medicines. The findings of papers I and IV suggest that to varying degrees, HTA limits the ability of conditional marketing authorisation pathways to expedite patient access to medicines that address an unmet need for a serious, life-threatening, or chronically debilitating diseases. This disconnect between conditional marketing authorisation and HTA raises questions about whether existing regulatory and HTA policies adequately safeguard patient interests.

On the one hand, regulatory agencies and HTA agencies have fundamentally different objectives. While regulatory agencies seek to ensure products have a positive benefit-to-risk ratio, HTA agencies evaluate relative clinical effectiveness and, in many cases, cost-effectiveness to inform pricing and reimbursement decisions. It follows that regulatory agencies and HTA agencies may arrive at different decisions on a medicine. At the same time, the risk to patients associated with HTA rejections or delays in approval is potentially the highest for conditionally approved medicines, given that these products are targeted towards life-threatening and chronically debilitating diseases. While complete harmonisation of regulatory decisions and HTA outcomes may not be pragmatic, it is likely that more can be done to tailor HTA processes to conditionally approved medicines. In particular, HTA agencies should consider implementing conditional reimbursement pathways, such as England's Cancer Drugs Fund [152]. These pathways provide time-limited reimbursement, which leads to greater flexibility for medicines with high levels of uncertainty that require evidence maturation or additional data collection. In principle this enables HTA agencies to better utilise data collected via confirmatory studies, but also real-world evidence [213]. However, use of these pathways should be restricted to limited cases to ensure that the added administrative burden of re-evaluating medicines does not outweigh the benefit of collecting more mature data.

Beyond adopting more flexible approaches to managing clinical uncertainty, HTA agencies should also be more proactive in clarifying evidence expectations for conditionally approval medicines at early stages in evidence generation planning. Enhanced engagement with regulatory agencies through joint early dialogue would help to mitigate negative HTA outcomes and avoid unnecessary delays in HTA approval. In particular, joint early dialogue should be considered for medicines which treat disease areas with ethical or practical barriers to evidence generation. Recently launched pathways in Europe including the EMA-EUnetHTA Parallel consultation procedure and the EUnetHTA-Multi HTA Early Dialogue provide a good roadmap for how this can be achieved, however limited evidence is available on their impact thus far [27, 154].

At regulatory level, there is a need for a comprehensive evaluation on the benefits of conditional marketing authorisation pathways. Previous literature on conditional marketing authorisation has highlighted a range of concerns regarding these pathways [138], including an increased frequency of post-market safety events and poor completion rates of confirmatory studies [139]. These findings coupled with issues identified at HTA level and a number of marketing authorisation withdrawals, raise questions about whether regulatory agencies have achieved the right balance in the trade-off between certainty of evidence vs disease severity and unmet need. In the same manner that HTA delays to potentially beneficial treatments present a risk to patients, approval of products with immature data also presents a risk. While regulatory agencies justify this risk by the absence of therapeutic alternatives, more work is needed to validate the real-world benefit of conditional approval pathways.

Multi-indication products present unique challenges to healthcare systems. Regulatory agencies have established pathways to promote development of medicines across multiple therapeutic indications, some of which even provide extensions to data exclusivity and market protection. However, findings from papers II indicate that adoption of multi-indication

medicines is highly variable and that manufacturers frequently withhold or sequence the launch of therapeutic indications under established pricing practices. According to healthcare payers in paper III however, the extent to which this is detrimental to patients is questionable, as payers express confidence that the withholding of indications typically only takes place when there are therapeutic alternatives available. However, it could be argued that this is a complacent view. By nature, healthcare payers are the most likely of any stakeholder group to emphasize the need for practicality and it is possible that they may wish to avoid making the investments needed to implement a more formalised IBP system, even if it is in the public and patient's best interest to do so. Even with therapeutic alternatives there is value for patients in having different treatment options. Many patients who stop responding to one therapy may benefit from having access to an alternative. Further, it is possible that in the absence of improved pricing systems, some R&D programs will never be initiated for secondary indications if pharmaceutical firms remain unconvinced that they can recoup their investment. Overall, while it is critical to recognise that there is low political willingness to implement formalised indication-based pricing, there is still a need to explore ways to improve existing pricing practices and by extension access to multi-indication medicines.

The suitability of weighted pricing approaches depends both on how accurately HTA systems can derive the value of individual indications (in order to set a fair price) and on how accurately expected usage can be calculated. Weighted pricing systems that calculate expected use ex-ante using epidemiological data, inherently expose pharmaceutical firms to more risk. If the use of a "lower value" indication is under-estimated, potentially because an alternative therapy is available or soon to be available, then manufacturers are negatively impacted by price erosion in the "higher value" indication. This risk may contribute towards the withholding of indications in weighted pricing markets. Implementation of ex-post rebates or pricing changes

based on actual usage, despite added administrative burden of tracking and evaluating this data, may help to mitigate this risk and improve access to multi-indication products.

Differential discounting provides an alternative approach employed by some countries, although it's use is largely limited by operational constraints. Supplying the same medicines at different rates requires strong monitoring capacity and the ability to track medicine use at indication level. Further, measures would be required to prevent off-label use of a medicine. It may be more feasible to facilitate different reimbursement prices for a medicine with multiple formulations that are used across different therapeutic areas. Alternatively, differential discounts could be realised ex-post through a rebate according to usage data at different levels.

"Price stickiness" or the lack of evidence that prices ever increase upon launch of a new indication likely also contributes to reduced access of multi-indication products. Apart from the USA where free pricing applies, healthcare payers could not identify any instances where the price of a medicine increased upon launch of a new therapeutic indication. Perceptions of a price ceiling based on the first-indication launched may contribute towards both pre- and post-development sequencing. In particular, the mandatory discounting policy recently implemented in Italy represents a fundamental shift away from "value-based pricing" towards cost-containment. Overall, price ceilings are likely to result in a market inefficiency and sub-optimal outcomes. Healthcare payers should have greater willingness to increase prices in the event an indication provides greater value.

In general, an important trend identified across healthcare payers was the shift away from complex agreements towards administratively simple financial agreements. This has important implications for both multi-indication medicines, which could benefit from indication-specific agreements, and conditionally approved medicines, which could benefit from complex outcome-based managed entry schemes. The fact that Italy in particular has shifted away from

complex indication-specific managed entry schemes towards a simpler model, despite extensive data monitoring capacity and infrastructure, should serve as a cautionary tale. While advances in data infrastructure, digital health, and legislation create new opportunities for complex access agreements (including pay-for-performance schemes), it is critical to ensure the benefits of these programs exceed the costs of implementing them [214].

Finally, it is not uncommon for HTA agencies and pharmaceutical firms to disagree on the value of product. Across papers I, II, and IV, a number of conditionally approved medicines and multi-indication medicines received negative HTA recommendations. In the short term, HTA serves to inform pricing and reimbursement decisions and aims to promote access to innovative treatments while maintaining financial sustainability. In the long-run, HTA provides value signals to manufacturers which create incentives to conduct further research and development to address outstanding health needs. Transparency in HTA processes plays a key role in the later. However, methods of incorporating social value judgments are often not defined in HTA processes leading to uncertainty surrounding the impact of these parameters on decision-making. Approaches such as multi-criteria decision analysis could improve the transparency of decision making through explicit weighting of different value domains [155]. Alternatively, HTA agencies should explore other approaches to make consideration of these parameters more explicit (e.g. sliding or dynamic cost-effectiveness thresholds) [215].

