London School of Economics and Political Science

Access to cancer medicines in Europe: An analysis of existing challenges and countries' responses

Alessandra Ferrario

A thesis submitted to the Department of Social Policy at the London School of Economics for the degree of Doctor of Philosophy, London, December, 2016

Declaration of authorship

I certify that the thesis I have presented for examination for the MPhil/PhD degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it). The copyright of this thesis rests with the author. Quotation from it is permitted, provided that full acknowledgement is made. This thesis may not be reproduced without my prior written consent. I warrant that this authorisation does not, to the best of my belief, infringe the rights of any third party.

I declare that my thesis consists of 63 373 words including footnotes, excluding references and appendices.

Statement of conjoint work

Chapter 7:
Alessandra Ferrario, Panos Kanavos, Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands, and Sweden, Social Science and Medicine, 124: 39-7, 2015

I designed the study, collected the data, performed the analysis, wrote the first draft of the paper and finalised it. Panos Kanavos provided feedback on drafts of the paper.

Chapter 8: Submitted as a technical report for the WHO consultation on fair pricing:
Alessandra Ferrario, Guillaume Dedet, Tifenn Humbert, The role of strategic procurement in increasing access to cancer medicine

I conducted the literature review with the support of Mackenzie Mills who run the search and conducted the title screening. I devised the search strategy, reviewed all the abstracts of the papers selected based on their titles, collected primary data from competent authorities on their experience with different procurement methods, I wrote the first draft of the chapter and finalised it. Guillaume Dedet and Tifenn Humbert provided feedback on the first draft of the paper.

Chapter 9: Conclusions
Parts of the subchapter on 'Policy implications' (more specifically point 4) 'Prices represent a barrier to access and efforts to address their impact are needed at national and international levels') are part of a perspective paper currently under-review by the WHO Bulletin:
Alessandra Ferrario, Tifenn Humbert, Panos Kanavos, Hanne Bak-Petersen, Improving access to medicines through strategic procurement: The role of inter-country collaboration

I conceptualized the paper, wrote the first draft and finalized it. Tifenn Humbert, Panos Kanavos, Hanne Bak-Petersen provided feedback on the first draft of the paper.

Abstract

Access to new cancer medicines, particularly their coverage and affordability, is a matter of great concern to payers, patients and the pharmaceutical industry. Yet, little comparative evidence on actual use and its determinants is available. This thesis aimed to analyse the extent to which access to cancer medicines varies across a sample of European countries, what determines these differences, whether they matter, and what are countries doing to improve access. These objectives were achieved through the use of quantitative and qualitative methods including multilevel mixed effects models, survival analysis and the complementary log-log transformation of the Cox proportional hazard model, literature reviews and interviews to inform the development of conceptual frameworks, and a comparative longitudinal analysis of the implementation of MEAs. Results show that there are wide cross-country differences in access to cancer medicines in Belgium, Estonia, Scotland, and Sweden. These differences were determined by time to entry of new medicines, medical need (i.e. incidence of the disease) and factors affecting treatment decisions (e.g. coverage, prices, and financing mechanisms). The added clinical value of medicines explained the shorter time to launch in Estonia and higher consumption in Scotland but not in the other countries. This emphasises the importance of health technology assessment processes in identifying and making cost-effective medicines available and limiting the utilisation of non-cost-effective ones. The latter is particularly important given the opportunity cost of funding new cancer medicines. Managed entry agreements have increasingly been implemented to address issues of uncertainty and high prices when making coverage decisions. Through their action on price, effectiveness and use, they are able to influence cost-effectiveness and budget impact, two key variables guiding reimbursement decisions. Some of the most important contributions from this thesis include: (1) the development of a blueprint to analyse access to cancer medicines in Europe quantitatively and qualitatively; (2) the identification of likely determinants of differences in access to cancer medicines which can guide policy-makers efforts in managing access to new therapies; and (3) the development of a conceptual framework for managed entry agreements which can support their design and evaluation.

Acknowledgements

I would like to thank my supervisors Dr Panos Kanavos and Prof. Alistair McGuire for their guidance and support.

A number of people helped me gaining access to data, replied to my many questions and facilitated the arrangement of interviews. In Belgium: Ellen Vanhaeren and Hans Van Der Meersch (former INAMI-RIZIV), Catherine Adriaens, Marc de Falleur, and Francis Arickx from the National Institute for Health and Disability Insurance (INAMI-RIZIV). In Estonia: Erki Laidmäe and Keili Kolves from the Estonian Health Insurance Fund, Ott Laius from the Estonian Medicines Agency, Marge Reinap from WHO, and Riina Sikkut. In Scotland: staff at the Scottish Medicines Consortium and NHS Scotland, in particular Lindsay McClure. In Sweden: Karl Arnberg from TLV, Mikael Hoffman from Nepi, and Ingrid Kössler.

I am very grateful to the oncologists who agreed to speak with me and the many people I spoke to and who inspired me in my research and writing process.

I would like to thank my dear friends and colleagues Elena Nicod (a very special thank you), Wei Yang, Hala Hourani, and Anna Sagan for their support and encouragement throughout the PhD journey. Finally, I would like to thank Sam, for reminding me that everything has a beginning and an end, and that the darkest hour of the night is before dawn.

It always seems impossible until it's done. Nelson Mandela

This thesis is dedicated to my loving parents who always believe in me.

Statement on editorial help

I gratefully acknowledge my friends Janice Lam, Lilian Li and Oliver Wouters for proofreading various chapters of this thesis.

Table of Contents

List of figures

List of tables

List of appendices

Abbreviations

AMC	Advance market commitment
ARV	Antiretroviral
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
CCPNM	Coordinating Commission for Negotiating the Price of Medicines and other Health Inputs
CED	Coverage with evidence development
CMA	Conditional marketing authorisation
CPI	Belgian Centre for Pharmacotherapeutic Information
DDD	Defined Daily Dose
DIMDI	German Institute of Medical Documentation and Information
DNDi	Drug for Neglected Diseases initiative
EHIF	Estonian Health Insurance Fund
EMA	European Medicines Agency
EMSO	European Society of Medical Oncology
ERP	External Reference Pricing
EU	European Union
FDA	Food and Drug Administration
HTA	Health Technology Assessment
ICER Institute	Institute for Clinical and Economic Review
ICER	Incremental Cost-Effectiveness Ratio
INAMI-RIZIV	National Institute for Health and Disability Insurance
ISD	Information Services Division
INN	International Non-proprietary Name
MEAs	Managed Entry Agreements
MCBS	Magnitude of Clinical Benefit Scale
MDGs	Millennium Development Goals
MMV	Medicines for Malaria Venture
MoSA	Estonian Ministry of Social Affairs
MSKCC	Memorial Sloan Kettering Cancer Center
NBHW	National Board of Health and Welfare

NCEs	New Chemical Entities
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NCCN	National Comprehensive Cancer Network
PAS	Patient Access Scheme
pCPA	pan-Canadian Pharmaceutical Alliance
PROs	Patient Reported Outcomes
PVAs	Price volume agreements
RCT	Randomised Clinical Trial
SDGs	Sustainable Development Goals
SMC	Scottish Medicines Consortium
TB	Tuberculosis
TLV	Swedish Dental and Pharmaceutical Benefit Agency
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UN	United Nations
US	United States
VBP	Value-Based Pricing
WHO	World Health Organization
WTO	World Trade Organization

Notes on the structure of this thesis

This thesis conforms to the requirements of a doctoral thesis from the London School of Economics and Political Science. It is in the form of a publishable papers thesis. Guidelines state that it should consist of a minimum of three papers of publishable standard and interlinked with each other, together with an introduction and conclusion. At least one of the papers should be single authored, and any other paper should be primarily authored by the Student. A specified detailed statement on the contribution of co-authors is provided. Word count should not exceed 100,000 words.

In line with the School's guidelines, this thesis consists of five papers which have either been published (Papers 2 and 4), are under peer-review (Paper 1), or are ready for submission in a peer-reviewed journal (Papers 3 and 5). An introductory chapter sets the scene and the background of this thesis by conducting a review of the literature on access to medicines. Chapter 2 outlines the hypotheses and research gaps which led to the formulation of the research questions of this thesis. Chapter 3 illustrates the methods used in this thesis. Chapters 4 to 8 represent the five publishable or published papers. Chapter 9 provides the overall conclusions of this thesis by addressing the hypotheses presented in Chapter 2, summarising the main contributions of this thesis, discussing the policy implications of the findings as well as the limitations of this thesis, making recommendations for policy and practice, and outlining areas for future research.

The introduction, literature review, research questions, methods and conclusions (Chapters 1-3, 9) are solely the work of the author. Panos Kanavos and a colleague (Elena Nicod) commented on draft(s) of parts of these sections.

Chapters 4 to 8

- Chapter 4: Alessandra Ferrario, Time to entry for cancer medicines: From EU-wide marketing authorisation to patients access in Belgium, Estonia, Scotland and Sweden (reviewed by Value in Health, I have submitted a revision based on the feedback received from the reviewers)

- Chapter 5: Alessandra Ferrario, Determinants of utilisation differences for cancer medicines in Belgium, Scotland and Sweden, European Journal of Health Economics [E-published ahead of print on 9 December 2016]
- Chapter 6: Alessandra Ferrario, A framework to understand differences in utilisation of HER-2 targeted medicines for breast cancer, submitted to the European Journal of Cancer Care, under review
- Chapter 7: Alessandra Ferrario, Panos Kanavos, Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands, and Sweden, Social Science and Medicine, 124: 39-7, 2015
- Chapter 8: Submitted as a technical report for the WHO consultation on fair pricing: Alessandra Ferrario, Guillaume Dedet, Tifenn Humbert, The role of strategic procurement in increasing access to cancer medicine, November 2016

1 Introduction

Access to essential medicines (medicines that satisfy the priority health needs of the population (WHO 2016b)) has been recognised as an fundamental component towards the fulfilment of States human right obligations to health (Hogerzeil 2006). Providing access to affordable essential medicines in developing countries was one of the targets of the Millennium Development Goals (target 8E, 2000-2015) (The official United Nations site for the MDG indicators 2012). The importance of access to medicines in the context of universal health coverage has been emphasised in the Sustainable Development Goals (SDGs). SDG target 3.8 calls for access to safe, effective, quality and affordable essential medicines and vaccines for all (United Nations 2016) not just in developing countries. Further, SDC target 3.b calls for supporting the research and development of medicines and vaccines for conditions that affect predominantly developing countries and to ensure access to them in line with the full provision of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreements (United Nations 2016). Despite these high level recognitions of their importance, almost 2 billion people worldwide lack access to essential medicines (United Nations 2008).

In 2012, there were 14.1 million new cancer cases and 8.2 million cancer deaths worldwide (Stewart and Wild 2014). The five most common cancer sites in men were the lung, prostate, colorectum, stomach and liver; in women, they were the breast, colorectum, lung, cervix and stomach (Stewart and Wild 2014). Together with surgery and radiotherapy, chemotherapy, targeted therapies and immunotherapies are key components of cancer treatment. Inequalities in access to cancer medicines across and within European countries have been highlighted in various studies (Cherny et al. 2016, Aggarwal, Ginsburg, and Fojo 2014).

Access to medicines is affected by a range of factors and decisions that occur well before the medicine is developed or available on the market. Investment priorities of the pharmaceutical industry and public and philanthropic bodies are a key factor in determining the therapeutic focus of foundation research and of research and development (R&D). Time to market also affects access to medicines for patients due to country variances in availability of expedited approval programmes and the criteria to obtain market access and flexibilities for medicines with incomplete evidence. Similarly, long pricing and reimbursement processes and restrictive coverage criteria can be a barrier to access. Therefore, it is important to take into

consideration the whole medicine's product life-cycle when analysing barriers and enablers to access to medicines.

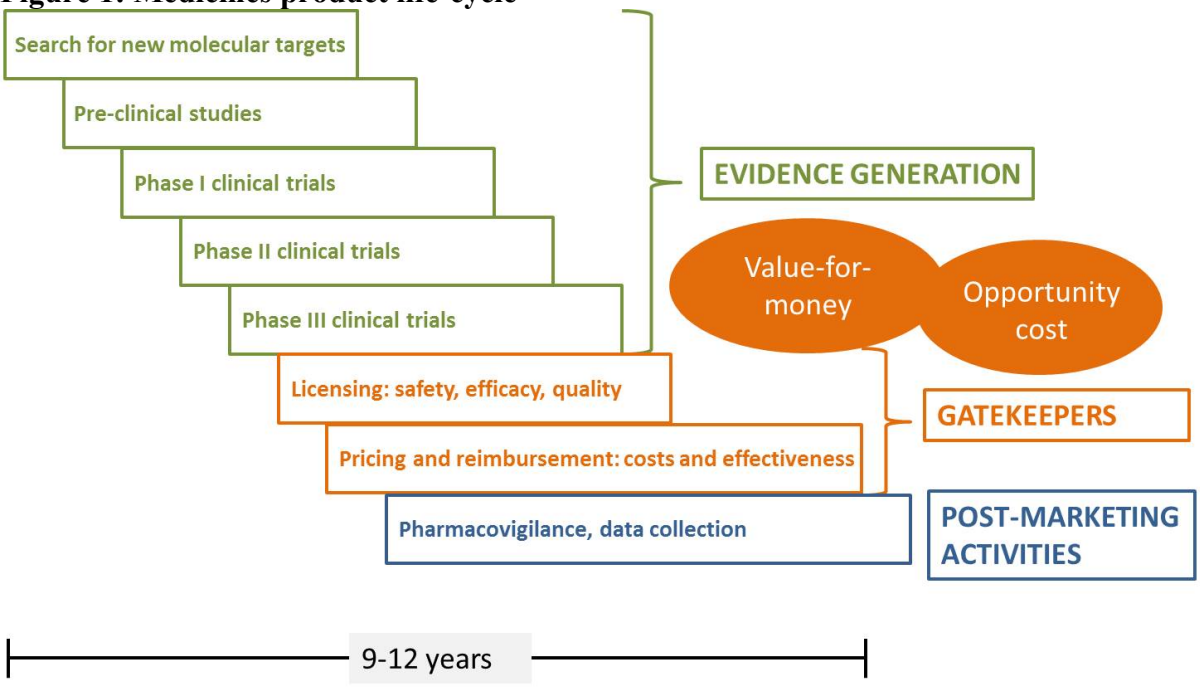
In the following subchapters, I will describe the product life-cycle and discuss factors affecting access to medicines at different stages of the cycle. Where relevant, I will also highlight specific factors relating to access to cancer medicines.

1.1 Medicines life-cycle and determinants of access

1.1.1 Research and development (R&D)

Research and development (R&D) starts with the search for new molecular compounds which have an effect on a particular disease. This is done in different ways, including the screening of thousands of molecules, the use of existing treatments in new indications or therapeutic areas and the design of specific molecular compounds which inhibit or stop the disease of interest. Promising molecular compounds are then channelled through a process of evidence generation to assess their safety and efficacy (Figure 1).

Figure 1: Medicines product life-cycle



Source: The author

The first step is pre-clinical research, *in vitro* and *in vivo* (animals), to establish whether the molecular candidate could cause serious toxicity in humans. If the results are positive, no

unacceptable levels of toxicity, clinical trials in humans are commenced. The aim of phase I clinical trials is to test safety and appropriate dosage in about 20 to 100 healthy volunteers or people with the disease (U.S. Food & Drug Administration 2016a). In phase II clinical trials, up to several hundred people with the disease are studied from several months to 2 years to assess the efficacy and side effects of the medicine (U.S. Food & Drug Administration 2016a). In phase III clinical trials 300 to 3000 volunteers with the disease are included in studies to test the efficacy and monitor adverse reactions over the course of 1 to 4 years (U.S. Food & Drug Administration 2016a). In phase IV clinical trials several thousand volunteers with the condition are followed to collect additional evidence on safety and efficacy post-launch (U.S. Food & Drug Administration 2016a).

According to a 2016 study claiming to be the largest study on clinical development success rate at the time of writing, the probability for a medicine entering phase I clinical trials to successfully complete phase III clinical trials is 11.3% (Thomas et al. 2016). The probability for a medicine entering phase I to obtain a marketing authorisation (MA) by the United States (US) Food and Drug Administration (FDA) is 9.6% (Thomas et al. 2016). Previous studies report similar results (Table 1). However, some studies highlight that the least successful stage is Phase II (Thomas et al. 2016, DiMasi et al. 2010, Kola and Landis 2004, Hay et al. 2014). while others highlight that the least successful stage is Phase III (Abrantes-Metz, Adams, and Metz 2004, U.S. Food & Drug Administration 2016a). High failure in phase II is justified by this being the last stage before the most expensive and risky phase III begins. The expensive and risky nature of phase III is due to the business, legal and ethical ramifications of use of a trial compound in humans. Failure of a molecular compound in phase III clinical trials represents a large loss for a pharmaceutical company. If phase II shows unpromising results, the molecular candidate is therefore unlikely to be advanced to phase III.

Table 1: Probability of success

	FDA website	BioMedTracker 2016	Biomedtracker 2013	DiMasi *et al.* 2010	Kola *et al.* 2004	Abrantes-Metz *et al.* 2004
Medicines included	NA	All medicines identified as 'Advanced' and 'Suspended' in the BioMedTracker database by development phase from January 1, 2006 to December 31, 2015	All medicines identified as 'Advanced' and 'Suspended' in the BioMedTracker database by development phase from January 1, 2003 to December 31, 2011, in the BioMedTracker database	New medicines with available dates of start of phase I for which phase I was started between 1993 and 2004 for the 50 largest pharmaceutical companies	Success rates from first-in-man (phase 0) for then large pharmaceutical companies in the US and Europe between 1991 and 2002	Medicines which began the FDA process for the first time between 1989 and 2002
Indications included	NA	All	Lead*	Lead*	Lead*	Lead*
Phase I to II	0.7	0.632	0.665	0.71	0.68	0.807
Phase II to III	0.33	**0.307**	**0.395**	**0.45**	**0.38**	0.577
Phase III to MA	**0.275**	0.581	0.676	0.64	0.55	**0.567**
Submission for MA to approval		0.853	0.864	0.93	0.77	NA
Phase I to approval		0.096		0.19		
Total number of medicines in the sample	NA	9985[†]		1737	NA	2328

Notes: *Lead: In Biomedtracker this is used to denote the most advanced indication in clinical development for a specific drug. [†]It refers to the number of transitions from one phase of a clinical trial to the next

Source: The candidate based on the literature (U.S. Food & Drug Administration 2016a, Thomas et al. 2016, Hay et al. 2014, DiMasi et al. 2010, Kola and Landis 2004, Abrantes-Metz, Adams, and Metz 2004)

These percentages are lower for oncology medicines. The likelihood to obtain a FDA marketing authorisation for a medicine entering phase I clinical trials was 5.1% for oncology *vs.* 9.6% for all other indications and 26.1% for haematology, the indication with the highest marketing authorisation success rate (Thomas et al. 2016). Research-focused pharmaceutical companies are essentially determining their R&D portfolios. Given they are profit-seeking enterprises, they will focus on therapeutic areas where they expect high returns, ideally, both in terms either unit price or volume or both.

The profitability of the therapeutic area has important implications for access to medicines, since therapy areas of focus will target diseases with relatively high prevalence and/or high unit cost. Both these factors can result in high budget impact for countries and patients which means that the likely recipients of such medicines will be countries with a relatively high gross domestic product per capita (Chirac and Torreele 2006, Kyle and McGahan 2012). Investment in R&D for new antibiotics is also affected by a number of disincentives. These include a series of challenges across all stages of development to commercialisation which make the market for antibiotics unattractive (Chorzelski et al. 2015). For example, the antibiotic market is dominated by off-patent medicines which are recommended for first-line treatment (Morel and Mossialos 2010). New on-patent antibiotics would only be prescribed after failure of previous treatments (Morel and Mossialos 2010). The risk of antibiotic resistance could shorten the life-time of new antibiotics, whose development is particularly expensive due to the costly nature of the clinical trials, above average, in this therapeutic area (Morel and Mossialos 2010). Further, antibiotics are administered over a short period of time (5 days to 2 weeks) and are curative (Morel and Mossialos 2010).

There is also a general disincentive to invest in the development of paediatric formulations due to the small market size (less than 10% of total pharmaceutical market), widespread use of off-patent medicines and smaller prevalence of chronic diseases in children than adults (Milne and Bruss 2008). For example, in the area of oncology, some cancers have been traditionally neglected and underfunded. Studies in the UK and US found the following common discrepancies in terms of burden of disease *vs.* research funding. These include bladder, oesophageal, liver, lung, pancreatic and stomach cancers in comparison to breast cancer, prostate cancer, and leukaemia (Lancet Oncology 2010, Carter and Nguyen 2012, Carter, Delarosa, and Hur 2015).