6.4 Key limitations

This section summarises the key limitations in studies I-IV. In study I, key limitations included the inability to assign weights to scientific and social value judgments, limitations to study scope, differences between Health Canada and EMA conditional approval pathways, and exclusion of withdrawn products. First, the mixed-methods approach enables consideration of a wide range of clinical, economic, and social value parameters that are included in the appraisal of health technologies. While decision-analysis facilitates capturing when a given parameter is raised, it is not possible to discern the weight of that parameter on the final outcome. For instance, the extent of unmet need or disease severity across two therapeutic areas is unlikely to be uniform. As such, while this study enables a characterisation of the types and frequencies of uncertainties and social value judgments raised for conditionally approved medicines, it likely does not fully account for the discrepancies seen across settings. Second, the scope of the study was limited to products with conditional approval in Canada or Europe between 2010 and 2017 and to HTA agencies in England, Scotland, France, and Canada. As such, results may not be generalisable to other HTA agencies or to medicines which did not go through conditional approval pathways. Third, slight differences exist between the eligibility criteria of the EMA CMA pathway and the NOC/C pathway. This places a limitation on our ability to properly compare how HTA agencies in Canada and Europe manage the high levels of uncertainty present in conditionally approved medicines, as some differences across settings may be a reflection of differences at regulatory level. Finally, this study excluded medicines that were withdrawn from the market following HTA evaluation, as HTA reports are no longer publicly available. This may bias results towards medicines with positive HTA outcomes.

In study 2, key limitations included restriction to a cohort of medicines that received marketing approval, limitations in geographic scope, restrictions on therapeutic area, lack of consideration of the impact of secondary-patents, and policy reforms during the study period. First, this study

focused solely on medicines that received marketing approval. Many medicines that undergo clinical trials do not go on to receive marketing approval and it is likely that several potential development programs for secondary indications are never initiated. As such our results do not permit us to comment on this element of pre-development sequencing. Second, this study is limited in scope to the USA, Europe, Canada and Australia and utilises these settings to define the first launch or "global launch" of an indication. It is possible that an indication may launch first in a jurisdiction outside of those listed above and that the "true" global launch sequence varies slightly from the sequence reported here. Third, scope was restricted to oncology products. The decision to focus on oncology was based on a) the frequency in which they a subject to drug re-purposing and b) their relevance from a decision-making context, given the burden of disease, challenges in evidence development, high treatment costs. Results may not be generalisable to other therapeutic areas. Fourth, no consideration is given to the impact of secondary patents and extensions in market exclusivity. Differences across settings in regulations surrounding secondary patents, data protection and market protection may impact the timing and overall decision to launch a subsequent indication. Finally, HTA reforms such as the AMNOG process in Germany (introduced in 2011) [169] and NICE reforms in 2016 relating to the Cancer Drugs Fund may influence study results [152].

In study 3, key limitations include number of participants, restriction in scope to healthcare payers, and lack of consideration of combination therapies. First, this study had a limited number of participants with only a single participant in all but one country. This is due to the requirement for senior experts, with over 10 years experience working in pharmaceutical policy and the nature of the topic (pricing of multi-indication products is a niche topic). Second, the study scope was restricted to a single stakeholder group in the healthcare system. These stakeholders were in the best position to comment on the feasibility and practicalities of implementing a formalised indication-based pricing system and on the value of doing so over

existing practices. Nevertheless, several stakeholder groups (including patients, clinicians, regulators, and pharmaceutical firms) have an interest in this topic, and it would be of interest expand analysis to these groups. Finally, it is increasingly common to see combination therapies in oncology. Secondary indications often include multiple therapies, which are associated with unique challenges at HTA and pricing level, given difficulties of attributing value across each component in a combination. The issue of combination therapies and pricing was not discussed in interviews.

In study 4, key limitations include sample size, sample selection, and exclusion of medicines that did not make an HTA submission or were withdrawn from market. First, the small number of conditional approvals during our study period places a limitation on the sample size and study power. In the later multivariate models with a higher number of variables, some covariates had high odds ratios and wide confidence intervals. Second, the external validity of findings may be limited from sample selection and scope of HTA agencies considered. It was not possible to include all standard drug approvals during the study period, given the time requirements and extent of data that is collected for each HTA evaluation. Further, the study was limited to HTA agencies in Scotland, England, France, and Canada. Finally, conditionally approved medicines without an HTA evaluation, or who's marketing authorisation was withdrawn at the time of data collection were excluded from the sample. This may bias findings on the extent of HTA barriers that conditionally approved medicines face, given omission of products with potentially larger issues in clinical evidence.

6.5 Ideas for future research

While the body of evidence on conditional approval and on policies for multi-indication medicines is growing, there are a number of interesting areas of future research that would be beneficial towards our understanding of whether existing practices adequately safeguard patient and public interests.

First, further research is needed to better understand the extent to which early or immature clinical data accurately predict clinical benefit. Research comparing clinical effect estimates of trials at the time of conditional approval with results from confirmatory studies would be of interest to help further categorise the level of uncertainty in conditionally approved medicines and level of risk that both regulators and HTA agencies take in their approvals. It would also be of interest to validate this against real world evidence on the use of conditionally approved medicines.

Second, research on the characteristics of conditionally approved medicines which were withdrawn from market and on conditionally approved medicines which do not submit for HTA approval would be of interest. While HTA data is unavailable on these products, analysis of regulatory reports could provide some insights on the conditions under which conditionally approved products are withdrawn from market and conditions under which manufacturers elect not to submit for pricing and reimbursement.

Third, it would be useful to validate findings of paper IV across a larger and more recent cohort of products and across other geographic settings. Due to the extent of data collection required, it was not feasible to include all standard approval drug-indication products in study IV. With more time, expansion of the data set to include a) more standard approval products, b) more recent approvals (both conditional and standard) and c) more HTA agencies (presuming

language barriers can be overcome), would increase study power and help to validate study findings.

Fourth, further research on clinical development of multi-indications would help us to better understand how pharmaceutical firms sequence the development of therapeutic indications prior to their launch. It would be of interest to conduct a meta-analysis and mapping of human clinical trials for multi-indication medicines in order to investigate a) development timelines and b) instances of development programs initiated but not completed.

Fifth, the claim that current pricing practices are fit-for-purpose and that therapeutic indications are only withheld when a therapeutic alternative is available requires further investigation and validation. A study examining the impact of in-patent competition on the launch of multi-indication products would provide interesting insights on the potential impact of pharmaceutical firms withholding the launch of therapeutic indications.

Finally, this thesis focused on firm entry into the pharmaceutical market under two conditions: a) conditionally approved medicines; and b) medicines with multiple therapeutic indications. A range of other factors outside the scope of this thesis are likely to influence firm entry and merit further research. Combination therapies, curative therapies, and therapies which received marketing authorisation under exceptional circumstances are likely to present health systems with unique challenges from a pricing and reimbursement perspective and could be interesting areas for future research on HTA through a similar mixed-methods approach.

6.6 Final thoughts

The current pipeline of innovative therapies is set to provide healthcare systems with tremendous opportunities but also a range of unique challenges. It is critical that regulatory and health technology assessment structures remain flexible and adaptable to the new challenges presented by innovative technologies. There is a fine policy balance between promoting access to innovative therapies, maintaining financial sustainability, and creating incentives for future R&D. As fiscal pressures grow in the coming years, these trade-offs are likely to becomes increasingly strenuous. Through the research in this thesis, my aim was to provide contributions to the literature on two topical areas of pharmaceutical firm entry where empirical evidence was scarce. My hope is that these studies provide a foundation for future work in this area and contribute to a much-needed policy debate on the role of regulatory agencies and HTA agencies in promoting access to innovative medicines.

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APPENDIX – DATA AND EMPIRICAL METHODOLOGY

This appendix chapter presents a detailed record of the data sources and empirical methodology employed in each of the four papers. Papers I, II and IV rely on extensive data collection from publicly available marketing authorisation and HTA reports. Paper III relies on primary data collected through semi-structured interviews.

A.1 Establishing a database on marketing authorisation and HTA approvals

One of the key limitations of research on HTA decision-making concerns challenges in data collection [39]. By nature, HTA is a complex process which involves aggregation of several sources of evidence and endpoints into a single decision based on either the relative clinical benefit of a medicine or the cost-effectiveness of a medicine compared to the current standard of care. While some HTA agencies publish detailed reports outlining the evidence submitted for assessment, their appraisal of the evidence and rationale for recommendation, many agencies do not publish their decisions. Further there are no publicly available datasets compiling HTA decisions and evidence submitted. As such, in order to assess HTA decision-making, and moreover to understand differences in the availability of medicines across settings, it is necessary to establish a de-novo dataset from publicly available decision reports.

A.1.1 Analytical framework

There are several schools of thought on the relevant variables which influence HTA decision-making. Early single-setting analysis have predominantly focused on the impact of clinical evidence, cost-effectiveness, disease area, availability of therapeutic alternatives (unmet need) and disease severity on HTA outcomes [53-57]. While results are not consistent across studies,

there are indications that performance of primary endpoint, cost-effectiveness, and disease severity a significantly associated with reimbursement recommendations.

More recently, Nicod and Kanavos have argued that HTA decisions are driven not only by the evidence submitted (clinical and economic) but also by the interpretation of this evidence [39]. In order, to effectively evaluate differences in the way HTA agencies assess a particular medicine it is necessary to not only identify differences in the evidence submitted by firms, but also in how agencies interpret this evidence. This is consistent with descriptive studies identifying differences in HTA methodology, acceptability of indirect comparisons and types of statistical methods employed across settings [21, 38, 44, 48, 189].

To construct a dataset which captures not only the evidence submitted to HTA agencies, but also the interpretation of evidence, I adopt a sequential mixed-methods research design, as outlined in the analytical framework developed by Nicod and Kanavos [39] (**Figure A.1**). This enables collection of the widest possible range of criteria which may influence HTA outcomes. The first stage of this research design involves qualitative analysis of HTA decision reports. HTA decision report text is screened to identify: a) the quality or strength of clinical and economic evidence submitted to HTA agencies; b) the interpretation of this evidence by HTA agencies; c) the role of this evidence on the final decision; and d) any additional parameters or social value judgments considered beyond clinical and economic evidence. The second stage involves coding of the collected data and quantitative meta-analysis of HTA decision-making.

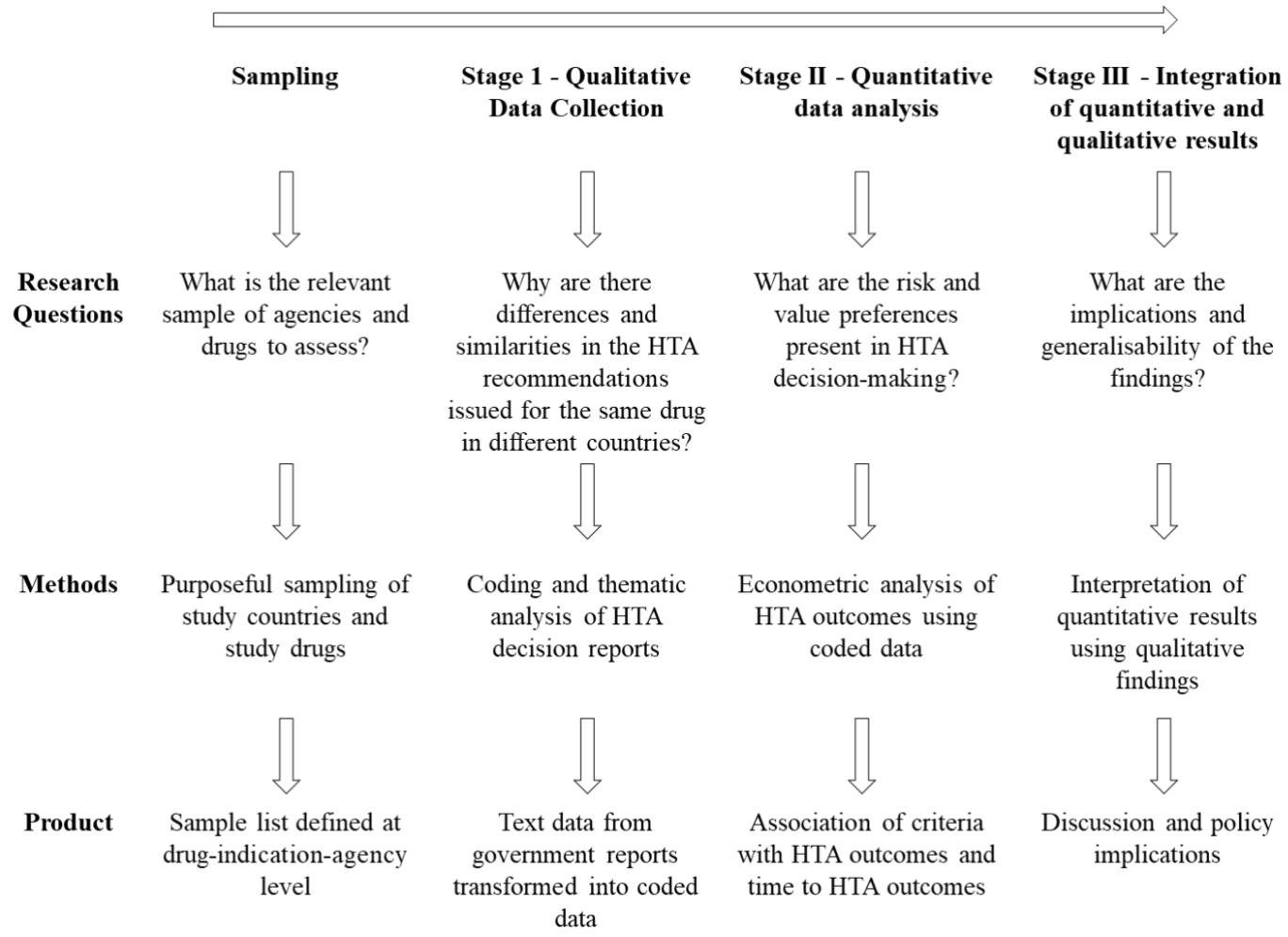

Figure A.1 - Mixed-methods research design for assessing HTA decision-making

Illustrates different stages of a mixed methods approach to simplify the complex interrelationships between different stages of the HTA process including submission of evidence (clinical and cost-effectiveness), interpretation of evidence (uncertainties and social value judgments) and the HTA recommendation (List/List with conditions/Do not list).