Therefore, the paucity of medicines to treat diseases of less wealthy countries, particularly low-income tropical countries with a different disease burden from high-income non-tropical countries, the current global shortage of antibiotics, and the limited availability of age-appropriate formulations for paediatric populations result in R&D gaps which represent a barrier in access to medicines, as needed products are not available. These research gaps are not aligned with the current global pharmaceutical R&D pipeline that often prioritises diseases that affect wealthier countries, adults, and are not easily curable through a short-, moderately expensive, treatment course. Nonetheless, therapeutic gaps are also evident in high-income countries. The Priority Medicines for Europe and the World 2013 report identified a number of treatment gaps which they defined as medicines that exist but are expected to soon become ineffective (e.g. due to resistance to antibiotics, antiretroviral medicines, and medicines against malaria), medicines that exist but whose delivery mechanism or formulation is inappropriate for the patients they are meant to treat (e.g. medicines for children and the elderly), and medicines which do not exist or which are insufficiently effective (e.g. medicines for neglected tropical diseases and rare diseases) (Kaplan et al. 2013).

The recognition of these issues has led to a number of initiatives to rectify the misalignment of the global R&D pipeline with the world's patients' needs. These include the creation of public-private product development partnerships like the Drug for Neglected Diseases initiative (DNDi) (Drugs for Neglected Diseases initiative (DNDi) 2016), Medicines for Malaria Venture (MMV) (Medicines for Malaria Venture (MMV) 2016), and the Clinical Development Partnerships joint initiative by Cancer Research Technology and Cancer Research UK (Cancer Research Technology 2016); the provision of funding support, covering the whole R&D pipeline from fundamental biology to clinical trials, for cancer with high unmet medical need (Cancer Research UK 2016); the introduction of incentives to stimulate the pipeline towards areas of unmet therapeutic need (e.g. advanced market commitments); and the introduction of regulatory initiatives such as the orphan designation[1]

[1] Regulation (EC) No 141/2000 OF the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF

and the Paediatric Regulation[2] at the European Union (EU)-level providing various financial incentives and waivers to stimulate the development of orphan medicinal products (i.e. for the diagnosis, prevention or treatment of conditions affecting not more than 5 in 10 000 persons in the EU or for which the return on investment would be insufficient to stimulate their development (EMA 2016c)) and paediatric medicines. Similar regulatory initiatives are also in place in the United States (the Orphan Drug Act, the Best Pharmaceuticals for Children Act, and the Paediatric Research Equity Act).

As of 2016, initial results of these initiatives include the delivery of for six new treatments for neglected tropical diseases by DNDi (2003-2015) (Drugs for Neglected Diseases initiative (DNDi) 2016), a number of achievements by MMV and partners including the development of dispersible artemisinin combination therapy for children (2009) and the receipt of WHO prequalification for artesunate injection (2010) just to mention a few (Medicines for Malaria Venture (MMV) 2016). An evaluation of the advance market commitment (AMC) for the development of pneumococcal vaccine found that the AMC had very little effect on speeding up the R&D outcomes, particularly marketing authorisation (The Boston Consulting Group 2015). However, it did contribute to increased availability through additional manufacturing capacity and uptake post-launch (The Boston Consulting Group 2015). A 2012 evaluation of the Paediatric Regulation found that of the 500 paediatric investigation plans approved by EMA since 2008, only a minority of them had been completed at the time of the review. However, because development cycles of medicines often last more than 10 years, the review concluded that it was too early to draw conclusions about the impact of the regulation (European Commission 2012).With orphan medicinal products there is evidence that the system has been exploited and that manufacturers first apply for an orphan indication and then later apply for a second non-orphan indication (Côté and Keating 2012, Drummond and Towse 2014) and withdraw from the orphan status. Further, widespread off-label use has been reported in the US (Daniel et al. 2016). Such concerns may be at least in part behind the recommendations of the council of the EU on the current legislation on orphan medicinal products in its conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States. They recommend the European Commission to conduct a study on the impact of the incentives in EU legislative instruments including orphan medicinal

[2] Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use 12 December 2006, http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

products and paediatrics on innovation, availability, deferred or missed market launches and accessibility (Council of the European Union 2016a).

In summary, funding priorities for R&D influence access to medicines by determining the therapeutic focus of the R&D pipeline. As the pharmaceutical industry is a profit-seeking enterprise, their investment priorities will focus on areas where high returns are expected. This reality has created therapeutic gaps in areas of unmet need which are characterised by low returns on investment. Public-private partnerships and other initiatives have sought to address this issue by providing a series of incentives to promote R&D in critical areas such as neglected tropical diseases, orphan medicines, antibiotics, and paediatric formulations. The impact of these initiatives is mixed. There are some positive results like the development new of products for neglected tropical diseases and improved access to pneumococcal vaccine through AMC. However, concerns have been raised about the impact of some of these initiatives in improving access, in particular the EU orphan medicines legislation and paediatric legislation and in speeding up R&D outcomes.

1.1.2 Medicines regulation with focus on marketing authorisation

The task of medicines regulatory authorities is to ensure that medicinal products on the market are safe and effective. As no medicine is completely safe, in practical term, this means that the benefits of taking a medicine should outweigh the risks of taking it. This is done through a comprehensive medicine regulatory process covering licensing of pharmaceutical establishments, regulation of clinical trials, marketing authorisation, inspection and control of the quality of medicines on the market, monitoring of distribution, safety and adverse medicines' reactions, and the provision of independent information on medicines to health professionals and the public (Rägo and Santoso 2008).

The presence of substandard, spurious, falsely labelled and counterfeit medicines represents a very important barrier to access to quality medicines and patient safety, and no country is immune to it ([No authors listed] 2010). However, countries with stringent regulatory authorities[3] are in a much stronger position to limit entry of such medicines into their markets and to take rapid and effective action once they are detected. In countries with weaker

[3] A Stringent Drug Regulatory Authority (SRA) is a regulatory authority which is either (a) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); or (b) an ICH Observer or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition (WHO 2011).

regulatory systems, this is a much bigger challenge (Caudron et al. 2008). In these countries there is also very limited evidence on the extent of the problem, particularly for non-communicable diseases including cancer (Wirtz et al. 2016). Medicines regulatory authorities, together with the International Criminal Policy Organization and international community (e.g. WHO, the International Medical Products Anti-Counterfeiting Taskforce) and donors have therefore a very important role to play in ensuring the quality of medicines available to patients. Use of substandard, spurious, falsely labelled and counterfeit medicines can have very serious consequences on patients' health and wellbeing and lead to resistance because of sub-therapeutic dosage (e.g. antibiotics and medicines against malaria) (Karunamoorthi 2014, Kelesidis et al. 2007). The latter will in turn reduce the number of effective medicines available to treat patients.

Medicines regulatory authorities can operate at national or international level. In Europe, the European Medicines Agency (EMA) was created in 1995 to harmonise (EMA 2016d) the work of national EU Medicines Regulatory Authorities and ensure that new medicines of important public health value, are marketable in all EU countries at the same time. In reality, medicines will not be available to patients in different EU countries at the same time due to manufacturer's launch strategies – which are affected by national pricing and reimbursement policies - and differences in coverage across countries. However, the work of EMA has enabled to overcome one hurdle, marketing authorisation. This is particularly important in small markets with limited economic power where, due to limited market attractiveness, the manufacturer may have never submitted a marketing authorisation request or submitted one with substantial delay.

Within the European Union and selected countries of the European Economic Area, there are two main procedures to obtain a marketing authorisation. These include a centralised procedure through the EMA and national procedures (EMA 2016d). A centralised marketing authorisation provides market access to all EU Member States. Use of the centralised procedure is mandatory for medicines treating HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases as well as the specialised areas of medicines for rare diseases, herbal medicines, medicines for children and advanced-therapy medicines (EMA 2016d). The national procedures include three different types of applications. The manufacturer can either apply to an individual country to obtain a marketing authorisation, as done in most countries worldwide.

Alternatively, marketing authorisation may be obtained via the decentralised procedure, whereby the medicine is approved by more than one EU Member State at the same time, or the mutual recognition procedure, whereby a medicine authorised in one EU Member State can be recognised in a second Member State (EMA 2016d). Since 2004[4], all cancer medicines are required to go through the centralised procedure which means that they are potentially available in all EU Member States at the same time.

In the EU, there are strict timelines for the authorisation of new medicines (originators), 210 + 30 days for the decentralised and national procedures and 90 + 30 days for the mutual recognition procedure (The European Parliament and the Council of the European Union 2004). To shorten times to access for patients, accelerated review options are available in the EU and other countries (e.g. US). The EMA accelerated review programme offers a reduction from a maximum of 210 days to 150 days to provide a decision on the marketing authorisation of medicines of public health importance and representing major therapeutic innovation (EMA 2016d). In an effort to expedite entry of medicines for seriously debilitating or life-threatening conditions, emergency medicines and orphan medicines in the absence of comprehensive data usually required to grant a marketing authorisation, conditional marketing authorisation was introduced (EMA 2016d). For medicines treating such conditions to be eligible for conditional marketing authorisation, some conditions need to be fulfilled. The expected benefits need to outweigh the risks and there is a realistic expectation that the manufacturer will be able to provide more comprehensive data on safety and efficacy so that a final decision may be reached (EMA 2016d). Medicines approved under exceptional circumstances are medicines for which collection of comprehensive data is not feasible (e.g. very rare conditions) or unethical. In contrast to conditional marketing authorisation whose aim, after collection of comprehensive information, is to obtain a full marketing authorisation, a marketing authorisation obtained under exceptional circumstances does not generally lead to a full marketing authorisation (EMA 2016d). The adaptive pathways (earlier called adaptive licensing) concept was introduced and piloted by EMA between 2014 and 2016 to enable early access to medicines addressing high unmet medical need. It builds on a longer term discussion about moving from a one-off marketing authorisation to a life-cycle approach (Eichler et al. 2012, Eichler et al. 2008) and is grounded in the principles of

[4] REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF Accessed: 8 November 2016

iterative development (gradual expansion of the eligible treatment population as additional evidence is collected), and the collection of real-life evidence to supplement clinical trials data and early engagement of stakeholders (e.g. patients and HTA bodies) in the medicine's development process (EMA 2016d). Rather than representing a new marketing authorisation path, adaptive pathway builds on existing approval mechanisms, particularly conditional marketing authorisation (EMA 2016b). If sufficient evidence to support the positive balance between benefits and risks is collected, a marketing authorisation will be granted (EMA 2016b).

In the US there are four expedited review programmes: accelerated approval, breakthrough, fast track, and priority review (FDA 2016b). Accelerated approval can be compared with the EMA conditional marketing authorisation as it allows early approval of medicines that treat serious conditions of unmet medical need based on surrogate endpoints (a marker that correlates with the clinical endpoint) (FDA 2016b). Phase IV confirmatory trials need to be conducted by the company after which, a full marketing authorisation may be granted (FDA 2016b). Breakthrough therapy designation aims to reduce the time needed to develop and review a medicine for the treatment of serious conditions if preliminary clinical data supports substantial added value over existing standard of care (FDA 2016b). A breakthrough therapy is eligible for fast track review. A fast track review is granted to medicines that treat serious conditions of high unmet clinical need to facilitate their development, through enhanced communication with the FDA during the development process, and accelerate their review by applying to the accelerated approval and priority review programmes if eligible (FDA 2016b). Priority review designation shortens the time of review of the application from 10 to 6 months. It is granted to medicines with the potential of improving effectiveness or safety of the treatment, diagnosis or prevention of serious conditions compared to existing treatments (FDA 2016b).

In 2015, 45 new molecular entities were approved in the US of which 31% were approved through fast track, 22% through breakthrough procedure, 53% through priority review and 13% through accelerated approval (some medicines were eligible to more than one expedited approval programme) (FDA 2016a). Oncology was the therapeutic area with the highest proportion of new medicines approved through expedited approval programmes and second after infectious diseases, in terms of number of new medicines approved by the FDA (107 between 1987-2014) (Kesselheim et al. 2015). 76% of all new cancer medicines approved

between 1987 and 2014 were approved through priority review, 48% through fast track, 30% through accelerated approval (Kesselheim et al. 2015).

The presence of substandard, spurious, falsely labelled and counterfeit medicines is a worldwide problem but some countries are in a better position than others to fight this growing threat. In countries with strong regulatory authorities and more generous coverage of medicines (whether these benefit all citizens or only a portion of them), the focus is increasingly on finding ways to enable faster access to new and potentially more effective medicines to patients. A number of challenges remain to be addressed in all countries including how to balance early access with the need for data on safety and efficacy.

1.1.3 Pricing and reimbursement

List prices of medicines in Europe are mostly regulated. This is done through negotiation, external reference pricing, value-based pricing, internal reference pricing, generic price capping, and regulation of supply chain mark-ups. A number of instruments are used to affect the actual total price paid and reduce total budget impact (independently of who pays). These include *ex-ante* price reductions on the list price such as confidential discounts (common in a number of European countries) and competitive prices obtained through tendering. *Ex-post* refunds can be implemented as rate-of-return regulation (e.g. UK), price-volume agreements (common in a number of European countries (Vogler et al. 2012, Ferrario and Kanavos 2013)) and performance-based agreements (e.g. Italy). To reduce public expenditure, co-payments may be introduced or increased. The use of all these regulatory instruments varies across countries, type of medicines (e.g. on-patent *vs.* off-patent, hospital *vs.* ambulatory, prescription *vs.* over-the-counter) and the actual medicine involved.

Current discussions and initiatives to improve access to new on-patent medicines, including new cancer medicines, have largely been focused on how to reduce their prices. Traditional tools to reduce prices of branded medicines have been mandatory price cuts, external and internal reference pricing, price volume agreements and regulation of generic prices. In the past decade, there has been increased interest and discussion on how to use more sophisticated pricing and reimbursement tools such as value-based pricing (VBP), performance-based agreements and indication-based pricing to increase access to on-patent medicines. Further, compulsory licensing, voluntary patent pools and de-linkage of R&D

from the final price of the medicine have also been discussed and implemented to improve access.

In 2010, the Government of the United Kingdom proposed implementing a system of VBP for assessing and pricing branded medicines (The Parliamentary Office of Science and Technology 2015). The aim of implementing VBP is to more closely link the price the NHS pays for a medicine with the clinical and other benefits it delivers (The Parliamentary Office of Science and Technology 2015). Despite the initial hope that VBP would provide a solution to challenge the introduction of new and high priced medicines, the expected major pricing reform did not materialise. Following two public consultations and the appointment of NICE to be responsible for value based assessment, a much modified plan to improve access to new medicines emerged. In addition to any methodological changes which may be implemented, three concrete changes were suggested by NICE in September 2014 (NICE 2014a). These include the establishment of– the Office for Market Access (NICE 2016b), an office for innovation within NICE, to advise companies on how to speed up the adoption of new medicines, devices and diagnostics by the NHS; the agreement on thresholds for NHS willingness to pay for new treatments, particularly special cases such as rare conditions and cancer; and the increased use of risk sharing between companies and the NHS through commissioning through evaluation for treatments that are not funded by the NHS (NHS England 2016b, NICE 2014a). VBP pricing is implemented in Sweden by the Dental and Pharmaceutical Benefit Agency (TLV) as part of the health technology assessment (HTA) process. If the medicine is considered to be priced over the value it delivers, it can only be reimbursed if the manufacturer lowers the price to a level which is comparable to its benefits. Sweden is the only country in Europe formally implementing VBP. Most other countries incorporate elements of value during the reimbursement process by conducting HTA (Paris and Belloni 2013). The use of value based pricing and value-driven pricing systems have been suggested in the US to reduce prices and promote research and innovation (Ocana, Amir, and Tannock 2016, Bach and Pearson 2015).

In the US, value-driven pricing systems involve the provision of incentives to encourage manufacturers to sell their medicines in line with their value and at a price which is sustainable for the health care system (Bach and Pearson 2015). This can be achieved through positioning medicines on different health insurance tiers based on the extent to which their price aligns to value (i.e. higher tier positioning for medicines priced in line with their value

and affordable to the health care system), exemption from mandatory discount programmes (e.g. the Health Resources and Services Administration, 340B medicines programme requiring mandatory discounts up to 50%), regulatory incentives (e.g. increasing the exclusivity period of a medicine by the FDA), (Bach and Pearson 2015). Formulary positioning according to value and affordability would incentivise the use of medicines on high tiers (with low co-payment) as opposed to medicines on lower tiers (with higher co-payments) for privately insured patients (currently there are some barriers to implement such system in Medicare). However, the distribution by industry of vouchers to cover co-payments of medicines in lower tiers of insurers' formularies undermines the incentive of lowering co-payments to encourage use of medicines priced according to their value (Ross and Kesselheim 2013, Dafny, Ody, and Schmitt 2016). Further, other authors have raised concern in the use of value to price medicines as this could make some medicines such as antibiotics unaffordable (Blumenthal 2016).

Performance-based agreements have been used to enable access to new medicines with subsequent price review to align, if necessary, the initial price with evidence on the medicines effectiveness in real-life (Garrison et al. 2013). They have been used in some European countries, notably Italy (Ferrario and Kanavos 2013). Due to the resource intensive nature of these agreements, which require monitoring of patients' response and claiming funds/stock back for non-responding patients, the implementation of these agreements has been limited in most European countries. In Italy these agreements are regularly used for expensive hospital medicines thanks to the availability of a system of monitoring registries to support their implementation and refund claims.

Indication-based pricing involves the application of different prices across multiple indications of the same medicine according to the value they deliver. Indication based pricing may be implemented as a simple discount on the list price which averages value-based prices across different indications (no need to link use to indication), as different list prices for different indications of a medicine (Mestre-Ferrandiz et al. 2015), or indirectly through the implementation of managed entry and risk-sharing agreements. The feasibility of implementing indication-based pricing is largely determined by the ability to link utilisation of a particular medicine to different indications, regimens and patient groups (Mestre-Ferrandiz et al. 2015). In the UK, an assessment of the feasibility of implementing indication-based pricing concluded that at the time of the assessment, a unique price averaging the value

of different indications may be the most feasible approach (Mestre-Ferrandiz et al. 2015). However, the potential offered by the Systemic Anti-cancer Therapy dataset[5] (SACT 2016) to implement individual prices across indications in the future has been recognised by different authors (Mestre-Ferrandiz et al. 2015, McNamara and McNamara 2014). In Italy, indication-based pricing is indirectly implemented through managed entry agreements and the monitoring patient registries. Medicines with different indications may be associated with different agreements (e.g. payment by result involving a refund for failure of achieving a certain pre-agreed outcome and cost-sharing which provides a discount on the first treatment cycle) or the same agreement with different features (e.g. payment by result with different performance endpoints and time of evaluation) (Carletto 2016).

While unlikely to be a viable solution in Europe (due to external reference pricing and parallel trade among other issues), differential pricing based on ability to pay has been used to increase access to HIV, tuberculosis and malaria medicines and vaccines in low- and middle income countries (Vogler et al. 2015). Despite these positive experiences, authors have suggested that it is inferior to competition in lowering prices (Moon et al. 2011). Confidential pricing agreements (e.g. confidential discounts, risk-sharing and managed entry agreements) offer a way to discriminate prices across countries without altering list prices. This is very important to manufacturers as the widespread use of external reference pricing (ERP) in Europe, a practice whereby countries set or inform the price of their medicines through the prices in other reference countries, has an impact on prices in other countries. Studies have found evidence of delayed launches and lack of launches which they attributed to the use ERP (Danzon and Epstein 2012, Danzon, Wang, and Wang 2005, Varol, Costa-Font, and McGuire 2012, Costa-Font, McGuire, and Varol 2015).

Increasingly, there have been calls to delink R&D costs from the final price of new medicines (UNITAID 2016, United Nations Secretary-General's high-level panel on access to medicines 2016). De-linkage can be achieved through grants, prizes and advanced market commitments, amongst other incentives (United Nations Secretary-General's high-level panel on access to medicines 2016). Finally, voluntary licensing and patent pooling has been used by the Medicines Patent Pool to improve access to HIV, hepatitis C and tuberculosis medicines in low- and middle-income countries (Medicines Patent Pool 2016).

[5] A national database collecting comprehensive information on systemic oncological therapies

Health technology assessment (HTA) is conducted in a number of European countries and beyond to inform coverage decisions. Information on budget impact generally complements evidence from HTA which addresses the question of whether the new technology represents value for money based on national willingness to pay. A positive coverage decision may be contingent on the implementation of a managed entry agreement, particularly financial agreements. These are agreements between the payer and manufacturer for the reimbursement of a health technology subject to specific financial conditions, use or health outcome results (Klemp et al. 2011). A number of these agreements have been implemented in Europe (Kwong et al. 2014, Ferrario and Kanavos 2013). Several studies have compared HTA decisions across countries, highlighting the divergence in decisions for the same technology (Korchagina et al. 2014, Lexchin and Mintzes 2008) and the reasons behind it (Nicod and Kanavos 2012, Nicod 2016, Clement et al. 2009), and the misalignment between HTA decisions and coverage decisions for orphan medicines (Kawalec, Sagan, and Pilc 2016). Access to medicines, particularly high cost ones, is largely determined by public coverage. However, less attention has been paid in analysing other determinants of access.