Source: the author, adapted from [39]

A.1.2 Data sources

Data was extracted from publicly available HTA reports and publicly available marketing authorisation reports. A full list of data sources is provided in **Table A.1**. Marketing authorisation agencies included in the dataset include the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), Health Canada, and the Australian Therapeutic Goods Administration (TGA). HTA agencies included the National Institute of Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Federal Joint Committee (G-BA), the Haute Authorité de Santé, (HAS), the Canadian Agency for Drugs and Technologies in Health (CADTH), The Institut national d'excellence en santé et en services sociaux (INESSS) and the Pharmaceutical Benefits Advisory Committee (PBAC). Additional data on characteristics of pivotal clinical trials were collected via clinicaltrials.gov.

Table A.1 - Marketing Authorisation Report and Health Technology Assessment Report Data Sources

Country/Region	Agency	Website
Marketing Authorisation Agencies		
Europe	European Medicines Agency (EMA)	https://www.ema.europa.eu/en
USA	U.S. Food and Drug Administration (FDA)	https://www.fda.gov/
Canada	Health Canada	https://www.canada.ca/en/ health-canada.html
Australia	Therapeutic Goods Administration (TGA)	https://www.tga.gov.au/
HTA Agencies		
England	National Institute of Health and Care Excellence (NICE)	https://www.nice.org.uk/
Scotland	Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/
France	Haute Authorité de Santé, (HAS)	https://www.has-sante.fr/
Germany	Federal Joint Committee (G-BA)	https://www.g-ba.de/english/
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	https://www.cadth.ca/
Canada (Quebec)	The Institut national d'excellence en santé et en services sociaux (INESSS)	https://www.inesss.qc.ca/

Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	https://www.pbs.gov.au/pbs/industry/listing/participants/pbac

A.1.2 List of variables extracted

A full list of variables collected via marketing authorisation reports, HTA reports and clinical trials.gov is provided in **Table A.2**. Variable selection was informed by a review of previous studies assessing determinants of HTA outcomes [39, 53-57]. Marketing authorisation reports were screened to extract data relating to marketing authorisation date, marketing authorisation pathway, marketing authorisation designations, pivotal trial design, pivotal trial performance, supplementary trial design and conditions of marketing authorisation. HTA reports were screened to extract data related to HTA outcome, HTA date, clinical evidence submitted, economic evidence submitted, clinical uncertainties, economic uncertainties, and social value judgments. Additional trial details were identified through clinicaltrials.gov.

Table A.2 - Full List of Variables Extracted for Dataset on Marketing Authorisation and HTA Approvals

GENERAL INFORMATION

Variable	Description
Molecule Name	International Non-proprietary Name (INN) of medicine
Brand Name	Company branded name of marketed medicine
Therapeutic Indication	Approved therapeutic label of marketed medicine, designating the intended and authorised use of a medicine in a specific patient population. For the included molecules, all approved therapeutic indications recorded from each regulatory agency (FDA, EMA, Health Canada, TGA).

MARKETING AUTHORISATION REPORTS

Variable	Description
MA Date	The date that marketing authorisation was granted for a specific therapeutic indication.
MA Type	The type of marketing authorisation granted to a specific medicine-indication pair. MA type is classified according to whether standard authorisation was granted, a conditional approval was granted (EMA – conditional marketing authorisation, FDA – accelerated approval, TGA – provisional approval, and Health Canada – Notice of Compliance with Conditions) or priority review was granted (EMA- accelerated assessment, FDA – priority review, TGA – priority review, Health Canada – priority review).
Orphan Designations	Whether or not a therapeutic indication received an orphan designation from the regulatory. The EMA and TGA orphan designations requires a prevalence of less than 5 in 10,000. The FDA orphan designation requires that the condition affects less than 200,000 in the USA. Health Canada does not have an Orphan Designation.
Therapeutic Area	The therapeutic area according to the Anatomical Therapeutic Chemical (ATC) classification system.
Study Design of Pivotal Trial	The study design of the pivotal trial used to support regulatory approval. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled).
Pivotal Trial Size	The number of patients enrolled in the pivotal trial.
Pivotal Trial Primary Endpoint	The name and type (surrogate or clinical) of endpoint selected as the primary endpoint in the pivotal trial. Clinical trials are primarily powered to detect statistically significant differences in the primary endpoint. Surrogate endpoints provide an indication or prediction of clinical benefit (e.g. progression free-survival (PFS) or overall response rate (ORR)). Clinical endpoints are hard clinical outcomes (e.g. Overall Survival (OS)).
Pivotal Trial Performance	The performance of the primary endpoint defined based on the trial protocol. Includes performance of active arm, performance of control arm, hazard ratio, confidence intervals, and significance (p value). For oncology indications, primary endpoints are predominantly either median progression-free survival (months) or median overall survival (months).
Supplemental Trial Design	The study design of any supplemental trials used to support regulatory approval. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled).

Marketing Authorisation Conditions	The specific post-marketing obligations imposed by regulatory agencies to fulfil the conditions of marketing authorisation. Conditions are classified according to the type of evidence generation requested (submission of follow-up data or completion of additional clinical trials).

HEALTH TECHNOLOGY ASSESSMENT REPORTS

Variable	Description
HTA Outcome	HTA outcomes are classified as List (L), List with conditions (LWC), List with conditions through a resubmission following an initial rejection (LWC after resubmission), Do not list (DNL), Do not list through a resubmission following an initial rejection (DNL after resubmission), or No HTA submission. In France, the HAS assigns a rating based on the absolute clinical benefit (SMR) and relative clinical benefit (ASMR). SMR ratings include Insufficient, Low, Moderate, and Important and determines the reimbursement rate for a medicine (not reimbursed, 15%, 30% and 65% respectively). The ASMR rating ranges from V (non-existent added benefit) to I (Major added benefit) and determines a medicines price. In order to qualify for a price premium an ASMR rating of I or II is needed. HTA outcomes for France are classified according to SMR and ASMR ratings (DNL – SMR insufficient, L – SMR Important and ASMR I or II, or LWC- all other combinations). In Germany, the G-BA assigns a rating based on the added benefit and level of proof: i) Major; ii) Significant; iii) Minor; iv) Non-quantifiable; v) no added benefit; and vi) lesser benefit; In addition to the added benefit rating, G-BA also provides a rating on level of proof (proof, indication of proof, or hint of proof). The G-BA added benefit ratings determine pricing, rather than the listing of a medicine. I classify "lesser benefit" or "no proof of added benefit" ratings as DNL, "Proof of major or significant added benefit" as L, and all other ratings as LWC. Note that medicines with lesser or no proof of added benefit may still be reimbursed in Germany based on reference pricing.
HTA Date	The date an HTA recommendation is issued.
Resubmissions	The presence of a previous assessment by an HTA agency for the same medicine-indication pair. Details are recorded on the date of the previous assessment and outcome of assessment.
Study Design of Main Trial for HTA	The study design of the main trial used to support HTA assessment. If undefined, the main trial is assumed to be the latest phase trial submitted. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled)
Main Trial Size	The number of patients enrolled in the main trial used to support HTA assessment.
Main Trial Primary Endpoint	The name and type (surrogate or clinical) of endpoint selected as the primary endpoint in the pivotal trial. Clinical trials are primarily powered to detect statistically significant differences in the primary endpoint. Surrogate endpoints provide an indication or prediction of clinical benefit (e.g. progression free-survival (PFS) or overall response rate (ORR)). Clinical endpoints are hard clinical outcomes (e.g. Overall Survival (OS)).
Main Trial Performance	The performance of the primary endpoint defined based on the trial protocol. Includes performance of active arm, performance of control arm, hazard ratio, confidence intervals, and significance (p value). For oncology indications, primary endpoints are predominantly either median progression-free survival (months) or median overall survival (months).
Supplementary clinical evidence	The study design of any supplemental trials used to support HTA. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled).
Type of Economic Model	The type of economic model submitted in support of HTA. Types of model include cost-effectiveness, cost-utility or cost-minimisation. The majority of submissions consider cost-utility analyses, expressed in Cost/QALY. Occasionally cost-effectiveness will also be considered (Cost/life year gained) or cost-minimisation analysis (a comparison of treatment costs under the assumption of equivalent therapeutic benefit/non-inferiority).
Cost-utility	The incremental cost-effectiveness ratio of a medicine-indication pair relative to the existing standard of care. Expressed in terms of cost/QALY.

Clinical Uncertainties	Clinical benefit: All issues raised regarding the magnitude of clinical of clinical benefit, including main patient populations and relevant subgroups
	Lack of evidence: All issues raised regarding a lack of clinical evidence, including lack of direct comparative evidence, lack of evidence on a subgroup, and lack of long-term data
	Study design: All issues raised regarding study design, including trial phase, blinding, study duration, low patient numbers, randomisation, cross over, and type of analysis
	Indirect comparison: All issues raised on the indirect comparison submitted, including type of indirect comparison, adjustment methods, and risk of bias
	Comparators: All issues raised on the appropriateness of the comparator chosen in the clinical trial or selected in the indirect comparison
	Generalisability: All issues raised on the generalisability of the trial population to the local population
	Clinical practice: All issues raised on the generalisability of the trial design to the local clinical practice including clinical pathway, dosage/formulation route, and administration
Economic Uncertainties	Modelling: All issues related to the clinical model, including sources of clinical evidence, treatment duration, extrapolation methods, time horizon, and perspective
	Model type: All issues raised relating to the appropriateness of the model type submitted (cost-effectiveness, cost-utility, cost-consequence, or cost minimisation)
	Comparator: All issues raised relating to the appropriateness of the choice of comparator used in the economic model
	Costs: All issues raised on the estimation of costs, including overestimation of costs, underestimation of costs, and omission of relevant costs.=
	Utilities: All issues raised on the utility values included in the model
	Cost-effectiveness: All issues raised on the value for money of a technology including the magnitude of the ICER and uncertainty around the ICER
	Sensitivity Analysis: All issues raised on the sensitivity analysis performed to demonstrate the robustness of the economic model
Social Value Judgments	Additional elements of value mentioned in the context of decision-making that are not captured in the clinical and economic evidence including disease rarity, disease severity, levels of unmet need, innovative mechanism of action, short life expectancy, administration advantages (oral vs subcutaneous) and special demographics of patient population (e.g. paediatric population).

ClinicalTrials.Gov

Variable	**Description**
Pivotal Trial Initiation Date	The date of initiation of the pivotal trial. The pivotal trial is identified through marketing authorisation reports.

A.2 Summary of empirical methods for papers I-IV

Detailed empirical methodologies are outlined in each of the respective chapters for papers I, II, III, and IV. This section provides an overview of the sample selection, research endpoints, and analysis performed in each paper. **Table A.3** provides a summary at the end of the section.

A.2.1 Paper I – How Do HTA Agencies Perceive Conditional Approval of Medicines? Evidence from England, Scotland, France and Canada

Paper 1 provides a cohort analysis of HTA recommendations on conditionally approved medicines. The methodology consists of three phases: sample selection, data collection and coding, and data analysis.

Sample selection for paper I

The scope of paper I was restricted England, Scotland, France, and Canada based on the following criteria: 1) presence of a conditional approval pathway; 2) HTA used to inform pricing and reimbursement; 3) public availability of MA and HTA decision reports; 4) language of MA and HTA decision reports (English and French). From these settings a total of two marketing authorisation bodies were included (European Medicines Agency (EMA) and Health Canada) and five HTA agencies (National Institute of Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Haute Authorité de Santé, (HAS), the Canadian Agency for Drugs and Technologies in Health (CADTH), The Institut national d'excellence en santé et en services sociaux (INESSS)). Australia was excluded from the study as the provisional approval pathway was not implemented until 2016 [97]. The USA was excluded from the study as HTA is not used to inform pricing and reimbursement decisions.

The unit of analysis in paper I is defined as a medicine-indication pair. The sample of medicines selected for paper I included all medicine-indication pairs with a conditional marketing authorisation between January 1st 2010 and December 31st 2017 in either the EMA or Health Canada and with a minimum of one HTA evaluation in NICE, SMC, HAS, CADTH or INESSS. The cut-off date was selected to ensure there was sufficient time for an HTA evaluation to have taken place following marketing authorisation.

Data collection and coding

Data collection and coding was performed in accordance with the mixed-methods research design described above. Variables included in paper 1 include molecule name, brand name, therapeutic indication, therapeutic area, MA date, MA type, pivotal trial study design, conditions applied to marketing authorisation, HTA outcome, HTA date, resubmissions, main trial study design, clinical uncertainties, economic uncertainties, and social value judgments. Uncertainties were double-coded according to the type of uncertainty, and whether or not the uncertainty was addressed by any means in the context of the decision (e.g. through stakeholder input).

Data analysis

Descriptive data analysis for paper I was performed to evaluate: a) HTA outcomes for conditionally approved medicines and the frequency with which coded parameters are raised, b) the alignment in clinical evidence submitted for regulatory approval vs HTA approval; c) the average number and types of clinical uncertainties raised for conditionally approved medicines; d) the average number and types of economic uncertainties raised for conditionally

approved medicines; and e) additional social value judgments (SVJs) raised during HTA of conditionally approved medicines.

First, descriptive statistics were performed on the aggregate sample (t-tests and chi-squared tests) to examine the association of HTA agency, therapeutic area, resubmissions, trial design, clinical uncertainties, economic uncertainties, and social value judgments with HTA outcome.