To enable access to medicines which are not covered or only covered under special circumstances, special funds have been developed in some countries. These include for example the Cancer Drugs Fund in England (NHS England 2016a), the Risk-Share scheme for rare conditions in Scotland (NSD NHS Scotland 2016) and the Solidarity Fund in Belgium (INAMI-RIZIV 2016a).

Prices affect affordability and inclusion in positive reimbursement lists. As such, the methods used to set prices have an important indirect impact on access. Likewise reimbursement methods and criteria to determine inclusion in the positive list play a central role in facilitating or limiting access. The impact of pricing and reimbursement on access is all the more important for medicines which are too expensive for patients to pay out-of-pocket either in full (for non-reimbursed medicines) or partially (for medicines requiring a co-payments).

1.1.4 Post-launch

The post-launch period is crucial to assess the safety of a medicine in a wider patient population than the one included in clinical trials (pharmacovigilance), promote quality use of medicines, assess the effectiveness of medicines in real-life, and ensure sustainable access.

1.1.4.1 Pharmacovigilance

Marketing authorisation is granted to new medicines which are considered to be safe and effective based on available evidence, usually clinical trials, prior to market launch. Clinical trial data rely on a limited sample of highly selected participants (elderly, people with comorbidities tend to be underrepresented and pregnant women and children are generally excluded) (Shenoy and Harugeri 2015, Devlin 2010, Blehar et al. 2013). As such the results of clinical trials are not necessarily generalizable to a wider patient group. Therefore, safety monitoring post-launch and pharmacovigilance play a very important role in identifying, quantifying, understanding, and preventing any known and unknown adverse reactions to medicines or any other issue linked to the use of a particular medicine (EMA 2016d). Authors have suggested that pharmacovigilance is much more than that, it is the "systematic monitoring of the process of pre-market review and post-market surveillance, which are linked through study design, product labelling, therapeutic outcomes, adverse events, hospital and clinician reporting systems, the pharmacy interface, compliance, and a complete understanding of real-world evidence." p. e487 (Pitts et al. 2016)

Medicines for the treatment of cancer are a priority area for pharmacovigilance due to their high toxicity and narrow therapeutic window (Pitts et al. 2016). Yet, a review of the evidence found a limited number of studies in the field of oncology (Baldo and De Paoli 2014).

1.1.4.2 Quality use of medicines

There are many tools and approaches to improve quality use of medicines. The WHO recommends twelve core interventions. These are the institution of 1) a national multi-disciplinary national body to coordinate medicine use policies and 2) drugs and therapeutics committees in districts and hospitals; 3) the implementation of clinical guidelines and 4) an essential medicines list; 5) training in problem-based pharmacotherapy for undergraduate students; 6) the requirement for continuous professional education to maintain and renew a license for health professionals; 7) supervision, audit and feedback provided to prescribers; 8) availability of independent information on medicines,; 9) education about medicines for

patients, their carer and the wider society; 10) minimisation and possibly elimination of perverse financial incentives leading to poor quality prescribing and medicine's use; 11) appropriate and enforced regulation and 12) sufficient public finances to ensure availability of essential medicines and competent staff (WHO 2002). Of particular relevance to the appropriate use of cancer medicines are clinical guidelines and formularies.

Clinical guidelines provide evidence-based information to health care professionals on how to prevent, diagnose, treat, inform advise and manage a particular health condition (NICE 2016c). They are based on a systematic review of the evidence on the subject - rated using well established approaches such as the Grading of Recommendations, Assessment, Development and Evaluation (GRADE working group 2016) - and should provide state of the art guidance on the management of a condition. In countries with strong implementation, clinical guidelines have an important influence on treatment decisions. In some countries, national and international guidelines for cancer are used to develop regional or hospital guidelines. Clinical guidelines may be accompanied by a medicines' formulary or essential medicines list. These are selections of medicines used to treat the most common medical conditions in a particular setting. The aim of developing these lists and using them to inform prescribing decisions is to improve quality of care, management and use of medicines, and to focus on a cost-effective use of resources (WHO 2016c). Both clinical guidelines and formularies may be available at different levels of the health care system. National or subnational clinical guidelines will generally reflect international best practices with local adaptation to meet budgetary requirements and to reflect the medicines actually reimbursed. Evidence on the impact of formularies as part of broader intervention to improve efficiency in procurement and quality use of medicines shows increased adherence to recommended medicines among primary care doctors from 83% of total prescribing volume in 2003 to 87% in 2009 in Stockholm, Sweden (Gustafsson et al. 2011). Further, developing an essential medicines list and using it for the selection of medicines in centralised procurement together with activities to promote quality use of medicines resulted in 30% savings on annual medicines expenditure in Delhi (Chaudhury et al. 2005).

1.1.4.3 Effectiveness in real-life

Greater availability of real-life data on medicines use and patient outcomes can provide information on safety, effectiveness, and patient relevant outcomes. Use of this information for comparative assessment studies can provide evidence to update or make a final

reimbursement decision and could also be used as a negotiation tool to better align price and value of new medicines. These arguments provided the rationale for the introduction of various coverage with evidence development agreements in Europe (e.g. performance-based agreements in France are occasionally used; coverage with evidence development in the Netherlands was discontinued). A number of initiatives are ongoing to collect real-life data to inform decision-making in health. These include for example various projects funded by the Patient-Centred Outcomes Research Institute PCORI in the US on comparative effectiveness research in real-life (PICORI 2016, Kogan et al. 2016, O'Brien et al. 2015), EMA adaptive pathways (EMA 2016d) and the Innovative Medicines Initiatives GetReal (IMI 2016). Methodological and data collection issues are currently still limiting the impact of real-life data on decision-making. As patient data are increasingly digitised the role played by real-life data in informing reimbursement decisions and clinical guidelines is likely to become increasingly important.

1.1.4.4 Ensuring sustainable access

Pharmaceutical procurement has an important role to play in securing competitive prices and ensuring availability of medicines (Ferrario, Kanavos, et al. 2016b). Strategic procurement practices – aimed at increasing efficiency in procurement (e.g. reducing the number of orders, generating economies of scale (WHO 2015b)) and creating a competitive environment - can reduce expenditure and free resources which can be used to improve access. Horizon scanning for new and emerging health technologies (the systematic monitoring of products in the R&D pipeline that are likely to enter the market in the next few years), HTA, and analysis of the product life-cycle (whether the product is still on-patent, about to go off-patent, or already off-patent) can inform negotiations and improve procurement outcomes (Ferrario, Kanavos, et al. 2016a). Further, a well-managed procurement cycle can help preventing stock-outs and shortages (Amaral and Blatt 2011). Shortages have become an increasingly frequent problem worldwide (Tan, Moles, and Chaar 2016a, EAHP 2014, Kweder and Dill 2013, Gray and Manasse 2012) and the subject of the World Health Assembly resolution 69.25 in May 2016 which urged WHO Member States and the Director General to take action to address this issue (WHO 2016a). They can be caused by manufacturing, supply chain and logistical issues, mismatch between supply and demand, economic reasons (e.g. old generic products which are not sufficiently profitable to produce or the intention to switch use to a patented medicine with the same or similar active ingredient), parallel trade, marketing strategies to increase prices (Council of the European Union 2016b, Silverman 2016b,

Iyengar, Hedman, et al. 2016, Matrix insight 2012). Shortages can negatively impact treatment and health care outcomes if the missing medicines do not have a close substitute. Given the multiple causes underlying shortages of medicines, a multipronged approach is needed to address them. The most concrete step taken so far to address shortages is the development of notification processes in a number of countries at national (e.g. US FDA and a number of EU Member States) and international level (e.g. EU EMA), increased dialogue with suppliers to understand the reasons for back orders (e.g. Denmark), and attempts by a few European countries to reduce parallel trade (Bochenek et al. 2016).

Post-launch activities include pharmacovigilance, ensuring quality use of medicines, evaluating effectiveness in real-life and ensuring access to cost-effective medicines and sustainable supply. If implemented, these activities can contribute to improved access to quality medicines. For example, strategic pharmaceutical procurement and quality use of medicines can achieve competitive prices and savings, which, if reinvested, can lead to greater access for patients.

1.2 Access to cancer medicines

1.2.1 Definition of access and global access indicators

In 1981, Penchansky and Thomas proposed a taxonomic definition of 'access' in the context of health policy and service research. They conceive access as a general concept summarising five dimensions which characterise the interaction between the patient and the health care system, notably availability, accessibility, accommodation, affordability and acceptability (also called the five A's) (Penchansky and Thomas 1982).

The Millennium Development Goal (MDG) 8, 2000-2015, aimed to develop a global partnership for development. In particular, sub-target 8E called for:
"In cooperation with pharmaceutical companies, [to] provide access to affordable essential drugs in developing countries (The official United Nations site for the MDG indicators 2012)."

And was measured by:
"The proportion of population with *access to affordable, essential drugs* on a sustainable basis is the share of the population that has essential medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's

walk from the homes of the population (The official United Nations site for the MDG indicators 2012)."

This definition of access to medicines covers three of the dimensions (availability, accessibility and affordability) proposed by Penchansky and Thomas (1981). To measure progress against this target, a range of indicators have been used. These include the percentage of countries with an essential medicines list updated in the past 5 years, availability, affordability and pricing of selected essential medicines in public and private health facilities, public sector expenditure on pharmaceuticals, availability of pharmaceutical policies and legislation which are conducive to better access to essential medicines (MDG Gap Task Force 2008, 2015). Due to paucity of data on these indicators in most countries, monitoring progress against MDGs target 8E has proven to be challenging. Although target 8E was still reported on in the MDG task force reports, it disappeared from the 2009-2014 MDG progress reports and was only mentioned again briefly in the 2015 MDG progress report (Gotham, Onarheim, and Barber 2016).

In 2003, the WHO and Health Action International (HAI) published the first edition of 'Medicine prices – a new approach to measurement', followed by an enhanced second edition in 2008 on 'Measuring medicines prices, availability, affordability and price components' (WHO and HAI 2008). A number of surveys worldwide have been conducted since 2003 using their methods (HAI 2016). The results of these surveys have been an important source of evidence in monitoring progress against MDG target 8E (MDG Gap Task Force 2008, 2010, 2012, 2013, 2011, 2014, 2009, 2015). Unfortunately, not all of the 189 United Nations member states which committed to achieve the MDGs are covered. Further, only some of the surveyed countries have conducted more than one survey round, hampering efforts to monitor progress.

Since 2008, the Access to Medicines Foundation has been publishing the 'access to medicines index' every two years (Access to Medicine Foundation 2016). This index ranks major pharmaceutical companies based on their efforts to improve access to medicines in developing countries (Access to Medicine Foundation 2016). The index does not publish information on common indicators to measure availability, accessibility, accommodation, affordability or acceptability. These issues are nevertheless included indirectly in the index which assesses seven technical areas (general access to medicine management; market

influence and compliance; research and development; pricing, manufacturing and distribution; patents and licensing; capacity building; product donation) against four strategic pillars which contribute with different weights to the final ranking (pharmaceutical companies commitments, 15%; transparency, 25%; performance, 50%; innovation, 10%) (Access to Medicine Foundation 2015). For example, the index does not provide indicators of individual medicines' prices or affordability for patients but it does capture whether a pharmaceutical company offers equitable pricing strategies which take into account socio-economic needs and affordability in countries covered by the index.

At country level, a number of household surveys have also been conducted. These tend to focus on use/purchasing of medicines and underuse of medicines (Paniz et al. 2010, WHO 2016d, Bertoldi et al. 2008). This information generally allows to measure availability and affordability of medicines.

While it is welcome to have such indicators, they present a number of limitations. The infrequency, limited geographical coverage and focus on a limited number essential medicines of the WHO/HAI survey and the focus on companies and low and middle income countries of the Access to Medicines Index means that there is very little comparable information publicly available on access to cancer medicines in high income countries. Most of the cross-country publicly available evidence on access to medicines in high income countries comes from studies on medicines' prices, expenditure, use and time to launch using commercial data from IMS Health (Danzon and Chao 2000, Danzon and Furukawa 2003, 2006, 2008, Kanavos and Vandoros 2011, Varol, Costa-Font, and McGuire 2012, Lanjouw 2005, Cockburn, Lanjouw, and Schankerman 2014, Danzon, Wang, and Wang 2005, Danzon and Epstein 2012, Wilking, Jönsson, and Högberg 2009, Jönsson et al. 2016, Wilking and Jönsson 2005, Leopold et al. 2014, Leopold et al. 2012) or other proprietary sources (Kyle 2007, 2006). These data are commercial and are usually only accessible against payment[6]. Various studies comparing prices of medicines in Europe have been conducted using data provided the Pharma Price Information (PPI) service of the Austrian Public Health Institute and complemented by publicly available data in non-European countries (Iyengar, Tay-Teo, et al. 2016a, Vogler, Vitry, and Babar 2016, Vogler, Zimmermann, and Babar 2016, Vogler, Kilpatrick, and Babar 2015, Leopold et al. 2012, Leopold et al. 2013). A number of studies

[6] The IMS Health has, on occasion, given access free of charge to older data for research purposes

on utilisation of medicines in Europe have been conducted using non-commercial data, however, few focus on cancer and they rarely include the inpatient sector.

1.2.2 Access frameworks

Various frameworks have been proposed to study access to medicines. These include the five A's framework by Penchansky and Thomas (1981), the four dimensions and indicators proposed during the consultative meeting by WHO-Management Science for Health (MSH) in 2000 (Center for Pharmaceutical Management 2003), WHO (2003) collective framework for equitable access to essential medicines (WHO 2004) updated from 2000 (WHO 2000), the access framework proposed by Frost and Reich in 2008 (Frost and Reich 2008) and access to medicines from a health system perspective by Bigdeli *et al.* (Bigdeli, Jacobs, et al. 2013). Further, the Ishikawa fishbone diagram developed in 1968 by Kaoru Ishikawa (Kaoru 1976) has been applied to study barriers to access to essential medicines indicated for the prevention and treatment of postpartum haemorrhage and pre–eclampsia and eclampsia (Ridge, Bero, and Hill 2010, Bigdeli, Zafar, et al. 2013, Tran and Bero 2015).

The WHO-MSH framework proposes a set of indicator to measure four dimensions of access, physical availability, affordability, geographical accessibility and acceptability (or satisfaction) and the crosscutting element of quality of products and services. It therefore goes back to the five A's framework by Penchansky and Thomas (1981). The updated 2003 WHO framework for equitable access to essential medicines focuses on four dimensions, namely, rational selection, affordable prices, sustainable financing and reliable health and supply. These include a range of sub-dimensions such as availability of national treatment guidelines and national lists of essential medicines, price information, generic policies, out-of-pocket spending and regulatory control for example (WHO 2004). The access framework by Frost and Reich (2008) is also based on the work by Penchansky and Thomas. Their framework is structured around the four A's of architecture, the organizational structure and relationships for access; availability, which emphasizes the supply components of access; affordability for various stakeholders; and adoption, which includes demand factors and acceptance. (Frost and Reich 2008). The most far reaching and comprehensive framework is the one developed by Bigdeli *et al.* (2013) which looks at access to medicines from a health system perspective and adopts a holistic view of demand-side barriers, takes into account the multiple dynamic relationships between health system building blocks and includes leadership and governance of the health sector at local, national and international level

(Bigdeli, Jacobs, et al. 2013). Further, it emphasises the role exerted by innovations, market forces and international agendas on the health and pharmaceutical sectors (Bigdeli, Jacobs, et al. 2013).

These frameworks were developed primarily with a view of studying access to medicines in low- and middle income countries – which are disproportionately affected by affordability and quality of medicines, responsible use of medicines, and supply chain problems - and are not specific to cancer medicines. As such, they are too broad and do not take into account some of the peculiarities affecting access to oncology medicines.

Few frameworks exist to study access to cancer or high cost medicines in countries with mature health care systems, which may not have major issues in the supply chain, but instead struggle more in establishing whether a new medicine represents good value for money, securing affordable prices, and inclusion in the list of reimbursed medicines have been published. One example is the work by Cohen *et al.* (2007) which identified eight sub-dimension of patient access to medicines to conduct an international comparison of access. These include marketing authorisation, time of marketing authorisation, reimbursement, cost sharing, conditions of reimbursement, time from marketing authorisation to reimbursement, the extent to which beneficiaries can choose between different medicines benefit schemes (e.g. in the US the medicines benefit package varies between insurers and patients can choose), and variation in coverage and cost sharing across the population (Cohen et al. 2007). While these factors are important in determining access to medicines, broader barriers to access such as access to timely diagnosis and financing of medicines are not included.

Benjamin *et al.* (2014) developed a conceptual framework of factors influencing patients' access to oral cancer medicines (Benjamin et al. 2014). The framework includes clinical aspects, physician's experience, patient's preferences, dialogue between the physician and the patient, patient characteristics and access to health services (Benjamin et al. 2014). In contrast to the framework by Cohen *et al.* (2007), which is designed to identify determinants of differences in access to cancer medicines across countries, the framework by Benjamin *et al.* (2014) is largely designed to compare access determinants between individual patients due to the inclusion of a number of patient and physician specific factors. As such, only a few national level factors are relevant for cross-country comparisons. More relevant is the discussion on system disincentives towards use of oral cancer medicines. The example

presented is the hospital per-case payment system in France, which provides an incentive not to shift chemotherapy provision through oral cancer medications from the hospital to the community to avoid a decrease in revenue (Benjamin et al. 2014). In the US, despite the introduction of the Cancer Drug Parity Act in 2006[7], the complexity of the reimbursement system and co-payments may be an important economic barrier for lower income patients to access oral cancer medicines (Benjamin et al. 2014). This framework thus sheds light on the important role played by financial incentives in limiting or enabling access.

Various literature reviews on access to cancer (Nolte and Corbett 2014), high cost (Wahlster et al. 2015) and new medicines (Lublóy 2014, Chauhan and Mason 2008) in high income countries have been conducted. These studies classify the identified determinants according to various frameworks and structures. Wahlster *et al.* (2015) classify barriers to access to high cost medicines in three levels: macro-, meso-, and micro-. At the macro- level, health system barriers such as affordability of the system (e.g. gross domestic product per capita); the decision making process for reimbursement (specifically, the use of HTA and time from marketing authorisation to reimbursement decision, and other factors influencing the decision-making process like lobbying by patient groups); and restriction on access and geographical variation in use can affect access (Wahlster et al. 2015). At the meso-level, hospital or regional system barriers such as differences in reimbursement of inpatient and outpatient medicines, more specifically, differences in budgets and decision-making processes across hospitals and/or regions (Wahlster et al. 2015). At the micro-level, patient barriers such as physician behaviour and communication in relation to the high costs of these medicines for the society, more specifically, the high costs for the patients and the influence of high-out-of-pocket costs on patients' choices (Wahlster et al. 2015). Nolte and Corbett (2014) review factors affecting use of cancer medicines, cancer outcomes, differences in stage at diagnosis on survival, and health system and service features that may explain variation in use of cancer medicines (Nolte and Corbett 2014). Lublóy (2014) reviews determinants of uptake of new medicines and classifies them in three levels. At micro-level, the socio-demographic and professional characteristics of medical professionals are considered (Lublóy 2014). At meso-level, the prescribing characteristics of doctors, the marketing efforts of pharmaceutical companies, interpersonal communication among doctors, medicines' attributes, and the characteristics of patients are reviewed (Lublóy 2014). At

[7] This act requires that health insurance providers offer coverage for oral anticancer medicines equivalent to intravenous chemotherapy (https://www.congress.gov/bill/114th-congress/house-bill/2739/text)

macro-level, government and health care organisation policies can affect uptake of new medicines (the latter group is acknowledged as important but not included in the literature review) (Lublóy 2014). As such, it is designed to study access at individual patient level. The framework by Chauhan and Mason (2008) reviews determinants of uptake of new medicines in secondary care with focus on the UK. They use Bonair and Persson's framework for the diffusion of innovation to classify determinants into: actors (secondary care colleagues, clinical investigators, pharma representatives, and patients), environmental factors (information/evidence, support structures, and incentives), and characteristics of the medicine (effectiveness, side-effects, convenience, cost, and uncertainty) (Bonair and Persson 1996, Chauhan and Mason 2008).

While a number of frameworks to analyse determinants of access to medicines have been developed, few focus on high-income countries and are specific to cancer medicines. Among the available frameworks specific to cancer medicines, only one of the frameworks reviewed includes financing of medicines but it is designed to understand determinants of use at patient level rather than population level. Further, most of the framework developed are not tested against utilisation data.