Second, a breakdown was provided on the different pivotal clinical trials designs (based on trial phase and comparator), conditions of marketing authorisation (the need to complete confirmatory trials or collect follow-up data), and main trial design supporting HTA submission (based on trial phase and comparator). Alignment between HTA and MA was assessed in terms of whether the main trial design submitted to HTA matched the pivotal trial or the confirmatory trial stipulated in the conditions of marketing authorisation.

Third, the average number and types of clinical uncertainties raised are analysed at agency level and are broken down according to HTA outcome. Clinical uncertainties considered include modest or low clinical benefit, lack of clinical evidence, poor study design, issues with indirect comparison submitted, inappropriate comparators, issues in generalisability of trial population, and issues in generalisability of clinical practice. Uncertainties are reported in terms of average number raised per assessment.

Fourth, the average number and types of economic uncertainties raised are analysed at agency level and are broken down according to HTA outcome. Economic uncertainties considered include modelling issues, inappropriate model type, inappropriate comparator, issues in cost inputs, issues in utility inputs, issues in cost-effectiveness estimate, and issues in sensitivity analysis. Uncertainties are reported in terms of average number raised per assessment.

Finally, a breakdown of SVJs raised during assessment of conditionally approved medicines is provided at agency level and according to HTA outcome. The SVJs considered include rarity,

severity, unmet need, innovation, short life expectancy, administration advantage and special demographics. SVJs are reported in terms of how frequently they are raised in assessments.

A.2.2 Paper II – Launch Sequencing of Pharmaceuticals with Multiple Therapeutic Indications: Evidence from Seven Countries

Paper II provides a comprehensive analysis of medicines with multiple therapeutic indications, with specific focus on regulatory vs HTA approval sequence and the characteristics of first-launched vs subsequently launched indications. The methodology consists of three phases: sample selection data collection and coding, and data analysis.

Sample selection

The scope of paper II was restricted to England, Scotland, France, Germany, Canada, and Australia based on the following criteria: 1) presence of a conditional approval pathway; 2) HTA used to inform pricing and reimbursement; 3) public availability of MA and HTA decision reports; 4) language of MA and HTA decision reports (English, French and German)). Additionally, the USA was included to provide a benchmark of global MA launch date and sequence. From these settings a total of four marketing authorisation bodies were included (European Medicines Agency (EMA), Food and Drug Administration (FDA), Therapeutic Goods Administration (TGA) and Health Canada) and six HTA agencies (National Institute of Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Haute Authorité de Santé, (HAS), the Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Benefits Advisory Committee (PBAC), and the Federal Joint Committee (GBA).

The unit of analysis in paper II is defined as a medicine-indication pair. FDA marketing authorisations were screened to identify medicines with a first approved therapeutic indication after January 1st, 2009 and a minimum of one additional indication approved prior to January 1st, 2019. Inclusion criteria were: 1) a minimum of one approved indication for the treatment of oncology during the study period (regardless of whether this is a first approval or subsequent); and 2) a minimum of two monotherapy indications approved during the study period.

Multi-indication medicines can be broadly grouped into three categories depending on the extent to which the various indications are similar. At the broadest level, a molecule can have multiple indications that span distinct therapeutic areas (e.g. oncology vs ophthalmology). Second, a molecule can have multiple indications across different diseases within a specific therapeutic area (e.g. melanoma vs lung cancer). Third, a molecule can have multiple indications that span different lines of therapy for a particular disease (e.g. 1st line vs 2nd line metastatic castrate resistant prostate cancer). Evidence requirements, market size, unmet need and strategic decision-making may vary according to the type of multi-indication medicine. In order to guide selection, priority was provided to include all three types of multi-indication medicines, medicines with monotherapy indications (in order to minimise the impact of combination therapies) and oncology indications.

Data collection and coding

Regulatory and HTA agency websites were screened to identify all MA and HTA reports available for the twenty-five selected multi-indication medicines. For all identified medicine-indication pairs, data was collected on molecule name, brand name, indication, MA date, MA type, orphan designation, pivotal trial study design, pivotal trial size, pivotal trial initiation date, pivotal trial primary endpoint type, pivotal trial primary endpoint outcome, HTA

outcome, HTA main trial design, HTA main trial primary endpoint, HTA main trial primary endpoint outcome and MCBS score. Within each multi-indication medicine, the first indication to receive regulatory approval across any of the FDA, EMA, Health Canada or TGA was designated as the "first indication" and all subsequent indications approved were designated as "subsequent indications".

Data analysis

Data was imported from Microsoft Excel into STATA SE Version 15.1 for analysis. The following endpoints were evaluated: a) alignment between global launch sequence, national regulatory approval and HTA recommendation sequence; b) differences in regulatory approval and clinical characteristics of first vs subsequent indication; c) differences in HTA outcome of first vs subsequent indications; d) clinical development time and HTA coverage recommendation time.

First, MA approval and HTA approval dates were mapped for all indications within each multi-indication medicine. Indications were provided a code according to global launch sequence (defined based on FDA approval sequence). Relative to the total number of globally launched indications, the total proportion of indications with regulatory approval and positive HTA coverage recommendations are tabulated. Additionally, the global launch sequence and HTA approval sequence are tabulated.

Second, descriptive statistics (t-tests and chi-squared tests) to investigate differences in the regulatory and clinical characteristics of first vs subsequent indications were employed to understand how manufacturers are prioritising the development of multi-indication medicines. MA type and availability of orphan designations provide indications of the extent to which disease severity, unmet need, and/or rare diseases are prioritised in initial launches. Both

quality of clinical evidence (pivotal trial design and size) and clinical performance (MCBS score) are compared across first and subsequent indications.

Third, descriptive statistics (chi-squared tests) were also employed to investigate whether subsequent indications are more or less likely to receive a positive HTA outcome than first indications.

Finally, survival analysis was employed to evaluate clinical development time and time from MA to HTA. Three events were defined: Pivotal trial initiation date was designated as T_0, Marketing authorisation date was designated as T_1, and HTA approval date was defined as T_2. Kaplan Meier plots were produced to illustrate differences in first vs subsequent indications for clinical development time (T_1-T_0) and for HTA coverage recommendation timeline (T_2-T_1). Statistical significance was measured using log-rank tests. Subgroup analysis was performed at country level and according to type of multi-indication medicine.

A.2.3 Paper III – Healthcare System Perspectives on the Assessment and Pricing of Oncology Multi-Indication Products: Evidence from nine OECD countries

Paper III presents primary data from semi-structured interviews with current and former healthcare payers and pharmaceutical policy experts on current pricing practices for multi-indication medicines and on the feasibility of implementing formal indication-based pricing policies across nine OECD countries. The methodology consists of four stages: analytical framework, development of interview guide and stakeholder selection, data collection, and data analysis.