1.2.3 Determinants of access to cancer medicines in high income countries

Studies have identified the following determinants of access to cancer medicines in high income countries: out-of-pocket payments, country's wealth indicators, financing of medicines including additional funding for cancer medicines, budgetary limitations, HTA and coverage decisions, prescribing practices, time of marketing authorisation, availability of the necessary skills, specialisation and equipment necessary for the administration of the medicine (Kelly et al. 2015, Benjamin et al. 2014, Richards 2010, Cherny et al. 2016, Cheema et al. 2012, Groot, Huijgens, and Uyl-de Groot 2006, Kos, Obradovic, and Mrhar 2008, Mason et al. 2010, OECD 2013, Wilking, Jönsson, and Högberg 2009, Jönsson et al. 2016, Chamberlain et al. 2014, Blommestein et al. 2014, Dranitsaris et al. 2005, Wilson and Cohen 2011, Wilking et al. 2010, Niezen et al. 2006). Not all these studies discuss determinants in the terms of utilisation data, some just discuss access in the terms of its determinants (e.g. out-of-pocket payments, coverage).

1.2.4 Current initiatives to improve access to medicines

Ensuring access to medicines is high on governments as well as the international agenda as confirmed by a number of current initiatives and developments aimed at improving access to medicines. In the following subchapters, I will present some of the main ones.

1.2.4.1 Increased voluntary collaboration to manage the introduction of new medicines

Challenges in managing the introduction of new medicines have prompted various initiatives to strengthen voluntary collaboration in horizon scanning, health technology assessment, negotiation and strategic procurement of medicines in Europe (Espín et al. 2016, Ferrario, Kanavos, et al. 2016a).

There are various levels at which countries can collaborate in pharmaceutical procurement (Figure 2). These vary from informed buying, where participating countries share information on prices, suppliers and HTA methodologies but also conduct their own procurement individually; to centralised contracting and procurement where participating countries conduct joint tenders through a central buying unit (Management Sciences for Health 2012).

Figure 2: Levels of collaboration in pharmaceutical procurement

Source: Figure developed by the author based on the classification proposed by Management Sciences for Health at p. 18.10 of (Management Sciences for Health 2012). Also published in (Ferrario, Kanavos, et al. 2016b)

In Europe, a number of initiatives have been set up in recent years to increase voluntary collaboration between countries or administrative areas of one country. At the highest level of collaboration, joint tenders, a voluntary cooperation between 24 EU governments was established to conduct joint procurement of pandemic vaccines and medical countermeasures[8] (European Commission 2014). As of September 2016, this cooperation was evaluating bids received of personal protective equipment for health workers, preparing the launch of a joint tender for the procurement of Bacillus Calmette–Guérin vaccine and tuberculin, botulinum anti-toxin and diphtheria anti-toxin (Sion 2016). It had also accelerated preparations for joint procurement of pandemic vaccines (Sion 2016). Further, it is investigating the possibility of organising joint procurement of direct acting antiretroviral medicines for Hepatitis C (Sion 2016). There are also joint procurement initiatives at regional and sub-national levels. These include the joint procurement of vaccine among the Baltic countries (preparatory phase as of September 2016) (Lobovs 2016) and the joint procurement between England and Scotland of recombinant factor VIII and IX (two tenders completed as of September 2016) (McClure 2016).

The following initiatives span different collaboration levels, from information sharing to group purchasing. In April 2015, Belgium and the Netherlands, later joined by Luxembourg, have signed a Memorandum of Understanding to collaborate on horizon scanning, HTA, information exchange and experiences, pricing and reimbursement including joint negotiation (Arickx 2016). On the 17th of June 2016, Austria signed a letter of intent to join the Benelux countries and the group is now referred to as 'Beneluxa' or 'coalition of the willing'. In June 2015, Bulgaria and Romania announced that they intend to jointly procure high cost medicines (Petrovsky 2015). During the same month, the Nordic pharmaceutical forum was set up (Nye Metoder 2015) aiming to achieve collaboration between payers of medicines in Denmark, Iceland, Norway and Sweden, share experiences and tackle common challenges jointly around new and expensive medicines, horizon scanning and supply chain safety (Nye Metoder 2015). In a further initiative, at the end of a ministerial meeting on 2-3 June 2016 in Sofia, the representatives of Bulgaria, Croatia, Estonia, Hungary, Latvia, The Former Yugoslav Republic of Macedonia, Romania, Serbia, Slovak Republic and Slovenia signed a declaration to collaborate on issues affecting access to medicines. Issues of mutual concern to

[8] Article 2 of the Joint Procurement Agreement provides that medical countermeasures are "any medicines, medical devices, other goods or services that are aimed at combating serious cross-border threats to health, as referred to in Decision 1082/2013/EU" (European Commission 2014).

the signatories of the Sofia declaration include the availability of essential medicines, high prices of innovative medicines, cost-effectiveness analysis, information sharing and mutual transparency in pharmaceutical policy (Representatives of Bulgaria et al. 2016).

Under the Dutch Presidency of the EU, the Council of the EU released a series of recommendations on how to strengthen the balance in the pharmaceutical systems in the EU and its Member States (The Council of the European Union 2016). In its recommendations, the Council invites Member States to strengthen voluntary collaboration, between relevant authorities and payers, on pricing and reimbursement issues with the aim to increase affordability and improve access (The Council of the European Union 2016). Further, the Council invites Member States and the European Commission to explore synergies between the work of HTA bodies and payers, and to strengthen collaboration between Member States, particularly under the 3rd Joint Action of the European Network of Health Technology Assessment (EUnetHTA) (The Council of the European Union 2016). Finally, the European Council invites the European Commission to conduct, with the close involvement of Member States, an analysis on the impact of incentives to facilitate investment in R&D and marketing authorisation provided by the EU legislation on innovation, availability and accessibility of both originators and generic medicines (The Council of the European Union 2016).

Building on this momentum, the World Health Organization Regional Office for Europe held a consultation on strategic procurement of medicines in Copenhagen in September 2016. The aim of the consultation was to assess the willingness of the Region's Member States to voluntary collaborate on strategic procurement, with focus on information sharing. Following positive feedback from Member States, the work started during the consultation will continue in 2017.

These initiatives demonstrate a growing interest from countries in Europe to increase voluntary collaboration on access to new medicines and other medical products. They aim to leverage economies of scale (joint negotiation and procurement) and sharing of information, experiences and tasks (horizon scanning, HTA, market intelligence, etc.) to obtain more competitive prices and enable greater access to medicines, vaccines and other medical technologies and goods.

1.2.4.2 A forum to discuss fair pricing

In an attempt to ensure that medical innovation is affordable and accessible to patients, medicines (old and new ones) are available when needed, and monopolies on off-patent products leading to price manipulation are avoided, the World Health Organization is planning a multi-stakeholder meeting including governments, patients and industry to develop a fair pricing model for medicines (Kieny 2016, Silverman 2016c). Such model aims to deliver affordable prices for countries and patients and a financial return to industry which is sufficient to justify further investments in research and development (Kieny 2016). To this end, a series of technical reports are being developed to inform the consultation (Silverman 2016c). These will cover issues of price drivers, in particular manufacturers, price setting strategies, R&D costs, processes and policies used by countries to regulate prices and their effectiveness and what return of investment is needed to generate sufficient incentives for industry to keep engaging in R&D (Silverman 2016c). The aim of the consultation is to push the agenda on pricing models forward by proposing new ways of thinking about price, which, if linked with the appropriate policies, can contribute to ensure sustainable access to cost-effective medicines to address patient's needs (Silverman 2016c).

1.2.4.3 High-Level Panel on Innovation and Access to Health Technologies recommendations

A High-Level Panel on Innovation and Access to Health Technologies was set up in November 2015 by the United National (UN) Secretary-General to review and select proposals and recommend solutions to address the policy incoherence between intellectual property rights, international human rights law, trade rules and public health with the aim of improving access to health technologies (United Nations Secretary-General's high-level panel on access to medicines 2016). The Panel was composed of 15 world renowned experts in different areas relevant to the subject of the report. These were supported by an Expert Advisory Group of 25 members (United Nations Secretary-General's high-level panel on access to medicines 2016). A public call for proposals on how to strengthen the promotion of innovation and access to health technologies was launched and 182 submissions from academia, think thanks, patient representatives, industry and members of the civil society were received and reviewed (United Nations Secretary-General's high-level panel on access to medicines 2016). Shortlisted proposals were selected and proponents invited for further queries. These informed the writing and final recommendations of the report.

The report makes some bold statements and recommendations. It raises concerns about undue pressures from Government and the private sector on countries wishing to implement flexibilities included in the TRIPS agreements such as compulsory licensing (United Nations Secretary-General's high-level panel on access to medicines 2016)**.** To address this, the Panel recommends that such situations should be reported to the World Trade Organization (WTO) and that punitive measures should be undertaken against offending WTO Members (United Nations Secretary-General's high-level panel on access to medicines 2016). It also highlights the issue of evergreening, one example of which is the grant of secondary patents on the basis of minor but important changes, as a barrier to generic or competitor entry (United Nations Secretary-General's high-level panel on access to medicines 2016). The high-level panel recommended WTO Members to make full use of the provisions in Article 27 of the TRIPS agreement by adopting and applying rigorous definitions of inventions and patentability that prevent evergreening and ensure that patents are only awarded for genuine innovations (United Nations Secretary-General's high-level panel on access to medicines 2016).

1.2.4.4 Lancet Commission report on essential medicines for universal health coverage

The report of the Lancet Commission identified five critical areas essential medicines policies should address: paying for a basket of essential medicines, making essential medicines affordable, assuring the quality and safety of medicines, promoting quality use of medicines, and developing missing essential medicines (Wirtz et al. 2016). A wealth of international evidence and experiences are presented to inform the development of sound essential medicines policies and support the Commission's recommendations. A monitoring framework is proposed to measure progress against the recommendations of the Commission. This is composed of 24 indicators covering the five critical areas identified. The Lancet Commission report represents an important reference and agenda setting document which has the potential to influence policy and practice. First, it summarises key issues affecting access to essential medicines on the path to universal health coverage. Second, it provides a range of recommendations and policy options to address these issues. Together, this provides key information to policy makers and other stakeholders in the pharmaceutical sector about what the issues are and what can be done to address them. Finally, it highlights key evidence gaps which should inform future research efforts. It thus contains a number of messages for decision-makers, payers, industry, patients, and researchers which can be leveraged on in promoting change. Most importantly, the monitoring framework provides a standardised tool to measure progress at country level, which is more comprehensive than previously

developed indicators to monitor progress in improving access to medicines as part of the Millennium Development Goals for example.

1.3 Value frameworks

In recent years, a number of value frameworks have been developed to assess cancer medicines, notably the American Society of Clinical Oncology (ASCO) value framework (Schnipper et al. 2016), the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) (Cherny et al. 2015), the Institute for Clinical and Economic Review (ICER Institute) value framework (Institute for Clinical and Economic Review 2016), the Memorial Sloan Kettering Cancer Center (MSKCC) Drug Abacus Price (Memorial Sloan Kettering Cancer Center 2016), and the National Comprehensive Cancer Network (NCCN) evidence blocks (National Comprehensive Cancer Network 2016). These frameworks have been increasingly discussed and compared in the literature (Chandra, Shafrin, and Dhawan 2016, Neumann and Cohen 2015, Schnipper and Bastian 2016, Westrich 2016, Basch 2016). The general agreement is that these frameworks are a very welcome first step in advancing the discussion around added value and pricing of new cancer medicines but need to be refined (Chandra, Shafrin, and Dhawan 2016, Basch 2016, Neumann and Cohen 2015, Young 2015). One point raised by various authors is that, despite the aim of some of these frameworks (ASCO, ESMO and NCCN) to inform joint decision-making between clinicians and patients, not all of them incorporate factors that matter to patients (e.g. symptoms, quality of life, work productivity, caregiver burden, unmet need, etc.) (Chandra, Shafrin, and Dhawan 2016, Basch 2016, Westrich 2016). Furthermore, these frameworks cannot be tailored to individual patient characteristics, weightings of preferences, and insurance coverage (Basch 2016, Westrich 2016). For example, although many of these frameworks have included patient out-of-pocket costs, they do not allow for customisation based on the patient's insurance plan (Basch 2016). This aspect is very important in the US were most of these frameworks are meant to be applied. In addition to patient-centeredness, elements of timeliness and equity, which others have identified as elements of value of cancer care, are not included (Young 2015).

These frameworks rely on numerous assumptions and arbitrary decisions, particularly regarding weighing and combining different dimensions into a final score and consideration of subjective expert opinion which make their results less robust (Chandra, Shafrin, and Dhawan 2016, Neumann and Cohen 2015, Young 2015). These challenges are in part due to

limited data availability (e.g. patient preferences and patient reported outcomes (PROs)) and lack of consensus around which dimensions should be included in the measurement of value. Concerning the first, it has been suggested that the current frameworks have missed the opportunity to highlight information deficits by penalising ratings of medicines which do not provide certain information (e.g. important PROs), as a way to incentivise their future collection (Basch 2016). In fact, the ASCO 2016 framework only mentions that much work is needed in the area of PROs and that future versions of the framework will facilitate incorporation of PROs into the estimation of the final value score (Schnipper and Bastian 2016). The development of such frameworks and their improvement over time should help address the second point. In fact, some of the critiques to the ASCO 2015 framework have been addressed in its 2016 update. Further critiques include the lack of budget impact considerations that are only taken into account in the framework by the ICER Institute. However, it was noted that the ICER Institute's maximum budget impact limit (US$ 904 million per year) penalises medicines meant to benefit a large number of patients (Chandra, Shafrin, and Dhawan 2016, Neumann and Cohen 2015). Authors have also noticed that the MSKCC Abacus value based price could have unintended consequences if prices of high-value medicines are increased but prices of low-value medicines are not decreased (Young 2015). Another important limitation is the exclusive focus in most frameworks on RCT data (excluding the ICER Institute framework which also includes observational data), (Chandra, Shafrin, and Dhawan 2016, Westrich 2016). While generally regarded as the gold-standard in terms of evidence, RCTs only measure efficacy and not effectiveness in real-life. In addition, study design, inclusion criteria and choice of comparator in the RCT can affect the validity of the efficacy estimate (Chandra, Shafrin, and Dhawan 2016) and it is therefore important to triangulate RCT data with data from other types of studies. Finally, the lack of a system-wide perspective on value was raised (Westrich 2016), particularly in relation to additional costs or savings to be generated by introducing a new medicine (Chandra, Shafrin, and Dhawan 2016).

Table 2 compares some of main features of these frameworks. The ASCO, ESMO, ICER Institute, and NCCN frameworks all aim to influence clinical practice. In addition, the ESMO, ICER Institute and MSKCC aim to influence public policy, in particular discussions around value for money. These frameworks strive to achieve their objectives through different methods and the estimation of summary indictors like the net health benefit score and cost per month of the ASCO framework, the magnitude of clinical benefit scale of the

ESMO framework, the level of care value and health system value of the ICER Institute assessment, the 'Abacus price' of the MSKCC pricing tool, and the evidence blocks of the NCCN framework.

Table 2: Comparison of value frameworks for cancer medicines

Framework	Objective	Data	Dimensions included	Outcome	Application
ASCO	Shared decision-making between the patient and the clinician which takes into account patient preferences, goals and financial circumstances	Prospective randomised trials comparing a new treatment with prevailing standard of care	Clinical benefit, toxicity, symptom palliation, cost	Net Health Benefit Score (NHB), cost per month	Clinical practice
ESMO	To distinguish treatments which bring substantial improvements in survival and/or quality of life from treatments whose benefits are limited and to include the former in ESMO guidelines	Randomised clinical trials	Clinical benefit, toxicity	Magnitude of Clinical Benefit Score (MCBS)	Public policy, development of clinical guidelines, clinical decision-making, assessing the clinical significance of research findings
ICER Institute*	To conduct evidence-based reviews of health interventions to help clinicians and patients knowing what works	Clinical trials, observational studies	Comparative clinical effectiveness, incremental cost for better clinical outcome, other benefits or disadvantages, contextual considerations	Care value	Clinical practice, public policy

Frame work	Objective	Data	Dimensions included	Outcome	Application
MSK CC	To determine appropriate prices for cancer medicines based on the value of a medicine	FDA package insert	Current price, efficacy, toxicity, novelty, R&D rarity, burden of disease, unmet need, prognosis, budget impact	Value-adjusted price	Pricing of medicines
NCC N	Shared decision-making between the patient and the clinician which takes into account the patient's own value system	RCTs, non-randomised trials, meta-analysis or systematic reviews, clinical case reports, case series and clinical experience	Efficacy, safety, quality of evidence, consistency of evidence and affordability	NCCR evidence blocks	Clinical decisions

Notes: *generic framework, not specific to cancer medicines

Source: The candidate based on (National Comprehensive Cancer Network 2016, Cherny et al. 2015, Schnipper et al. 2016, Institute for Clinical and Economic Review 2016, Memorial Sloan Kettering Cancer Center 2016)

There are different ways in which these frameworks can contribute to improved access to cancer medicines. Frameworks that aim to influence clinical practice by guiding shared decision-making between clinicians and patients, may lead to a different treatment choice than if no framework had been applied and the decision was taken solely by the doctor. The ESMO framework aims to give prominence to medicines with a high magnitude of clinical benefit score in their clinical guidelines. ESMO clinical guidelines are an important reference in Europe and worldwide and have thus the potential to influence clinical practice in a number of countries. The provision of a user-friendly comparison tool like the NCCN evidence blocks can help patients and their clinicians in deciding on the best treatment course. Indeed, prioritisation according to the magnitude of benefit has been suggested as a guiding principle in developing national essential medicines lists (Magrini et al. 2015). The

evidence and methodologies used to generate the final scores in each of these frameworks therefore have a key impact on their ratings and potentially on access, which makes their continuous improvement crucial.

There are several ways in which these frameworks may influence access, including, influencing pricing and reimbursement processes. Dissemination of evidence on clinical and economic added value can be used by payers in pricing negotiations thus potentially influencing pricing and reimbursement decisions, depending on the time this information becomes available. ESMO also suggests that medicines with a high magnitude of clinical benefit score should be prioritised for accelerated reimbursement review (Cherny et al. 2015). Further, evidence from these frameworks can be used by payers as a credible benchmark when negotiating prices with manufacturers. If their use becomes widespread, these frameworks can have an important impact in identifying medicines with high clinical added value which should be prioritised for use in clinical practice over medicines with more limited clinical added value.

The development of value frameworks is part of broader discussion around prioritisation of treatment which takes into account value for money, financial sustainability, and patients' preferences. There are examples of frameworks to guide commissioning and prescribing decisions in line with value well before the recent efforts by ASCO, ESMO and others. Before the National Institute for Health and Care Excellence (NICE) in England started to issue guidance on use of medicines in the NHS, clinicians and health authorities had to find ways to deal with lack of national guidance. This is still in part the case nowadays for medicines not assessed by NICE. A consortium of six health authorities in Greater Manchester developed evidence thresholds based on cost-effectiveness to guide commissioning decisions in the late nineties (Foy et al. 1999). In the 1997-8 priority list for commissioning, the consortium agreed to fund all medicines rated as having clinical-effectiveness over and above existing treatments (Foy et al. 1999). Their impact assessment of new interventions was based on survival and quality of life, compared, where possible, with standard treatment (Foy et al. 1999). Other treatment outcomes assessed included tumour response rates, symptom responses, side effects, and overall costs (Foy et al. 1999). Another prioritisation effort from England in the pre-NICE era was the development of an approach to guide commissioning decisions for new treatments for advanced cancer. This was done by a group of clinicians and health authorities in South London around the same

time as the Greater Manchester consortium. The South London approach was based on survival, quality of life and strength of evidence (Ferguson et al. 2000). Although a specific funding threshold was not defined, the authors reported that the estimation of the additional funding made available after the prioritisation exercise was largely based on the cost of providing treatments prolonging median survival by 3 months or more and improving quality of life (Ferguson et al. 2000). This evidence should be based on at least one high-quality RCT and supporting non-randomised phase II data, ideally meta-analysis or two-high quality RCTs (Ferguson et al. 2000). The ASCO working group on clinically meaningful outcomes for cancer clinical trials, came to similar conclusions. Each of the four therapeutic sub-groups of experts – on pancreatic, lung, breast and colon cancer - identified 2.5 to 6 months improvement in median overall survival as the minimum incremental improvement over standard therapy that would represent a clinically meaningful outcome (Ellis et al. 2014). This work informed the definition of the categorical scores and weights of the clinical benefit component of the ASCO value framework (Schnipper et al. 2015).

Value frameworks have also been developed in other areas of cancer care particularly in preventive and non-pharmacotherapeutic areas. Examples include value frameworks on how the value of cancer screening strategies varies with their intensity (Harris et al. 2015), as well as frameworks for prostate brachytherapy, proton beam therapy and robotic-assisted prostatectomy based on clinical and PROs over time-driven activity-based costing (Thaker, Pugh, et al. 2016, Thaker, Ali, et al. 2016), and for head and neck cancer treatment (de Souza and Seiwert 2014).

2 Gaps in the literature and hypotheses, research question, structure of the thesis

2.1 Gaps in the literature and hypotheses

2.1.1 Frameworks to study access to cancer medicines in high income countries

The review of the literature on access to cancer medicines highlighted the paucity of frameworks to study access to cancer medicines. The majority of available frameworks were designed to study access to essential medicines in low- and middle income countries (Center for Pharmaceutical Management 2003, WHO 2004, Frost and Reich 2008). One framework focused specifically on cross-country comparison of access in high-income countries but included a limited number of broad factors and was not specific to cancer (Cohen et al. 2007). Few studies include financial arrangements at hospital level (Benjamin et al. 2014) and hospital level clinical guidelines and practice as possible determinants of variations in use.

2.1.2 Variations in access to cancer medicines and their determinants

There is a limited number of studies comparing utilisation of cancer medicines across countries (Richards 2010, Kelly et al. 2015, Wilking, Jönsson, and Högberg 2009, Jönsson et al. 2016, Wilking and Jönsson 2005, Kos, Obradovic, and Mrhar 2008). However, not all of them used statistical methods to test correlation between possible determinants of use and actual use of cancer medicines (Richards 2010, Kelly et al. 2015, Wilking, Jönsson, and Högberg 2009, Wilking and Jönsson 2005, Kos, Obradovic, and Mrhar 2008). If they used them there were methodological limitations (e.g. very small sample (Jönsson et al. 2016)) or the focus was on understanding subnational variations in use of cancer medicines (Crawford et al. 2012, Patel et al. 2007, Crawford et al. 2009, Wilking et al. 2010). Only a few papers presenting utilisation data employed a qualitative framework to systematically compare health system features that may affect access to cancer medicines (Groot, Huijgens, and Uyl-de Groot 2006). Further, some studies analysed determinants of access to cancer medicines but did not measure actual utilisation levels (Benjamin et al. 2014, Cherny et al. 2016, Cohen et al. 2007).

2.1.3 Interventions to improve access to cancer medicines

In response to high prices of new cancer medicines, many countries have introduced changes in their pricing and reimbursement policies as well as procurement strategies in an attempt to improve access. One such example is the introduction of managed entry agreements, a

heterogeneous group of agreements between payers and manufacturers to facilitate access to new medicines in a context of uncertainty, high prices and budgetary limitations. A number of cross-sectional studies and discussion papers have been published on the subject of managed entry and risk-sharing agreements, yet limited evidence is available on their governance structure and their impact. Discussions around access to cancer medicines have tended to focus on prices and coverage decisions. Less attention has been given to the role of strategic procurement in improving access to cancer medicines. . Learning from existing experiences in strategic procurement at national and international level can provide useful lessons learned for improving access to cancer medicines.

2.1.4 Hypotheses

The review of the literature highlighted the limitations of existing frameworks to study access to cancer medicines in high-income countries, limited evidence on variations in use of cancer medicines in Europe and their determinants and limited evidence on how countries are addressing challenges in access to cancer medicines. Based on the evidence reviewed and the identified literature gaps, the following hypotheses were formulated. The first three hypotheses focus on variations in access and their determinants, while the last two focus on countries' responses to improve access:

1. Variations exist in access to cancer medicines across different European countries and these can be substantial
2. Differences in access are determined by a number of factors beyond HTA recommendations. These include for example prices of medicines, how medicines are financed including special funding arrangements and limitations on the number of patients treated, and the sector/s where they are dispensed
3. Variations in access to medicines do not always reflect the added clinical value of new medicines
4. Managed entry and risk-sharing agreements are increasingly used to facilitate entry of new medicines however their impact on time to entry, use and reduction of uncertainty is still largely unknown
5. A number of countries have used elements of strategic procurement to increase access to medicines. However, more efforts are needed at national and international levels to increase the efficiency of procurement and ensure sustainable access to medicines at affordable prices

2.2 Aim and research questions

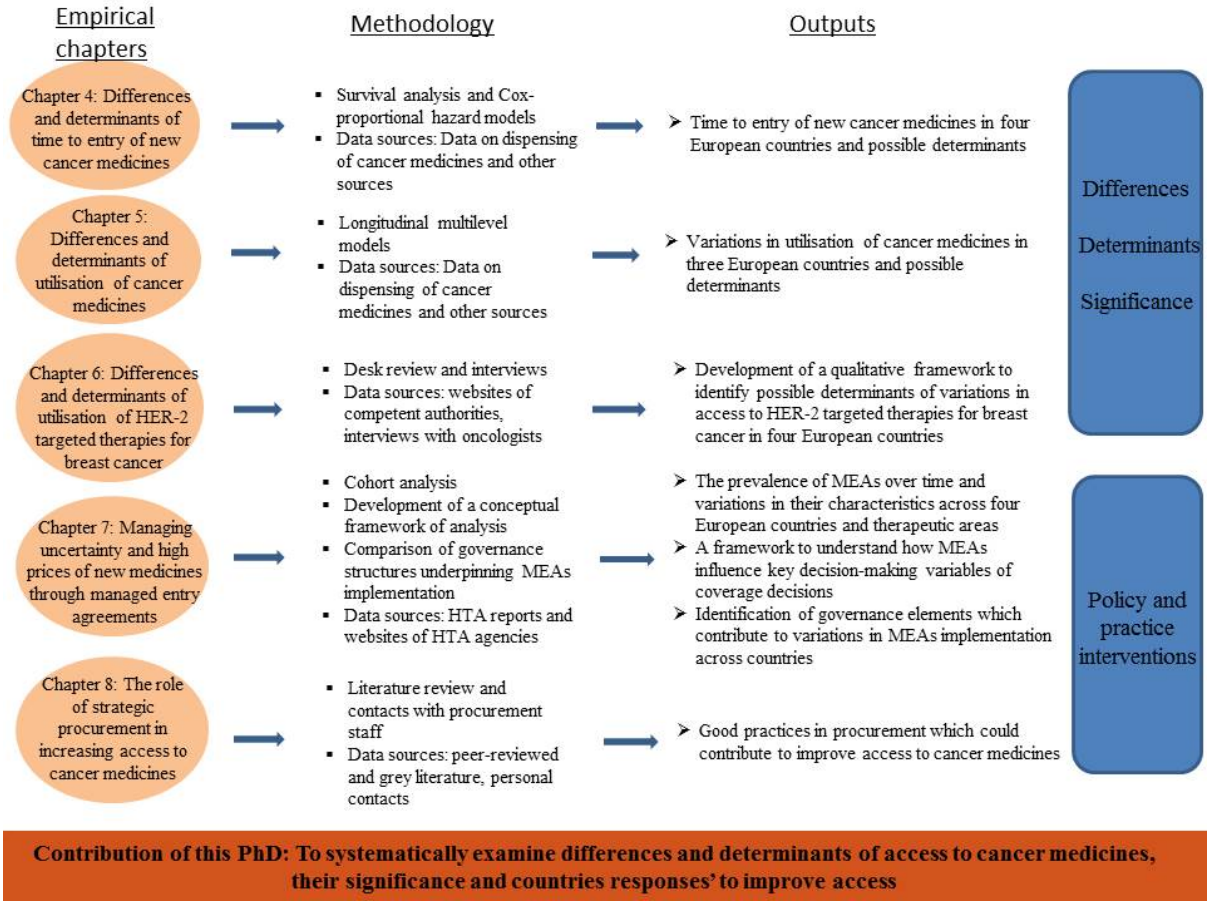
The literature review highlighted the need for formal testing of the impact of possible determinants of variations in access to cancer medicines, the lack of a qualitative framework to study access to cancer medicines in high-income countries, and the limited evidence available on countries responses to existing challenges. These led to the formulations of five hypotheses. Based on the literature reviewed and the hypotheses derived from the identified gaps in the literature, the overarching aim of this thesis is to systematically examine differences and determinants of access to cancer medicines, their significance and countries responses' to improve access. To address this aim, four research question were formulated. In the following paragraphs, I outline the four research questions and explain how the individual empirical chapters contributed to address each of them.

1. Are there differences in access to cancer medicines across European countries and how large are they?
   This research question is addressed by (i) investigating time to entry for new cancer medicines in four European countries using survival analysis and the complementary log-log transformation of the Cox-proportional hazard model (Chapter 4), (ii) analysing utilisation of cancer medicines and their determinants in three European countries by means of longitudinal multilevel models (Chapter 5), and (iii) developing a framework to help understand utilisation differences focusing on HER-2 targeted medicines for breast cancer building on interviews and a review of the relevant literature, clinical guidelines as well as national official websites (Chapter 6).
2. What determines these differences?
   Using the quantitative methods described, Chapter 4 tests the correlation between time to launch and possible determinants, Chapter 5 tests the correlation between variations in utilisation and possible determinants, and Chapter 6 uses a qualitative framework to explore possible reasons for the observed variations in utilisation.
3. Do these differences in access matter?
   Chapter 4 and 5 test the correlation between two indicators of the added clinical value of new medicines and time to entry and use. These indicators are the rating by the independent Drug Bulletin Prescrire and the ESMO Magnitude of Clinical Benefit Scale rating.
4. How are countries responding to these challenges to improve access?

Having identified some of the existing challenges in access to cancer medicines in selected European countries, Chapter 7 and 8 investigate how countries are responding to these challenges. Chapter 7 studies the implementation of managed entry agreements in four European countries by means of a comparative longitudinal analysis of the implementation of MEAs, reviews the governance structures around them and proposes a framework to understand how MEAs influence key decision-making variables of coverage decisions. Chapter 8 reviews the role of strategic procurement through a literature review and contacts with staff involved in national pricing negotiations and procurement.

Finally, Figure 3 shows how each empirical chapter contributed to the aim of this thesis.

Figure 3: Conceptual framework of the PhD thesis



2.3 Structure of the thesis

This thesis is composed of nine chapters. The first chapter reviewed the literature on determinants of access to cancer medicines along the product life-cycle, frameworks to study

access to cancer medicines, determinants of access current initiatives to improve access and the development of value frameworks. Chapter 2 summarised the gaps identified in the literature and presented the hypotheses and research questions of this thesis. Chapter 3 provides an overview of the methods used in the individual chapters of this thesis. Chapter 4 to 8 are the publishable papers of this thesis, some of which have already been published while others are being peer-reviewed. Their structure includes the following sub-sections: an introduction, methods, results, discussion and conclusions. Chapter 4 studies time to entry for new cancer medicines from EU-wide marketing authorisation to patients access in Belgium, Estonia, Scotland and Sweden. Chapter 5 analyses the determinants of utilisation differences for cancer medicines in Belgium, Scotland and Sweden. Chapter 6 develops a framework to understand differences in utilisation of HER-2 targeted medicines for breast cancer. Chapter 7 studies how countries deal with uncertainty and high prices of new medicines by conducting a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Chapter 8 reviews the role of strategic procurement in increasing access to cancer medicines. Finally, Chapter 9 draws the overall conclusions of this thesis and their policy implications, summarises the main limitations of this research and proposes future areas of research.

3 Methods

This thesis used a mix of quantitative and qualitative methods including longitudinal multilevel models, survival analysis and the complementary log-log transformation of the Cox proportional hazard model, literature reviews, interviews, and a comparative longitudinal analysis of the implementation of MEAs. While the specific methods used in each paper are described in more detail in Chapters 4 to 8, this section provides an overview and more details about the extensive data extraction process to develop the four quantitative databases used in this thesis. These include a longitudinal database of 46 cancer medicines to study time to launch, a longitudinal database of 31 medicines to study differences in utilisation across countries, a longitudinal database on use and determinants of HER-2 targeted therapies for breast cancer, and longitudinal data on the introduction and implementation of managed entry agreements.

3.1 Measuring access to medicines

As described in the introduction, access to medicines has been measured in different ways. Due to difficulties in measuring accessibility, accommodation, and acceptability, studies on access to medicines have often focused on physical availability of the medicine in pharmacies and/or health facilities and affordability for patients. In this context, a number of studies on price comparisons have also been conducted. In this thesis, I focus on different aspects of access to cancer medicines and its determinants. In Chapter 4, I investigate access from the perspective of availability on the market in the study countries (i.e. time to entry). In Chapters 5 and 6 I study access by comparing levels of utilisation of cancer medicines in the study countries and their determinants. Chapter 7, analyses the contribution of managed entry agreements in improving access by managing high prices and uncertainty around cost-effectiveness and quality use of medicines. Finally, Chapter 8 reviews country experiences in improving procurement outcomes (e.g. obtaining more competitive prices, improving selection and use of medicines, reducing the number of stock-outs) in an attempt to improve access to medicines.

3.2 Study countries for this thesis and geographical coverage

The core study countries of this thesis are Belgium, Estonia, Scotland, and Sweden (Chapters 4 to 6). These were chosen based on availability of non-commercial data on utilisation of cancer medicines in both, hospital and ambulatory settings and the intention to include a mix

of Western and Eastern European countries to study variations in access of cancer medicines. Key information and indicators on these countries is provided in Appendix 1. The thesis as a whole draws from the experience of other European and non-European countries to learn about approaches used worldwide to improve access to medicines (Chapters 7 and 8) and inform the conclusions (Chapter 9) of this thesis. Specifically, Chapters 4 to 6 investigate determinants of access to new cancer medicines in the study countries of this thesis. Chapters 7 and 8 study some of the approaches different countries – the study countries and other European and non-European countries - are using to improve access to medicines. Chapter 8 in particular adopts a global scope with the intention of identifying good practices in improving access to medicines through strategic procurement, independently of where they are implemented. It was not possible to include Estonia in Chapter 5 due to lack of publicly available data on reimbursement by medicine-indication (dates and decisions). It was not feasible to obtain this information for 31 medicines on request due the extensive time it would have required the Estonian Health Insurance Fund to extract these data.

3.3 Development of a database on time to launch of new cancer medicines and possible determinants

In Chapter 4, I analyse time to entry of new cancer medicines in the four study countries of this PhD. I obtained quarterly data on utilisation of a sample of 46 cancer medicines in hospital and ambulatory sectors covering the period 2000-2015 as indicated in Table 3. The sample of cancer medicines includes all medicines falling under anatomical therapeutic chemical (ATC)-L01 (antineoplastic agents)/L02 (endocrine therapies), which received EU-wide marketing authorisation between 2000 and 2014. As the focus of this thesis is on new cancer medicines, I excluded generics and new brands of previously approved international non-proprietary names (INNs). I also excluded orphan medicines as this group of medicines is quite distinct, it is mostly associated with very high entry prices and targets at least initially a small patient population. As current practice, research on orphan medicines is generally conducted on this medicines group only and would therefore require separate analysis.

Table 3: Data collected on the use of cancer medicines in the study countries

	Data source	Variables	Frequency	Time period
Belgium	National Institute for Health and Disability Insurance (RIZIV-INAMI)	ATC level 5 (active ingredient), defined daily doses, expenditure	Quarterly	Q1 2001 - Q2 2015 (ambulatory sector); Q1 2002 - Q2 2015 (hospital sector)
Estonia	Estonian State Agency of Medicines	INN, ATC-5, brand name, number of packs, pack size, strength, expenditure	Quarterly	Q1 2000 - Q1 2015 (ambulatory and hospital sectors)
Scotland	Information Services Division (ISD) Scotland	INN, number of units (e.g. tablets, vials), strength	Monthly	April 2004 - August 2015 (ambulatory sector); April 2007 - May 2015 (hospital sector)
Sweden	Swedish eHealth Agency (eHälsomyndigheten)	ATC-5, brand name, number of units (e.g. tablet, vial), number of packs, pack size, strength, expenditure	Monthly	January 2000 - December 2014 (ambulatory and hospital sectors)

Notes: Q: quarter

These data were used to identify the first quarter in which a medicine was first used (launch time) in each country. Dates of EU-wide marketing authorisation for the first approved indication of each medicine, whether the medicine was approved under conditional marketing authorisation, the ATC group at level 5 (active ingredient), and the company name of the marketing authorisation holder were obtained from the European Medicines Agency Public

Assessment Reports available on the EMA website. I requested dates of manufacturer submissions of a reimbursement dossier for the first submitted indication to the relevant authority in each country (the National Institute for Health and Disability Insurance in Belgium, the Estonian Health Insurance Company and the Estonian Ministry of Social Affairs, the Scottish Medicines Consortium, the Swedish Dental and Pharmaceutical Benefits Agency). Dates of reimbursement decision or HTA recommendation were generally available on the websites of these authorities with the exception of Estonia where they had to be requested. In Estonia, reimbursement requests are handled separately depending on whether the medicine is submitted for reimbursement in the hospital or ambulatory sector. Reimbursement requests for the ambulatory sector are made by manufacturers, whereas reimbursement requests for the hospital sector are done by clinicians. I therefore requested this information separately to each relevant authority. A few rounds of follow-up were required to obtain full information (e.g. the initial information provided contained some gaps relating to the date of submission and/or reimbursement and inconsistencies which needed clarification). Information on manufacturer headquarters was identified through the company's website. This was included to test whether having a local manufacturer headquarters correlated with increase probability of launch. Since there are only two generic manufacturers (i.e. no manufacturers of branded medicines) in Estonia and findings from a previous study suggested that having a local sales representative increases the likelihood of launch (Ferrario, Reinap, et al. 2016), I used this information for Estonia instead of local manufacturer's headquarters used in the other countries. The list of local sales representative in Estonia was obtained from the website of the Estonian Association or Pharmaceutical Manufacturers (APME 2016). As Scotland is part of the UK, no distinction was made whether the manufacturer was based in England or in another jurisdiction of the UK.

The expected volume was estimated based on actual defined daily doses (DDDs)[9] consumed in the relevant pharmacological subgroup (ATC level 3), lagged by one quarter. The same approach was used in other studies (Costa-Font, McGuire, and Varol 2015, Danzon and Epstein 2012) due to lack of data on the number of expected patients in each country studied. DDDs were estimated using information on total milligrams (mg) of active ingredient used divided by the reference DDD and multiplied by thousands. Since DDD for cancer medicines are mostly not defined by the WHO Collaborating Centre on Drug Statistics Methodology,

[9] "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults." http://www.whocc.no/ddd/definition_and_general_considera/ (accessed 15 November 2016)

the DDD of the Belgian Centre for Pharmacotherapeutic Information (CPI), (2016) were used instead. If they were not defined by the CPI, the German Institute of Medical Documentation and Information (DIMDI 2016) was used instead. If not defined by the CPI or the DIMDI, I used the smallest approved formulation by the EMA. Substantial data cleaning was required to estimate the total mg of active ingredient of each INN included in the analysis. This is because each country reports data in a different way and uses different codes for its variables. As a result, follow-up with the relevant authority (INAMI in Belgium, ISD in Scotland, TLV and eHälsomyndigheten in Sweden, and SAM in Estonia) was required to verify whether the national variables had been interpreted correctly. In Scotland, volume is measured based on the number of units (e.g. vial, tablet) dispensed. In Belgium, volume is measured based on the number of pricing units dispensed, which may not always correspond to the actual unit dispensed (e.g. vial, tablet). For example, trastuzumab, a targeted medicine for the treatment of breast and stomach cancer, is available as powder for infusion (150 mg) and, as of June 2013, also as subcutaneous injection (600 mg/ 5 ml). Until 2013, the unit of pricing for the infusion was 150 mg, as of 2013, a second unit of pricing for the infusion, 75 mg, was introduced. So although the strength of the vial was 150 mg in both cases, in the second case, the number of units reported ('Quantity 2013': 68,619; Table 4) refers to 75 mg rather than 150 mg.

Table 4: Excerpt of dispensing data as reported in Belgium

Setting	DENO2 (brand name)	CONDI (unit of pricing)	Mode of administration	Quantity 2011	Quantity 2012	Quantity 2013
Hospital	HERCEPTIN	1 flacon injectable x 150 mg trastuzumab	INJECTION	85,756	94,188	74,629
Hospital	HERCEPTIN	75 mg x 150 mg trastuzumab	INJECTION	0	0	68,619

In Sweden, both the number of doses and packs are reported (Table 5). The number of doses equals the number of tablets (e.g. Afinitor), capsules, or vial of concentrate powder without solvent (e.g. Alimta) per pack times the number of packs dispensed. However, this is not the same for vials of concentrates for infusion with solutions (e.g. Avastin). In this case, the number of doses represents the number of millilitre solution (not the number of vials) times the number of packs.