Analytical framework

An analytical framework was produced with three core themes in order to meet research objectives and facilitate development of a semi-structured interview guide. The three core themes considered in the analytical framework include 1) current practices for multi-indication medicines; 2) impact of current practices on manufacturer launch strategy; and 3) future expectations on indication-based pricing. Research endpoints were defined for each of the three core themes. In terms of current practices for multi-indication medicines, research endpoints included HTA policies for multi-indication medicines, pricing and reimbursement policy for multi-indication medicines, and monitoring capacity and data infrastructure for tracking medicine use at indication level. In terms of impact on manufacturer launch strategy, endpoints included differences in characteristics of first vs subsequent indications and withholding/sequencing of indication launch. Finally, research endpoints for future expectations on indication-based pricing included performance of current pricing system and barriers to implementation of indication-based pricing.

Development of interview guide and stakeholder selection

A semi-structured interview guide was developed in accordance with the analytical framework described above. The interview guide consisted of ten questions relating to current assessment and pricing practices, challenges in monitoring and data infrastructure, observations on manufacturer launch strategy and expectations for future reform on multi-indication medicine policy. The full list of interview questions is available in Chapter 4.

Current and former members of health insurance organisations, healthcare payers, or health technology assessment agencies and pharmaceutical policy experts in 14 countries were invited to participate in semi-structured interviews. The countries included (France, England,

Switzerland, Italy, Spain, Belgium, Germany, Russia, Poland, Turkey, Australia, the USA, and Canada). Countries were selected to capture a range of a) both high- and middle-income settings; b) countries with both large and small market sizes (in terms of population); c) countries with different health financing systems. Invitations for interviews were sent between April 2020 and June 2020.

Data collection

Semi-structured interviews were conducted between June 2020 and October 2020. Prior to participation, interview respondents were provided with a participant information sheet and consent form. The research methodology for paper II was subject to standard institutional ethics review processes, given the inclusion of human participants. No significant ethical issues were raised by the review. All interviews were anonymised to protect the identity of the respondents. The duration of interviews was 45 minutes to 60 minutes and took place virtually using Zoom software. Interview responses reflect the individual views of the stakeholders participating rather than the official position of the healthcare organisations within the included individual settings.

Data analysis

All interviews were recorded and transcribed using the Rev transcription service (https://www.rev.com). Interview transcripts were imported into NVivo 12 for coding and thematic analysis. Interview text was coded in accordance with the research endpoints identified in the analytical framework: a) assessment policy for multi-indication medicines; b) pricing and reimbursement policy for multi-indication medicines; c) monitoring capacity/data infrastructure for multi-indication medicines; d) characteristics of first vs subsequent

indications; e) withholding of indications; f) performance of the current system; and g) barriers to implementation of IBP.

Insights identified were analysed across the three main themes of the analytical framework. The assessment policy for multi-indication medicines was coded in terms of whether any differences are present in the HTA process or requirement for subsequent indications vs first indications. Pricing and reimbursement policy is coded in terms of the methodology employed by a setting for pricing following launch of an indication extension. Possible values included indication-based pricing, weighted pricing, differential discounting model or alternative pricing scheme. Additional codes were provided if evidence was given on whether price increases can occur following launch of an indication extension. Monitoring was coded on a scale of low, medium high or very high, based on ability to track a medicine use at indication level. Low monitoring capacity reflects no ability to differentiate use of a medicine at indication level. Very high monitoring capacity indicates a country routinely and actively collects data on the use of a medicine at indication level.

The second core theme concerns the impact of current practices on manufacturer launch strategy. Participants were asked to identify differences in the characteristics of first indications vs subsequent indications. Characteristics were coded in terms of salient features of the first indication to launch and included unmet need, disease prevalence, disease severity, price and disease stage. Additional codes were assigned for text with observations of manufacturers withholding or sequencing indications.

The final theme concerned future expectations for pricing of multi-indication medicines. The performance of the current system was coded on a binary scale in terms of whether or not it is perceived as fit-for-purpose or if reforms are needed. Barriers to implementation of IBP were

coded in terms of feasibility, technical/legal requirements, and political willingness for implementation.

A.2.4 Paper IV – HTA Barriers for Conditional Approval Drugs

Paper IV provides an econometric analysis of the determinants of HTA outcomes, with a specific focus on whether conditional approval medicines face additional barriers to HTA approval over and above medicines with standard authorisation. The methodology consists of three stages: sample selection, data collection, and analysis. Model specification was informed via a conceptual variable matrix which outlines hypothesized impact of different variables (disease characteristics, trial characteristics, uncertainties, and SVJs) on HTA outcome (see Chapter 5). In terms of therapeutic area, oncology medicines and orphan medicines are predicted to have a negative impact on the likelihood of HTA approval, given challenges in evidence generation in these disease areas. In terms of trial characteristics, higher quality evidence (inclusion of phase III studies, active comparators and clinical endpoints) is predicted to have a positive impact on HTA outcomes. In terms of uncertainties, unresolved issues are predicted to have a negative impact on HTA outcomes, while resolved uncertainties are predicted to have an ambiguous outcome). Finally, SVJs such as disease severity, unmet need, administration advantage and quality of life are predicted to have a positive impact on HTA outcomes when raised as these indicate consideration of value beyond clinical and economic evidence.

Sample selection

Similar to paper I, the scope of paper IV was restricted England, Scotland, France, and Canada based on the following criteria: 1) presence of a conditional approval pathway; 2) HTA used to inform pricing and reimbursement; 3) public availability of MA and HTA decision reports; 4) language of MA and HTA decision reports (English and French). From these settings a total of two marketing authorisation bodies were included (European Medicines Agency (EMA) and Health Canada) and five HTA agencies (National Institute of Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Haute Authorité de Santé, (HAS), the Canadian Agency for Drugs and Technologies in Health (CADTH), The Institut national d'excellence en santé et en services sociaux (INESSS)). Australia was excluded from the study as the provisional approval pathway was not implemented until 2016 [97]. The USA was excluded from the study as HTA is not used to inform pricing and reimbursement decisions.

The unit of analysis in paper IV is defined as a medicine-indication-agency trio. The sample selection for paper IV took place in two stages. First, EMA and Health Canada MA approvals were screened between January 1st 2010 and December 31st 2017 to identify all conditionally approved medicine-indication pairs. These medicine-indication pairs were then cross-referenced with included HTA agencies to identify conditionally approved medicine-indication pairs with a minimum of one HTA evaluation in NICE, SMC, HAS, CADTH or INESSS. The cut-off date was selected to ensure there was sufficient time for an HTA evaluation to have taken place following marketing authorisation. Second EMA and Health Canada medicine approvals were screened to identify a representative sample of standard approval medicine-indication pairs using the same cut-off dates. Selection was based on 3 criteria: 1) a minimum of one HTA recommendation in the included HTA agencies; 2) inclusion of a similar proportion of cancer vs non-cancer medicines relative to the conditional approval sample; 3) inclusion of a similar distribution over time (based on marketing authorisation year). Sample

selection of the standard approval medicine-indication pairs represents a limitation of paper IV. Data extraction for the entire sample of standard approval medicine-indication pairs over this time-period was beyond the scope of this study. As a result, the external validity of findings may be limited.