Table 5: Excerpt of utilisation data as reported in Sweden

Product	Channel	Year	Total expenditures (measured in pharmacy selling prices)	Doses	Packs	Patient co-payment SEK
Afinitor, tablett 10 mg Novartis Sverige AB - 30 tablett(er)	Hospital	2012	4,666,625	3,750	125	0
Afinitor, tablett 5 mg Novartis Sverige AB - 30 tablett(er)	Dosage	2012	210,400	240	8	209,590
Afinitor, tablett 5 mg Novartis Sverige AB - 30 tablett(er)	Prescription	2012	10,993,400	12,540	418	10,738,381
Alimta, pulv till konc till inf-vätska, lösning 500 mg Eli Lilly Sweden AB - 1 styck	Hospital	2012	67,252,827	5,231	5,231	0
Alimta, pulv till konc till inf-vätska, lösning 500 mg Eli Lilly Sweden AB - 1 styck	Outpatient - order	2012	326,436	24	24	0
Avastin, konc till inf-vätska, lösning 25 mg/ml Roche AB - 16 milliliter	Prescription	2012	96,536	128	8	0
Avastin, konc till inf-vätska, lösning 25 mg/ml Roche AB - 16 milliliter	Hospital	2012	47,695,207	64,383	4,024	0
Avastin, konc till inf-vätska, lösning 25 mg/ml Roche AB - 4 milliliter	Outpatient - order	2012	9,995	12	3	0

Understanding these peculiarities in the reporting of different countries was crucial to accurately estimate the number of DDDs dispensed and required careful inspection of the datasets and follow-up with competent authorities in the study countries.

The expected price per DDDs was estimated based on the average price (weighted by volume) per DDD in the pharmacological subgroup (ATC level 3). Information on prices was obtained by dividing the expenditure for each medicine-strength-formulation by the total number of DDD consumed and multiplied by thousand. No expenditure data were provided by IDS Scotland due to the confidential nature of the discounts provided to the NHS. I did ask for gross expenditure but this was not available and could not be provided. I therefore had to embark on an extensive data extraction process of list prices from historical hard-copies of British National Formulary available for in-house use only at the Wellcome Library. British pounds and Swedish krona were converted into Euros using the historical exchange rates on the OANDA website (OANDA website 2016). A weighted average price per DDD was then calculated for each pharmacological subgroup and quarter.

In Chapter 4 on time to launch, data on FDA expedited approvals were extracted from different lists on the FDA website (accelerated approval (US Food and Drug Administration 2016a), breakthrough (US Food and Drug Administration 2016b), fast track (US Food and Drug Administration 2016d), and priority review (US Food and Drug Administration 2016e)). In addition, I consulted the medicine's search function of the FDA (US Food and Drug Administration 2016c) and the annual new drug approvals reports published by the FDA since 2011 (U.S. Food & Drug Administration 2016b). I compared my findings with information from a study on drug development and FDA approval published in the New England Journal of Medicine (Darrow and Kesselheim 2014) for cross-validation. Sometimes additional expedited programmes were granted for new formulations and/or new indications a few years from the first approval. I did not include these programmes for the estimation of the expedited programme variable I used in the complementary log-log analysis on the hazard (probability) of launch in Chapter 4. Instead, I only took into account expedited programmes up to the EMA approval. The rationale behind is that these programme are unlikely to play role in signalling high value of a medicine and potentially expediting time to entry in the EU since they occurred after EMA approval. An annual subscription to the independent Drug Bulletin Prescrire was purchased to access data on all medicines assessments to extract the rating of additional clinical value in comparison to available treatments in the EU given by

Prescrire (2016). The ESMO magnitude of clinical benefit scale ratings for solid tumours were extracted from a peer-reviewed paper published by ESMO (Cherny et al. 2015).

3.4 Survival analysis

Many statistical methods assume that rates at which events occur are constant over the time period studied (Kirkwood and Sterne 2003). However, this is often not the case and statistical methods that allow deviating from this assumption should therefore be employed. For example, in Chapter 4, I conduct a longitudinal study on time to launch of new medicines (i.e. the time a new medicine is first used in a particular country). In this case, the probability a medicine will be launched in a particular country following marketing authorisation is not constant but changes over time. Statistical methods for survival analysis enable to describe, explain, or predict the probability of an event happening and the timing (Allison 2010). For example, it enables to estimate the hazard rate, the instantaneous probability of an event occurring at a particular point in time (h(t)) as well as the survival function (S(t)), the probability of an individual not to experience the event of interest (e.g. death or launch of a medicine) up to and including time t (Kirkwood and Sterne 2003). Most importantly survival analysis allows to handle right censoring, which defines observations (individuals) for whom the time of the event is not known because it has not occurred by the end of the observation period (Allison 2010). An important assumption is that censored and not censored individuals have the same probability of surviving (Kirkwood and Sterne 2003). In other words, that the probability of being censored is independent from the probability of the event of interest happening. This is called non-informative censoring.

Survival curves can be estimated using life tables and the Kaplan-Meier method. Life tables are used when the timing of the event of interest occurs is only known approximately by a discrete time period (e.g. the medicine was launched in the first quarter of 2014 but we do not know the exact day the medicine was launched). An example of how a life table is constructed is provided in Table 6 using data from Chapter 4 on time to launch of new medicines.

Table 6: Example of a life table using data from Chapter 4 on time to launch

Interval month (i) since a medicine obtained a EU-wide marketing authorisation (MA)	Number of medicines at the beginning of the interval (a_i), i.e. with MA but not launched yet	Number of medicines launched during the interval (d_i)	Number of medicines censored during the interval (c_i), i.e. not launched by the end of the observation period	Number of medicines at risk of being launched $n_i=a_i-(c_i/2)$	Probability of a medicine being launched $r_i=d_i/n_i$	Probability of non-launch $s_x=1-r_i$	Cumulative probability of non-launch from time of EU-wide marketing authorisation $S(x)=S(i-1)* s_x$
0	46	1	1	45.5	0	1	1
1	44	0	1	43.5	0	1	0.98
2	43	1	1	42.5	0.02	0.98	0.96
3	41	7	0	41	0.17	0.83	0.79
4	34	5	1	33.5	0.15	0.85	0.67
5	28	8	1	27.5	0.29	0.71	0.48
6	19	1	1	18.5	0	1	0.45
7	17	3	0	17	0.18	0.82	0.37
8	14	1	0	14	0.07	0.93	0.35
9	13	1	0	13	0.08	0.92	0.32
10	12	0	1	11.5	0.00	1.00	0.32
11	11	2	0	11	0.18	0.82	0.26
12	9	0	1	8.5	0.00	1.00	0.26
13	8	1	0	8	0.13	0.88	0.23
14	7	0	0	7	0	1	0.23
15	7	1	1	6.5	0.15	0.85	0.19
16	5	1	0	5	0.20	0.80	0.15
17	4	1	0	4	0.25	0.75	0.12
18	3	0	0	3	0	1	0.12
19	3	0	0	3	0	1	0.12
20	3	0	0	3	0	1	0.12
21	3	0	1	2.5	0	1	0.12
22	2	0	0	2	0	1	0.12
23	2	0	0	2	0	1	0.12
24	2	0	0	2	0	1	0.12
25	2	0	0	2	0	1	0.12
26	2	0	0	2	0	1	0.12
27	2	1	0	2	0.50	0.50	0.06
28	1	0	0	1	0	1	0.06

Interval month (i) since a medicine obtained a EU-wide marketing authorisation (MA)	Number of medicines at the beginning of the interval (a_i), i.e. with MA but not launched yet	Number of medicines launched during the interval (d_i)	Number of medicines censored during the interval (c_i), i.e. not launched by the end of the observation period	Number of medicines at risk of being launched $n_i=a_i-(c_i/2)$	Probability of a medicine being launched $r_i=d_i/n_i$	Probability of non-launch $s_x=1-r_i$	Cumulative probability of non-launch from time of EU-wide marketing authorisation $S(x)=S(i-1)* s_x$
29	1	0	0	1	0	1	0.06
30	1	0	0	1	0	1	0.06
31	1	0	0	1	0	1	0.06
32	1	0	0	1	0	1	0.06
33	1	0	0	1	0	1	0.06
34	1	0	0	1	0	1	0.06
35	1	0	0	1	0	1	0.06
36	1	0	0	1	0	1	0.06
37	1	0	0	1	0	1	0.06
38	1	0	0	1	0	1	0.06
39	1	0	0	1	0	1	0.06
40	1	0	0	1	0	1	0.06
41	1	0	0	1	0	1	0.06
42	1	0	0	1	0	1	0.06
43	1	0	0	1	0	1	0.06
44	1	0	0	1	0	1	0.06
45	1	0	0	1	0	1	0.06
46	1	0	0	1	0	1	0.06
47	1	0	0	1	0	1	0.06
48	1	0	0	1	0	1	0.06
49	1	0	0	1	0	1	0.06
50	1	0	0	1	0	1	0.06
51	1	0	0	1	0	1	0.06
52	1	0	0	1	0	1	0.06
53	1	0	0	1	0	1	0.06
54	1	0	0	1	0	1	0.06
55	1	0	0	1	0	1	0.06
56	1	0	1	0.5	0	1	0.06

The expected time from EU-wide marketing authorisation to launch is given by $0.5+\sum S(x)$ (formula to estimate life expectancy) and equals 11 quarters (2.85 years) in the above example.

The Kaplan-Meier method is used when the exact timing of the event is known (e.g. day). The advantage of this method is that it avoids the assumption that individual lost to follow up are censored half-away through the discrete time period (e.g. mid-month or mid-quarter) which is the assumption made using life tables. Table 7 shows how the survival curve is estimated using the Kaplan-Meier method. The expected time to submission is again given by the formula $0.5+\sum S(x)$ and equals 680 days (1.86 years).

Table 7: Example of Kaplan-Meier estimate of the survival curve using data from Chapter 4 on time to submission of a pricing and reimbursement dossier

Time in days (t)	Number of medicines at risk of being submitted	Number of submissions at time t (d_t)	Number of lost to follow-up at time t (c_t), i.e. no submission	Risk of submission (r_t)	Probability of non-submission $s_t=1-r_t$	Submission (survivor) function $S(t)=S(t_{previous})*s_t$
0	44	5	0	0.11	0.89	0.89
8	39	1	0	0.03	0.97	0.86
10	38	1	0	0.03	0.97	0.84
11	37	1	0	0.03	0.97	0.82
14	36	1	0	0.03	0.97	0.80
17	35	1	0	0.03	0.97	0.77
20	34	1	0	0.03	0.97	0.75
21	33	1	0	0.03	0.97	0.73
25	32	1	0	0.03	0.97	0.70
42	31	1	0	0.03	0.97	0.68
50	30	1	0	0.03	0.97	0.66
56	29	1	0	0.03	0.97	0.64
80	28	1	0	0.04	0.96	0.61
87	27	1	0	0.04	0.96	0.59
94	26	1	0	0.04	0.96	0.57
96	25	1	0	0.04	0.96	0.55
119	24	1	0	0.04	0.96	0.52
129	23	1	0	0.04	0.96	0.50
165	22	1	0	0.05	0.95	0.48
192	21	1	0	0.05	0.95	0.45
196	20	1	0	0.05	0.95	0.43
210	19	0	1	0.00	1.00	0.43
271	18	1	0	0.06	0.94	0.41
300	17	1	0	0.06	0.94	0.38
315	16	1	0	0.06	0.94	0.36
415	15	1	0	0.07	0.93	0.34
417	14	1	0	0.07	0.93	0.31
490	13	1	0	0.08	0.92	0.29
539	12	1	0	0.08	0.92	0.26
576	11	1	0	0.09	0.91	0.24
768	10	1	0	0.10	0.90	0.22
872	9	1	0	0.11	0.89	0.19
937	8	1	0	0.13	0.88	0.17
991	7	0	1	0.00	1.00	0.17
1079	6	1	0	0.17	0.83	0.14
1136	5	1	0	0.20	0.80	0.11
1738	4	1	0	0.25	0.75	0.08
1914	3	1	0	0.33	0.67	0.06
2270	2	1	0	0.50	0.50	0.03
5220	1	0	1	0.00	1.00	0.03

The cumulative hazard function (also known as hazard rate or failure rate) is the total hazard experienced up to time t and is calculated by summing the risks at each time the event occurs ($H(t) = \sum \frac{di}{ni}$ and $H(t) = - \log(S(t))$). If the time when the event of interest happens (e.g. launch of a medicine in a particular country) is only known on a discrete scale (e.g. months or quarters) a linear transformation of the Cox-proportional hazard model is needed to estimate the hazard function (Costa-Font, McGuire, and Varol 2015). This is the complementary log-log transformation (cloglog). In Chapter 4, I use the Kaplan-Meier method to estimate time to submission of a reimbursement dossier ($t_1 - t_0$) and time to reimbursement decision ($t_2 - t_1$) as time of EU-wide marketing authorisation (t_0), time of submission (t_1) and time of reimbursement decision (t_2) are all known up to the exact day. I use the life table method to estimate time to launch ($t_3 - t_0$) as time of launch (t_3, first use of a medicine in the country) is only known on a discrete scale (month or quarter). Similarly, I use the complementary log-log function to estimate the hazard of launch and test the impact of a set of variables on the probability of launch due to the discrete nature of the launch data.

3.5 Development of a database on utilisation of cancer medicines and possible determinants

In Chapter 5, I analyse variations in use of cancer medicines across countries and their determinants. I selected a sample of 31 cancer medicines (ATC-L01/L02) which obtained EU-wide marketing authorisation between 2000 and 2013. As in Chapter 4, I excluded generics, orphan medicines, and new brands of previously approved international non-proprietary names (INNs). I used data on dispensing of medicines as a proxy for utilisation. The source of the data is the same as Chapter 4 (see Table 3) with two additional variables for Belgium (number of pricing units and strength) and the exclusion of Estonia due to lack of data on the number of reimbursed indications over time. Medicines utilisation was the dependent variable in the longitudinal multilevel model in Chapter 5.

The model included a total of nine independent variables. This includes six continuous variables, notably the number of years since a medicine obtained EU-wide marketing authorisation for the first indication; the number of years since a positive reimbursement decision was awarded for the first indication; the median price per DDD; time (year 1-6); total pharmaceutical expenditure per capita and year (euros); and the average rating of clinical added value across all indications assessed by the independent Drug Bulletin

Prescrire (1-7 were 1 represents highest level of added clinical value, 6 the lowest level and 7 reserved judgment due to insufficient evidence)

In the following paragraphs, I will describe the data source for these variables and, where relevant, how they were estimated. I extracted information on the date of EU-wide marketing authorisation for the first indication and, if applicable, the date of authorisation of additional cancer indications (only authorisation of indications for different types of cancer (e.g. stomach cancer) than previously (e.g. breast cancer) approved were counted, not extension of indications within already approved cancers (e.g. new early breast cancer, previously only metastatic cancer)). This was a rather onerous exercise as it required to go through a number of European Public Assessment reports associated with a particular medicine to identify the date when new cancer indications were approved. I extracted information on the date of positive reimbursement decision for each reimbursed indication (defined as different types of cancer) of a medicine from the websites of national competent authorities. In contrast to Chapter 4, which only takes into account the date of positive reimbursement decision for the first indication, in Chapter 5 I also extracted information on all subsequently approved cancer indications until December 2014. Information on the implementation of managed entry agreements was obtained from Chapter 7.

Data on the use of medicines in each country indicated the setting in which medicine was dispensed. In Belgium and Scotland utilisation data distinguish between use in the ambulatory *vs.* hospital sector. In Sweden four different channels of distribution are possible (prescription, outpatient order, dosage and hospital). Prescription is the regular procedure whereby a patient visits a doctor, receives a prescription, and goes to a pharmacy to obtain the medicine. Outpatient order is when, for example, the primary care unit has ordered the drug and dispense it to the patient in the doctor-patient meeting. Dosage is when the package is manipulated by the pharmacist and the patients receive tablets/other form rather than a package. This option is common with elderly patients. Upon advice of TLV, these channels were identified as ambulatory use (prescription, outpatient order and dosage) and hospital use.

Price per DDD for each medicine (ATC-5) was estimated by dividing expenditure by the total number of DDDs used. For medicines with more than one strength and/or formulation, this was calculated as a weighted average of the relative proportions of different forms of the

same INN used. Again for Scotland, price information from the British National Formulary extracted in Chapter 4 was used. As an indicator of the added clinical value of a medicine, data on medicine rating by the independent Bulletin Prescrire from Chapter 4 were used. Pharmaceutical expenditure per 1000 capita was estimated using data on total pharmaceutical expenditure in a given country and year, divided by the number of inhabitants in a given year.

3.6 Longitudinal multilevel model

The resulting panel dataset on utilisation of cancer medicines and the determinants to be tested in the regression model covered the time period from 2008 to 2013. Panel data or longitudinal data are repeated measurements, taken on the same subject, in this case the same medicine, over time (Rabe-Hesketh and Skrondal 2012). Multilevel regression analysis can capture variation between subjects and over time (Rabe-Hesketh and Skrondal 2012). Chapter 5 analyses annual data on the use of medicines ('subjects', level 1) in three different countries (level 2) between 2008 and 2013 (repeated measurements). To analyse these data, a mixed effects model – including a fixed and a random component - was chosen after several consultations to discuss model options with staff from the Methodology and Statistics Department at the LSE.

$$y_{ijk} = \alpha_{kj} + \beta_k X_{ijk} + t + t^2 + k + t*k + t^2*k + v_k + u_j + e_{ijk}$$

where i=year, j=medicine and k=country, X_{ijk} is a vector of all the independent variables included, u_j is the medicine specific random effect, v_k is the country specific fixed effect and e_{ijk} is the error term.

In this model, each medicine has its own intercept $u_j + e_{ijk}$ (random component). Time is included as a linear and as a squared term ($t + t^2$) to allow for non-linear increase in use over time. A country specific fixed effect takes into account unmeasurable differences between countries (k). The interaction between time and time squared ($t*k + t^2*k$) allows for different slopes and therefore different magnitude of increase or decrease in utilisation in each country and over time. The logarithm of DDD per 1000 capita was used in the model due to non-normal distribution of the untransformed dependent variable (y_{ijk}). This model was fitted in Stata 13 using the mixed command (StataCorp 2013) to test whether there was a correlation between utilisation of cancer medicines and the variables included in the model.

3.7 Population of the framework on determinants of access to HER-2 targeted therapies

Using information from the literature on the determinants of access to cancer medicines, in Chapter 6, I developed a framework to identify possible determinants of access to HER-2 targeted therapies for breast cancer (trastuzumab, lapatinib, pertuzumab and trastuzumab emtansine). The framework was divided into determinants of medical need (burden of disease) and treatment decisions (diagnosis, clinical guidelines, pricing and reimbursement, financing and patient characteristics). A review of national websites (official statistics websites, cancer registry websites, competent authority in pricing and reimbursement websites, health insurance websites) and relevant literature (e.g. WHO Observatory health in transition reports and peer-reviewed literature) was conducted to populate the framework. Interviews served two main purposes, first, to complement missing information from the literature, in particular regarding financial arrangements for cancer medicines at hospital level and hospital level clinical guidelines. Second, it served to validate, clarify if needed, and update information from official websites and the literature.

3.8 Interviews

In Chapter 6, individual telephone interviews were conducted with up to two oncologists specialised in breast cancer in the countries studied. Two oncologists from different geographical areas (capital and another main cancer centre) were interviewed in Belgium (Brussels and Leuven), Estonia (Tallinn and Tartu), Scotland (Edinburgh and Glasgow) and Sweden (only one oncologist from Gothenburg accepted the invitation to talk despite two more were invited). More information on the interviewee's profiles is provided in Chapter 6. Interviews followed a semi-structured questionnaire with some core questions common across countries and some additional questions in countries where information from the literature required validation or clarification. Interviews lasted between 30 to 45 minutes and, in some cases, were followed by email exchange if clarifications or further data were needed. I transcribed interviews as they were conducted.

3.9 Development of a database on managed entry agreements

A comparative longitudinal analysis of the implementation of MEAs on the implementation of managed entry agreements was conducted in Chapter 7. A database on all managed entry agreements implemented in Belgium, England, the Netherlands, and Sweden was developed. Data on managed entry agreements implemented in Belgium, England and Sweden

implemented as of late 2011/ January 2012 (depending on the date the country responded to the survey) from a study conducted by the author (Ferrario and Kanavos 2013) was used as a basis to develop the database. I also contacted the competent authorities I worked with as part of this previous study, to update the data up to December 2012 and to include all agreements, up to the first agreement ever implemented in the country, including any discontinued agreements. I searched the list of patient access schemes in England (to update the findings) (NICE 2016a) and Scotland (SMC 2015). I used this information to analyse the number of active agreements over time ('prevalence') and the number of new agreements introduced each year ('incidence'). I conducted a review of governance frameworks around managed entry agreements in each country studied and followed up with competent authorities if clarifications were needed.

3.10 Literature review

Chapter 8 conducts a comprehensive literature review to evaluate the impact of different pharmaceutical procurement methods on prices, volume, stock-outs and quality use of medicines. The PICO(ST) framework (population, intervention, comparison group, outcome, setting and type of study) was originally developed to review the medical literature to address a clinical question but it has also been used to answer a non-clinical question. It is recommended for use in systematic reviews of interventions by Cochrane collaboration (The Cochrane Collaboration 2011). I applied it to develop a search strategy to address the following question (Table 8).

Table 8: PICOST framework

PICOST	Description (inclusion criteria)	Key words for literature search
Population/people involved	Any institutional body or agent conducting public procurement of medicines (Ministries of Health, national and international procurement bodies, hospitals, etc.)	pharmaceuticals OR drugs OR medicines OR "medicinal products" OR "medicinal product" OR "pharmaceutical products" OR "pharmaceutical product" OR medicaments OR medicament
Intervention	Public procurement of medicines including open tender, restricted tender, competitive negotiation and direct procurement	tender OR tendering OR procurement OR negotiation OR "reverse auction" OR "preference policy" OR "rebate contracts" OR rabattvertäge OR rabattvertraege
Comparison	This could take different forms (e.g. tender prices *vs.* pharmacy purchasing prices)	-
Outcome	Price, expenditure, availability (including supply security), quality use of medicines	price OR prices OR expenditure OR availability OR volume OR "sustainable supply" OR "stock-outs" OR shortage OR "quality use" OR "rational use" OR "quality of care" OR "appropriateness of care"
Situation/setting	High-income countries, hospital and ambulatory sectors	-
Type of study	RCTs, quasi-experimental, cohort and case-control studies, cross-section study, descriptive studies	-

I decided not to include search-terms relating to comparison group and type of study as these may not be clearly specified in all eligible articles in order not to limit the scope of the studies

included. I did not include search terms for setting due to the global scope of the review. The identified keywords were used to search the following databases or search engines (PubMed, Web of Science and Google Scholar). A title and abstract screening were conducted to exclude studies which did not meet the inclusion criteria outlined in Table 8. The prisma diagram is available in Chapter 8 (I retrieved 1190 papers and reports across three databases (PubMed, Web of Science and Google Scholar). 341 were excluded because duplicates. Following title and abstract screening to exclude papers that did not meet the inclusion criteria outlined in the PICOST framework, another 820 articles were excluded. A total of 29 papers were selected for inclusion. Follow-up of references let to the inclusion of another 8 papers. The final number of articles and reports included was 37 (Figure 17).

).

3.11 Contributions of this thesis

I developed four quantitative databases through extensive data extraction processes from publicly available data sources for the purpose of this thesis. These were complemented by a wealth of data that were not readily available in the public domain but had to be requested to competent authorities in pricing and reimbursement, health insurance organizations and clinicians. These two processes resulted in the creation of previously not available data to analyse and compare use of cancer medicines, their determinants and strategies to improve access in Europe and beyond. Further, I developed comparable evidence on utilisation of cancer medicines using data not readily available in the public domain and which required extensive cleaning and standardisation in order to be compared. Finally, this thesis provides evidence on countries with limited published data on access to cancer medicines (Estonia).

4 Time to entry for new cancer medicines: From EU-wide marketing authorisation to patients access in Belgium, Estonia, Scotland and Sweden (Paper 1)

4.1 Summary

In this chapter, I aim to do three things. First, to quantify the time from EU-wide approval to first use (launch) of a medicine and number of launches in Belgium, Estonia, Scotland, and Sweden as of June 2015. Second, to assess whether possible delays and lack of launches affected medicines with high or low expected additional clinical benefit. Third, to identify possible determinants of the probability of a medicine to be launched. I do this by using survival analysis and the complementary log-log transformation of the Cox proportional hazard model. I collected the following data from official sources, personal contacts with competent authorities and the literature: dates of EU-wide marketing authorisation (t_0), manufacturer submission for reimbursement (t_1), coverage decision (t_2), first use (t_3) and medicine ratings by the independent drug bulletin Prescrire, the ESMO magnitude of clinical benefit and FDA expedited approval in the study countries for a sample of 46 cancer medicines which obtained EU-wide marketing authorisation between 2000 and 2014. I find that on average, the expected time from EU-wide marketing authorisation (t_0), to first use of a medicine (t_3), was shortest in Sweden, 14.3 months, followed in Belgium 26.8 months, and was longest in Estonia, 63.9 months. In the all country model, medicines with shorter times to submission for reimbursement, local manufacturers headquarter (or local sales representative), an FDA priority review or a combination of expedited approval programmes, and medicines launched in Scotland and Sweden, were associated with higher hazard of launch. Longer times since EU-wide approval initially correlate with an increased hazard but as time further elapses they negatively affect the hazard of launch. My findings show wide disparities in the time new cancer medicines become available in different European countries despite a common marketing authorisation date. The average time to first launch and the number of non-launches is particularly are particularly long/high in Estonia. The lack of correlation between time to launch and Prescrire and ESMO ratings suggests that more efforts are needed to ensure that launch of medicines with high clinical added value is prioritised over medicines with uncertain value.

4.2 Introduction

The patient access to new medicines in Europe W.A.I.T. indicator shows that, for medicines approved between 2011 and 2014, the median time from European Union (EU)-wide marketing authorisation to patient access ranged from 42 days in Germany to 895 days in Lithuania (EFPIA 2015). Out of the 135 medicines within the scope of the analysis, 113 were available in Denmark vs. 28 in Lithuania (EFPIA 2015).

In the EU, a marketing authorisation may be granted by European Commission based on the scientific advice of the European Medicines Agency (EMA). This process, known as the centralised procedure, was introduced in 1995 and since 2004 it is compulsory for new cancer medicines not approved before 20 May 2004 (European Parliament and European Council 2004). It involves a single application, a single evaluation and a single authorisation throughout the EU (EMA 2015). Once an EU-wide marketing authorisation has been granted, a medicine can in principle be marketed in every EU country and selected countries of the European Economic Area (Iceland, Liechtenstein, and Norway).

In practice, patient access to new prescription medicines, particularly costly ones, will be severely limited if the medicine is not covered by the publicly funded health care system. Manufacturers will therefore generally make a reimbursement application to the national competent authorities of the countries in which they intend to market their medicines. Given that pricing and reimbursement is a national competence, processes and requirements vary across the EU. The overall timeframe within which pricing and reimbursement procedures should be completed however is set by European Commission in the Transparency Directive to 180 days for innovative products and 90 days for generic products (The Council of the European Communities 1988).

Studies on launch of new medicines have shown that price regulation, weak intellectual property rights, small market size and low expected prices were correlated with longer time lags between the first global launch and individual country launches (Table 9).

Table 9: Literature review on time to launch of new medicines

Medicines included	Time period and geographical coverage	Findings	Reference
85 new chemical entities covering different therapeutic areas	Launches between 1994 and 1998 in the outpatient sector in 25 countries	Only 55% of the potential launches occur. The United States (US) experienced the highest number of launches (n=73) and a mean lag of 4.2 months, while Japan experienced the lowest number of launches (n=12) with mean lag of 23.5 months. After controlling for a number of variables, the study finds that expected prices or market size affect both the number of launches and time to launch.	(Danzon, Wang, and Wang 2005)
1482 unique molecules covering different therapeutic areas	Launches between 1980 and 2000 in G7 nations (United States, Japan, Germany, France, Italy, the United Kingdom, and Canada)	Market characteristics alone correctly predict entry for only about 30% of the sample. Including firm's characteristics however improves this prediction substantially. A new chemical entity is 1.5 times more likely to be launched in markets that share a border or a language of a manufacturer's country of headquarters.	(Kyle 2006)
1444 new chemical or	Launches between 1980	This study confirms the influence of price	(Kyle 2007)

Medicines included	Time period and geographical coverage	Findings	Reference
molecules entities	and 2000 in 28 countries (21 of which were OCED members at the time the study was conducted)	regulations on launch patterns in the country imposing them and beyond.	
836 new pharmaceuticals	Launches between 1982 and 2002 in 68 countries at all income levels	Only 20% to 50% of all drugs launched globally were on the market in any country after 10 years. The percentage was 60% to 85% for high revenue blockbuster medicines. Price regulation and intellectual property rights were found to affect launch times.	(Lanjouw 2005)
642 new chemical entities covering different therapeutic areas	Launches between 1983 and 2002 in up to 76 countries at all income levels	Only 41% of the total products were launched in more than 25 countries. Price regulation was found to delay entry, while more extensive patent protection, health policy institutions and economic and demographic factors were found to reduce time to entry.	(Cockburn, Lanjouw, and Schankerman 2014)
22397 new chemical entities	Launches between 1999 and 2008 in 20 countries (major OECD markets	This study finds that price regulation, market size, and regulation affect launch times of new medicines. Their effect is however counteracted by	(Costa-Font, McGuire, and Varol 2015)

Medicines included	Time period and geographical coverage	Findings	Reference
	plus South Africa)	firm's economies of scale, the therapeutic importance of specific product innovations and market size.	
New molecular entities (sample size not stated)	New molecular entities which obtained marketing authorisation between 2009 and 2013 across 18 developed countries	Large variation in time to launch (90 to 430 days) and time to reimbursement from launch (90 to 540 days) among 18 developed countries were found in this study. Countries were classified in three groups: fast launch and reimbursement, fast launch but slow reimbursement, slow launch but fast reimbursement after launch. In countries with slow launch, first-in-class molecules and oncology medicines were, on average, launched faster than other molecules.	(Hickson et al. 2015)
New molecular entities (sample size not stated), formulations and combinations with EMA approval between January 2009 and May 2014	Launches between January 2009 – March 2013 and launches between April 2013 to May 2014 in France, Germany, Italy, Spain, UK, USA.	Longer post-regulatory times were found in Italy and Spain for products launched between April 2013 to May 2014 *vs.* previous years. Oncology medicines seem to be approved faster than others in the UK (16 *vs.* 20 weeks) and the same applies to orphan drugs in France (46 *vs.* 50 weeks).	(Mycka et al. 2014)

Medicines included	Time period and geographical coverage	Findings	Reference
29 drugs marketed between July 1987 and March 1990 (D'Sa 1994; D'Sa 1995); new chemical entities available worldwide between 1978 and 1987	Teaching and non-teaching hospitals in British Columbia, Canada (D'Sa 1994, D'Sa 1995); Israel (Sax 1989)	Other studies have focused on differences in formulary adoption within one country (D'Sa 1994; D'Sa 1995), and differences in launch times between a particular country and major markets (Sax 1989).	(D'Sa, Hill, and Stratton 1994, D'Sa, Hill, and Stratton 1995)

Few of these studies focus specifically on time to entry of new cancer medicines in Europe and its determinants. Cancer is a major contributor to the global burden of disease. In 2012, there were 14.1 million new cancer cases and 8.2 million cancer deaths worldwide (Stewart and Wild 2014). Together with surgery and radiotherapy, chemotherapy, targeted therapies and immunotherapies are a key component of cancer treatment. Despite their importance, variations in access to cancer medicines across and within European countries have been highlighted in various studies (Cherny et al. 2016, Aggarwal, Ginsburg, and Fojo 2014). Differences in access may be driven by many factors, one of which is time to entry of new medicines in individual European countries. A better understanding of the time required for new cancer medicines to enter different EU-markets and whether time to entry correlates with the added clinical value of a medicine is therefore important to improve access.

Further, none of the studies reviewed included Estonia where there is scarce evidence on the extent of perceived delays in entry of new cancer medicines and their importance. As the country is conducting a review of its pharmaceutical system with the view of identifying areas where more could be done to improve access to medicines (Ferrario, Reinap, et al. 2016), it is timely to shed light on this issue. Previous studies tended to benchmark delays against the date of first global launch. However, some of the medicines studied may not even have a marketing authorisation in all the study countries at the time the first global launch occurs. Finally, launch delays or lack of launch matter if the medicine is likely to bring significant added value to patients, or if a medicine with the same therapeutic value enters the market at same price or lower price than the comparator as it promotes competition. We found limited attempts at linking launch delays with the associated added value of a medicine. Some studied did include measures of therapeutic importance like the mentions of a medicine in medical journals indexed by Medline (Kyle 2007, 2006), global molecule sales and total markets launched in (Costa-Font, McGuire, and Varol 2015), inferior or superior molecules based on mechanism of action and input from physician and the literature (Danzon and Epstein 2012) which may not necessarily correlate with higher therapeutic benefit.

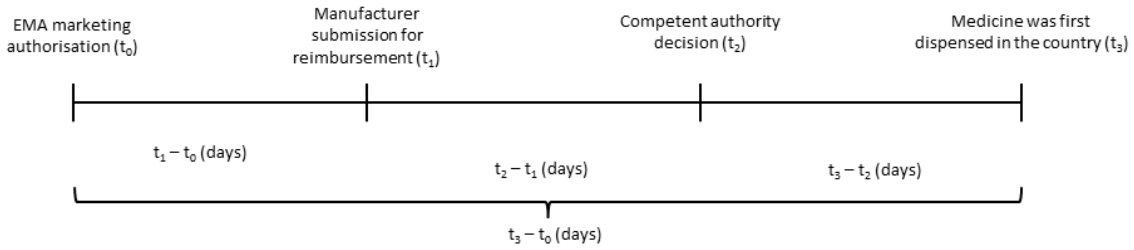
In this study, we analyse time to entry of cancer medicines (ATC-L01/L02) which obtained central EU-wide marketing authorisation between 2000 and 2014 in a selection of medium-sized European markets (Belgium, Estonia, Scotland and Sweden). In particular, we aim to address the following objectives. First, to quantify the time from EU-wide approval to first use (launch) of a medicine and number of launches in the study countries as of June 2015.

Second, to assess whether possible delays and lack of launches affected medicines with high or low expected additional clinical benefit. Third, to identify possible determinants of the probability of a medicine to be launched.

4.3 Methods

This study examines four time points in a medicine's life-cycle to estimate time to entry and its components. The reference date is the date an EU marketing authorisation was issued (t_0) (Figure 4).

Figure 4: Overview of times studied



The first time lag is determined by the number of days elapsed between t_0 and the date the manufacturer submits a reimbursement dossier (t_1). The second time lag measures the number of days needed for the assessment of the medicine (t_2- t_1)[10] while the third time lag represents time from EU-wide marketing authorisation to first use of the medicine (t_3- t_0). In all the study countries, a national level coverage decision is not needed before the medicines can be prescribed, meaning that use often precedes the final coverage decision for the first indication. We therefore decided not to include the t_3- t_2 lag in the analysis.

4.3.1 Selection of study countries and medicines and data sources

Belgium, Estonia, Scotland, and Sweden were chosen as study countries for their diversity in terms of expected launch times and number of launches, and data availability (i.e. access to procurement data for the hospital and outpatient sectors). Despite the convenience nature of the sample, we believe the four countries represent a very interesting study group given the expected differences in times to launch and number of launches (due to different pricing and reimbursement processes but most importantly different levels of health care spending per

[10] This does not include time stops and can therefore not be considered as a reference for compliance with the EU-Transparency Directive.

capita, Table 10). Despite their diversity, all countries have a relatively small population size in comparison to larger EU countries and they all have system of mandatory health insurance in place.

Table 10: Similarities and differences in key elements of the public health insurance system in the study countries

	Belgium	**Estonia**	**Scotland**	**Sweden**
Mandatory health insurance	Yes, financed mainly through social security contributions and administered by sickness funds	Yes, funded mainly through payroll contribution and administered by the national health insurance fund	Yes, tax funded and administered by the national health service (NHS)	Yes, mainly tax funded and administered by the county councils
Total health expenditure per capita, PPP$ per capita, WHO estimates	4392	1668	3066	5219
Public health expenditure as percentage of total health expenditure	78%	79%	83% (UK)	84%
Pricing	External reference pricing, negotiation	External reference pricing, negotiation	Rate-of-return regulation, branded medicines spend cap (since 2014) for medicines included in the Pharmaceutical Pricing	Value-based pricing, negotiation

			Regulation Scheme (voluntary agreement between the Association of the British Pharmaceutical Industry and the UK Department of Health)	
Use of managed entry and risk-sharing agreements	Yes	Yes	Yes	Yes
Use of HTA in coverage decisions for cancer medicines	Yes, all new cancer medicines (for which the manufacturer makes a reimbursement submission) are reviewed by National Institute for Health and Disability Insurance who conducts an HTA and budget impact analysis	Decisions on coverage of cancer medicines used in hospitals are made based on submissions by oncologists. Elements of HTA may be included in the submission. If an HTA analysis is not included in the submission, the Estonian Health Insurance Fund conducts one (for hospital medicines, for	Yes, all new cancer medicines (for which the manufacturer makes a HTA submission) are reviewed by the Scottish Medicines Consortium (SMC) which assesses the manufacturer HTA submission and budget impact analysis	Most new cancer medicines (for which the manufacturer makes a HTA submission) are reviewed by NT-council with support from TLV (conducting the economic evaluation)

		outpatient medicines HTA is always included in the manufacturer submission		
Purchasing of medicines	Discounts off the list price may apply at hospital level	Discounts off the list price may apply at hospital level	Discounts off the list price may apply at hospital level	Discounts off the list price may apply at hospital level.

Sources: WHO Health for all database, WHO Global health expenditure database (£ per Int$), Nuffield Trust data (health expenditure per capita Scotland).

Note: Health expenditure per capita in Scotland in 2014 was calculated as the average of the reported expenditure by the Nuffield Trust in the reporting periods 2013/14 and 2014/15 divided by the £ per Int$ in 2014 from the WHO Global health expenditure database.

Using the anatomic therapeutic chemical (ATC) search function for European Public Assessments Reports on the website of the EMA, we identified all antineoplastic (ATC-L01) and endocrine (ATC-L02) medicines authorised by the EMA (112 medicines). We did not include immunostimulants (ATC-L03) medicines because only some of these medicines are indicated for cancer treatment. Medicines which were either withdrawn post-approval, suspended or refused were not included. We selected all medicines authorised by the EMA between 2000 and 2014 (total: 99). Further, we excluded generic (22) and orphan medicines (24). There were no biosimilar medicines or medicines approved under exceptional circumstances but there were six medicines approved with a conditional marketing authorisation (see supplementary material for definition) in the remaining sample of 53 medicines (different branded names). We excluded 7 medicines which were new brands of INNs approved before 2000. The final sample of medicines (different INNs) included in the analysis was 46.

We define the time a medicine first becomes available (launch) as the month or quarter in which a new medicine was first procured either in hospital or ambulatory settings. Data on medicines utilisation were provided by national competent authorities (The Estonian State Medicines Agency (SAM), The National Institute for Health and Disability Insurance in Belgium (INAMI-RIZIV), NHS Scotland (ISD) and Swedish eHealth Agency (ehälsomyndigheten)). These data were available on a monthly basis from (April) 2007 to 2014 in Scotland and from 2000 to 2014 in Sweden and on quarterly basis from the first quarter of 2002 to the second quarter of 2015 in Belgium and from the first quarter of 2000 to the first quarter of 2015 in Estonia. The data covered both hospital and ambulatory settings. In Scotland and Belgium, data for the ambulatory sector was available up to 2000 and 2001 respectively.

The choice of variables was based on the literature reviewed in the introduction (e.g. expected price and volume, therapeutic group, time since marketing authorisation). The effect of price regulation on time to launch has been established in previous studies and all the countries included in this study regulate prices in one way or another. Therefore assessing the impact of price regulation would have not added value to the existing literature. Instead what this study adds are stronger indicators of added value (Prescrire and ESMO-MCBS which actually consider clinical added value) as opposed to previous studies which looked at, for example, the number of citations in Medline as a proximal indicator of the importance of the

medicine. We further contribute to the existing literature by adding, conditional marketing authorisation, time of submission of a reimbursement dossier and award of expedited approval by the FDA which were not included in previous studies on time to entry. Table 11 provides summary statistics of the variables used in the survival analysis.