Data collection

Data collection and coding was performed in accordance with the mixed-methods research design described above. Variables included in paper IV include molecule name, brand name, therapeutic indication, MA date, MA type, Orphan Designation, therapeutic area, HTA outcome, HTA date, HTA main trial design, HTA main trial primary endpoint, clinical uncertainties, economic uncertainties, and social value judgments. Uncertainties were double coded according to the type of uncertainty and according to the impact on decision-making (overcome or not-overcome).

Data analysis

Data was coded in Microsoft Excel and imported into STATA SE Version 17.0 for analysis.

Maximum likelihood logistic regression models were constructed to assess the association of collected variables with two dependent variables: a) type of marketing authorisation pathway and b) HTA outcome.

First, univariate binomial logistic regression models were constructed to explore the association of collected variables with type of marketing authorisation pathway (conditional marketing authorisation or standard marketing authorisation). The dependent variable for

univariate analysis ($Y_{1/0}$) was coded as 1 for medicine-indication-agency trios with conditional approval and 0 for medicine-indication-agency trios with standard approval:

$$Y_{1/0}\begin{pmatrix} Y = 1, & if\ conditional\ approval \\ Y = 0, & if\ standard\ approval \end{pmatrix} \quad (1)$$

Independent variables included therapeutic area, orphan status, pivotal trial phase, pivotal trial comparator, pivotal trial endpoint, scientific value judgments raised by HTA agencies (clinical and economic uncertainties), social value judgments raised by HTA agencies, submission history and HTA outcome.

$$Logit\left(Y_{1/0}\,|X_1 = x_1\right) = \beta_o + x_1\beta_1 \quad (2)$$

Odds ratios, 95% confidence intervals and p-values are reported.

$$Odds\left(Y_{1/0}\,|X_1 = x_1\right) = \exp(\beta_o + x_1\beta_1) \quad (3)$$

Second, multivariate binary logistic regression models were used to explore the association of collected variables with HTA outcomes. The dependent variable for multivariate analysis ($Z_{1/0}$) was coded as 1 for a medicine-indication-agency trios with an HTA outcome of List (L) or List with criteria (LWC) and 0 for medicine-indication-agency trios with an HTA outcome of Do not List (DNL).

$$Logit\left(Z_{1/0}\,|X_1 = x_1\right) = \beta_o + x_1\beta_1 \quad (4)$$

Independent variables included type of marketing authorisation pathway, therapeutic area, orphan status, pivotal trial phase, pivotal trial comparator, pivotal trial endpoint, scientific value judgments raised by HTA agencies (clinical and economic uncertainties), social value

judgments raised by HTA agencies, submission history and HTA outcome. The general specification of the multivariate model was:

$$Logit(Z_{1/0}|X_{iat} = x_{iat}) = \beta_o + x_{iat}\beta' + d_i\gamma' + a_a\zeta' + t_t\eta' + \varepsilon_{ia} \qquad (5)$$

Where x_{iat} is a vector of HTA characteristics (submission history, clinical evidence, scientific value judgments, and social value judgments) for medicine-indication "i", agency "a", and assessment year "t" and d_i is a vector of disease characteristics (therapeutic area and orphan status) that are agency-invariant. To control for heterogeneity across agencies and over time, we include agency fixed effects (a_a) and time fixed effects (t_t). Odds ratios and robust standard errors adjusted for clustering at molecule level are reported. I additionally calculate average marginal effects (ME) to examine inter-agency differences and the impact of interactions in the model.

Finally, survival analysis was employed to evaluate time from MA to HTA. Two events were defined: Marketing authorisation date was designated as T_0 and HTA approval date was defined as T_1. Kaplan Meier plots were produced to illustrate differences in conditionally approved and standard approved medicines for time from MA to HTA (T_1-T_0). Statistical significance was measured using log-rank tests. Subgroup analysis was performed at country level.

Table A.3 - Summary of Research Methods for Papers I-IV

Paper	Research Objectives	Sample Selection	Data sources	Research Endpoints	Type of Analysis
I	1) To examine the evidence gap between marketing authorisation agencies and HTA agencies for conditionally approved medicines in England, Scotland France and Canada; and 2) To determine how HTA agencies in these four countries interpret and appraise clinical and economic evidence submitted for conditionally approved medicines.	All conditionally approved medicines between 2010-2017 with a corresponding HTA evaluation in one of England, Scotland, France and Canada.	49 publicly available MA reports and 102 HTA reports	a) HTA outcomes for conditionally approved medicines and the frequency with which coded parameters are raised b) the alignment in clinical evidence submitted for regulatory approval vs HTA approval; c) the average number and types of clinical uncertainties raised for conditionally approved medicines; d) the average number and types of economic uncertainties raised for conditionally approved medicines; and e) additional social value judgments (SVJs) raised during HTA of conditionally approved medicines	Descriptive Statistics
II	1) To map the marketing authorisation and HTA coverage recommendation sequence of multi-indication oncology medicines with the view to understanding patterns in indication launch and whether these hold across different health care systems; and 2) To compare and contrast the first indication launched for a medicine, with the subsequent indications in terms of clinical trial characteristics, regulatory approval timelines, coverage decisions and HTA coverage recommendation timelines and access to market in order to understand how manufacturers prioritise development indications	Cohort of 31 medicines with multiple therapeutic indications approved between 2010-2019.	398 publicly available MA reports and 473 HTA reports	a) alignment between global launch sequence, national regulatory approval and HTA recommendation sequence; b) differences in regulatory approval and clinical characteristics of first vs subsequent indication; c) differences in HTA outcome of first vs subsequent indications; d) clinical development time and HTA coverage recommendation time.	Approval Sequence Mapping Descriptive Statistics Survival Analysis
III	1) To review current practices (over the period of the past 5 years) of price-setting and paying for medicines with multiple distinct indications with emphasis on oncology; 2) To assess the impact of said pricing practices on firm entry and the launch of multi-indication medicines; and 3) To identify issues around the practicality of indication-based pricing (IBP) implementation relating to political willingness, legal/regulatory structures, administration, and/or data infrastructure.	Current and former healthcare payers and pharmaceutical policy experts across nine OECD countries.	Primary data from 10 semi-structured interviews	a) assessment policy for multi-indication medicines; b) pricing and reimbursement policy for multi-indication medicines; c) monitoring capacity/data infrastructure for multi-indication medicines; d) characteristics of first vs subsequent indications; e) withholding of indications; f) performance of the current system; and g) barriers to implementation of IBP	NVivo Thematic Analysis

IV	1) To compare and contrast the health technology assessment of medicines that have received conditional marketing authorisation relative to those that have received standard marketing authorisation. 2) To examine whether differences in the characteristics of conditional approval medicines and standard approval medicines lead to a higher probability of HTA rejection or delays in HTA approval.	All conditionally approved medicines between 2010-2017 with a corresponding HTA evaluation in one of England, Scotland, France and Canada and a representative sample of standard approval medicines selected based on therapeutic area and approval year.	132 publicly available MA and 339 HTA reports	a) differences in the characteristics and assessment of conditionally approved medicines and medicines with standard authorisation b) determinants of HTA outcomes c) time from MA to HTA for conditional vs standard approval medicines	Descriptive Statistics Multivariate Logistic Regression Survival Analysis