Table 11: Descriptive statistics of the variables used in the survival analysis

Medicines (common across countries, N=46)	Total	Frequency	Mean	Median	SD	Min	Max
Categorical variables							
Medicine approved with conditional marketing authorisation							
-Yes	6	13.0%					
-No	40	87.0%					
Therapeutic group (baseline: other antineoplastic agents L01X)							
-L01B Antimetabolites	3	6.5%					
-L01C Plant alkaloids and other natural products	2	4.3%					
-L01D Cytotoxic antibiotics and related substances	1	2.2%					
-L01X Other antineoplastic agents	36	78.3%					
-L02B Hormone antagonists and related agents	4	8.7%					
FDA expedited approval programme							
-No EAP	9	19.6%					
-Fast track only	3	6.5%					
-Priority review only	11	23.9%					
-Combination	23	50.0%					
Continuous variables							
Year of EU-wide marketing authorisation (2000-2014)			2009	2011	4.5	2000	2014

Country specific variables	Total	Frequency	Mean	Median	SD	Min	Max
Belgium (44 medicines, 407 medicine-quarters at risk)							
Local manufacturer headquarters							
-Yes	2	4.3%					
-No	42	95.7%					
Expected price per DDD (lagged 1 quarter) in the therapeutic class (ATC-3) in Euro			76.7	24.5	100.4	0.00	389.1
Expected volume (lagged 1 quarter) at therapeutic class (ATC-3) in thousands DDDs			306.6	239.5	418.2	0.00	2361.8
T1-T0 (quarters) (N=41 medicines with submission)			3.1	0.9	4.6	0.008	18.6
T2-T1 (quarters) (N=39 medicines with decision)			6	3.7	4.7	1.9	21.4
Estonia (46 medicines, 634 medicine-quarters at risk)							
Local sales representative							
-Yes	31	67.4%					
-No	15	32.6%					
Expected price per DDD (lagged 1 quarter) in the therapeutic class (ATC-3) in Euro			65.9	11.5	154.3	0	2432.9
Expected volume (lagged 1 quarter) at therapeutic class (ATC-3) in thousands DDDs			18.4	13.4	27.6	0	248.6
T1-T0 (quarters) (N=30 medicines with submission)			5.7	3.9	6.7	0.01	35.5
T2-T1 (quarters) (N=19 medicines with decision)			10.6	8.9	7.9	2.8	38.5

Scotland (N=31, 173 medicine-quarters at risk)							
Local manufacturer headquarters							
-Yes	6	15.2%					
-No	25	84.8%					
Expected price per DDD (lagged 1 quarter) in the therapeutic class (ATC-3) in Euro			106.6	80.4	91.1	0	261.54
Expected volume (lagged 1 quarter) at therapeutic class (ATC-3) in thousands DDDs			93.7	30.7	213.3	0	1023.6
T1-T0 (quarters) (N=25 medicines with submission)			1.2	0.7	1.4	0.08	5.6
T2-T1 (quarters) (N=19 medicines with decision)			2.5	1.8	1.5	1.2	7.6
Sweden (N=46, 279 medicine-quarters at risk)							
Local manufacturer headquarters							
-Yes	0	0%					
-No	46	100%					
Expected price per DDD (lagged 1 quarter) in the therapeutic class (ATC-3) in Euro			93.8	25.8	100.9	0	389.1
Expected volume (lagged 1 quarter) at therapeutic class (ATC-3) in thousands DDDs			159.6	138.3	292.5	0.00	2601.42
T1-T0 (quarters) (N=32 medicines with submission)			2.4	0.5	5	0.008	26.3
T2-T1 (quarters) (N=32 medicines with decision)			4.5	2.8	5.2	1.2	28.3

The date of EU-wide marketing authorisation for cancer medicines (ATC-L01/L02) approved between 2000 and 2014 was obtained from the European Public Assessments Reports (EMA 2015). Manufacturers' submission dates for reimbursement were only available online for Belgium (INAMI-RIZIV 2015) while for all the other countries they had to be requested to national competent authorities (The Estonian Health Insurance Fund (EHIF) and the Estonian Ministry of Social Affairs (MoSA), Scottish Medicines Consortium (SMC), and The Swedish Dental and Pharmaceutical Benefit Agency (TLV)). Decision dates and the outcome of these decisions were mostly available from competent authorities' websites (INAMI-RIZIV 2015, TLV 2016c, SMC 2016a) apart from Estonia where they had to be requested to the EHIF and MoSA. Both date of submission and date of decision refer to the first indication of a medicine which was submitted and obtained a positive coverage decision in each country. Expected volume, measured in thousands defined daily doses (DDD) in the therapeutic class (ATC-3, pharmacological subgroup) one quarter prior EU-wide marketing authorisation, was estimated using utilisation data. Where available, the defined daily doses by the World Health Organization Collaborating Centre on Drugs Statistics Methodologies were used (WHO Collaborating Centre for Drug Statistics Methodology 2016). If these were not available, the following additional resources were used in this order: the Belgian Centre for Pharmacotherapeutic Information (2016), the German Institute of Medical Documentation and Information (DIMDI 2016), or we used the smallest approved formulation by EMA. Expected prices per DDD were estimated using utilisation data in Belgium, Estonia and Sweden were information on expenditure was provided. It was not possible to obtain information on expenditure for hospital medicines in Scotland due to the confidential nature of the discounts offered at that level. Historical British National Formulary prices (2000-2015) were used instead. The estimated average prices per thousand DDDs were weighted by volume. Information on manufacturers was taken from the European Public Assessments Reports, we then search online where the headquarters of company was located. Since there are no originator manufacturers in Estonia, availability of local sales representatives was used instead of local manufacturer headquarters. The list of manufacturers with local sales representatives was taken from the Association of Pharmaceutical Manufacturers in Estonia (APME 2016). Data on the US Food and Drug Administration (FDA) expedited approval programmes (accelerated approval, breakthrough, fast track and priority review) was extracted from the FDA website, the FDA novel drug summaries and a review of FDA Approvals between 1938 and 2013 (Darrow and Kesselheim 2014). This formed the pre-launch evidence on the expected clinical added value of the medicine. Post-launch data was

extracted from two sources, the independent Drug Bulletin Prescrire (2016) and the European Society of Medical Oncology (ESMO) magnitude of clinical benefit scale (MCBS) (ESMO 2015) (see Supplementary material for information on these two rating systems). Prescrire and ESMO-MCBS were chose because they are independent authoritative reviews of clinical effectiveness, they have been used in other studies (Vitry, Shin, and Vitre 2013, Lexchin 2015, 2014, Jönsson et al. 2016), and, in the case of ESMO-MCBS, were peer-reviewed.

4.3.2 Survival analysis

Survival analysis is the method of choice for analysis of time to event data where the probability of the event happening over time is not constant, the data are usually continuous, the data may be incomplete (censoring), and the data are always larger or equal to zero. Standard regression analyses do not handle censoring (they just exclude incomplete observations) and may be inadequate to handle data that is only positive and has a non-normal distribution (unless the data are transformed).

Life table methods were used to estimate the expected time from EU-wide marketing authorisation to first use (T_3-T_0) of the medicines included in the sample. Data on time of first use was available by month or quarter and life table methods enables to handle such discrete time intervals. In contrast, Kaplan-Meier methods require events to occur on a continuous scale (e.g. day) which was available for T_0, T_1, T_2 but not T_3. If the event of interest (submission, positive decision, or first use) did not occur at the end of the observation period (June 2015), the observation was considered censored (or lost to follow-up) in the survival analysis. I refer to medicines which were not launched by June 2015 as 'non-launched' bearing in mind that they could still be launched in the future.

Regression analysis of survival data involves the estimation of the hazard of the event of interest to occur. The hazard rate is the instantaneous probability of an event occurring at a particular point in time (h(t)), in this case the probability at a particular time t that the medicine will be launched. The Cox-proportional hazard model is used for continuous events, while for discrete event the complementary log-log model is used (cloglog):

$$h_{jk}(t) = 1 - \exp(-\exp(h_0(t) + z_{jkt}\beta + y_t^{'} + c_k) \quad \text{or}$$

$$\text{cloglog}(h_{jkt}) = h_0(t) + z_{jkt}\beta$$

where $h_{jk}(t)$ is the hazard at time t for medicine (j) and country (k) and $h_0(t)$ is the baseline hazard and β summarises the independent regression variables.

A time dependency parameter (y_t) was included in the model which measures time (in quarters) since EU-wide approval, a linear and quadratic specifications were added as well as country fixed effects (c_k). The final dataset for the cloglog analysis includes one observation for each medicine-quarter at risk, i.e. from the quarter in which the medicine receives EU-wide marketing authorisation to the quarter when the medicine is launched (non-censored medicines) or the end of the observation period (June 2015) for censored medicines. The dependent variable is specified as a binary variable taking the value of 0 in all quarters before launch and 1 in the quarter the medicine is launched. We run an all-country model (with four variants for different samples) and four country models (with two variants for different samples) using the statistical software Stata® 14.1, StataCorp.

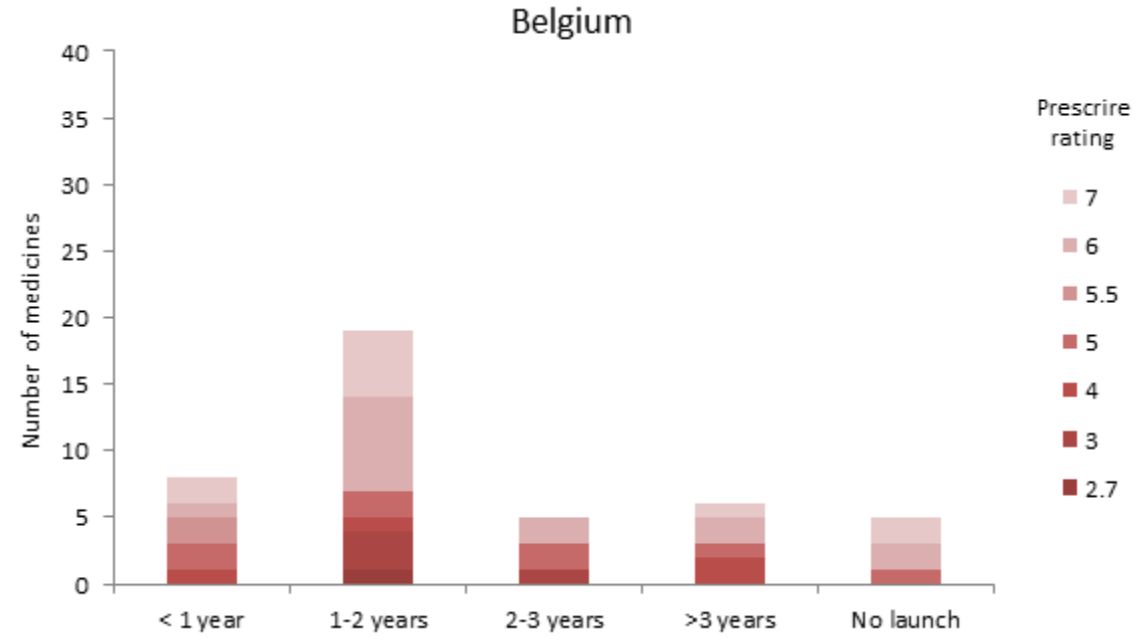
4.4 Results

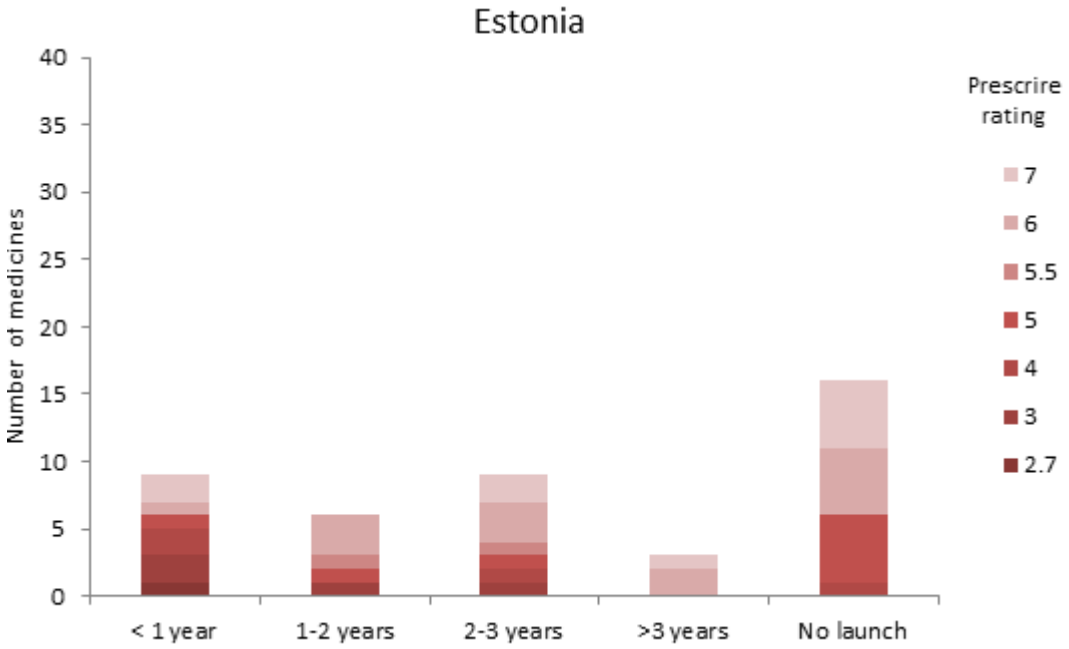
4.4.1 Descriptive analysis

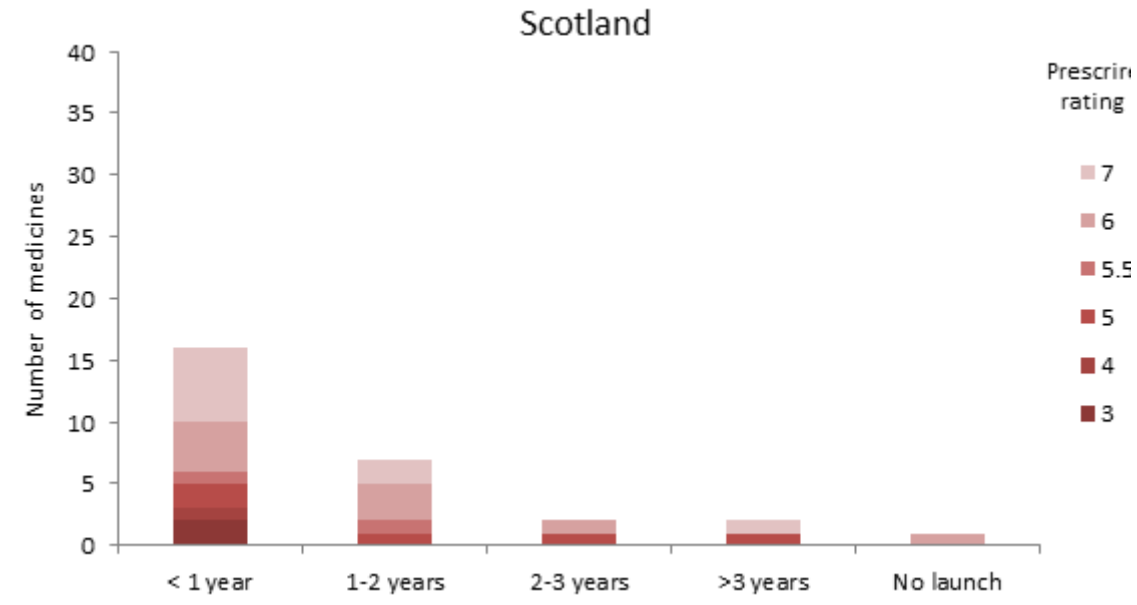
The descriptive analysis addresses the objectives of quantifying the time from EU-wide approval to first use (launch) of a medicine and number of launches in the study countries as of June 2015 and to assess whether possible delays and lack of launches affected medicines with high or low expected additional clinical benefit.

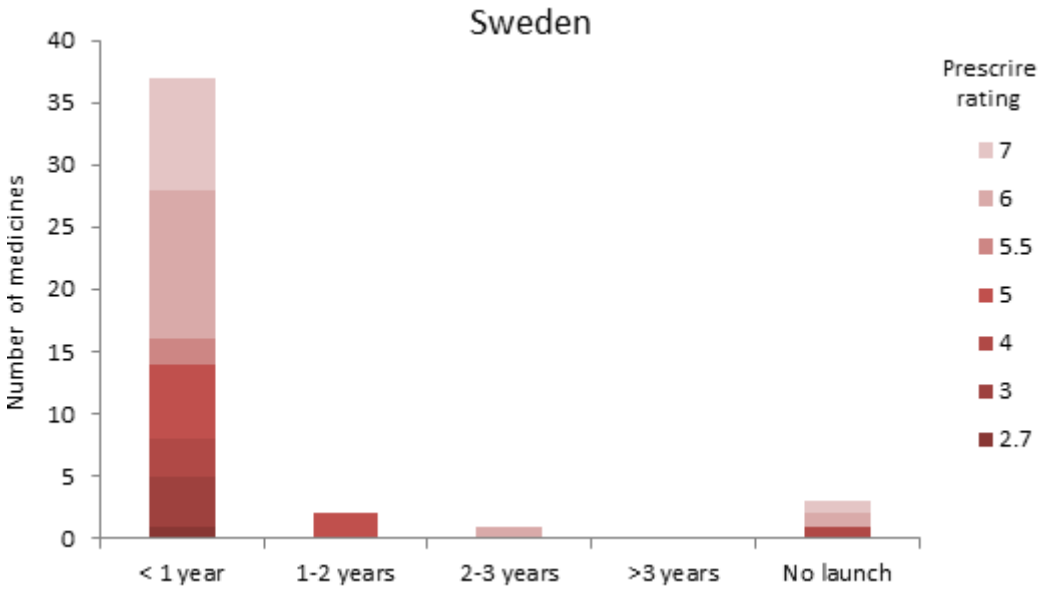
On average, the expected time from EU-wide marketing authorisation (T_0), to first use of a medicine (T_3), was shortest in Sweden, 14.3 months (43 launches, 3 non-launches), followed in Belgium 26.8 months (39 launches, 7 non-launches), and was longest in Estonia, 63.9 months (27 launches, 19 non-launches). For medicines which obtained EU-wide marketing authorisation after April 2007, the average time to launch in Scotland was 12.7 months (29 launches, 2 non-launches). Sample-wide (46 medicines, including also medicines for which date of first use was not known), only 2 medicines were not used between April 2007 and June 2015 in Scotland. No medicine was not available in any country, two medicines were not available in 3 countries, 6 medicines were not available in 2 countries and 13 medicines were not available in one country as of June 2015. Figure 5 provides the distribution of launches and non-launches by time and Prescrire rating (see Appendix 3 for break down by ESMO-MCBS rating).

Figure 5: Time to launch and distribution of launches and non-launches by Prescrire rating









In Sweden most medicines with Prescrire rating (N=43) are launched within one year of marketing authorisation (n=37), followed by Scotland (n=16), Estonia (n=9), and Belgium (n=8). In Belgium most medicines are launched between one to two year of marketing authorisation (n=19), while in Estonia, a number of medicines included in our sample had not yet been launched as of June 2015 (n=16).

4.4.2 Regression analysis

The regression analysis tests the correlation between possible determinants of the probability of a medicine to be launched.

In the all country model 1, medicines with shorter times to submission for reimbursement, local manufacturers headquarter (or local sales representative), an FDA priority review or a combination of expedited approval programmes, and medicines launched in Scotland and Sweden, were associated with higher hazard of launch (Table 12). Longer times since EU-wide approval initially correlate with an increased hazard but as time further elapses they negatively affect the hazard of launch. Most of these variables remain significant in the all country model 2 (subsample of medicines with submission) and all country model 3 (subsample with Prescrire rating). Model 2 includes time from submission to decision but the latter does not seem to affect the hazard of launch. Rating by Prescrire does not affect the hazard of launch in model 3, meaning that higher ratings of clinical added value by Prescrire were not associated with higher hazard of launch. In model 4 (subsample of medicines with ESMO-MCBS rating), the hazard of launch does not seem to be affected by the ESMO-MCBS rating and the only significant variables are the country dummies, meaning that the hazard of launch is different between countries, and the time since EU-wide marketing authorisation. The latter model is based on a smaller sample as ESMO-MCBS ratings were only available for a limited number of medicines for the treatment of solid cancer tumours.

Table 12: Cloglog regression analysis

Model 1: Full sample	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.09***	0.015	-6.72	0	-0.12679	-0.06954
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	0.16	0.28126	0.58	0.56	-0.39	0.71
Local manufacturer headquarter or sales representative (Estonia), baseline (no local headquarter/representative)						
-Local headquarter/representative	0.83*	0.32	2.58	0.01	0.20	1.46
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	0.48	0.44	1.09	0.28	-0.38	1.34
-L01C Plant alkaloids and other natural products	-0.37	0.44	-0.84	0.402	-1.24	0.5
-L01D Cytotoxic antibiotics and related substances	-0.06	0.82	-0.08	0.94	-1.66	1.53
-L02B Hormone antagonists and related agents	0.64	0.36	1.78	0.07	-0.06	1.35
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.0015	0.001	1.29	0.19	-0.0008	0.004
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	5.13E-08	2.80E-07	0.18	0.854	-4.97E-07	6.00E-07

Model 1: Full sample	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.44	0.46	0.96	0.34	-0.46	1.35
-Priority review only	0.77*	0.31	2.48	0.013	0.16	1.38
-Combination	1.08***	0.29	3.78	0	0.52	1.65
Year of marketing authorisation	-0.03	0.03	-0.99	0.32	-0.09	0.03
Belgium	0.65	0.36	1.82	0.07	-0.05	1.34
Scotland	1.57***	0.33	4.8	0	0.93	2.22
Sweden	3.07***	0.40	7.6	0	2.28	3.86
Time since EU-wide approval (quarters)	0.35***	0.06	5.61	0	0.23	0.48
Time since EU-wide approval (quarters), squared	-0.01	0.003	-4.35	0	-0.02	-0.007
Constant	-4.64	0.67	-6.9	0	-5.96	-3.32
Log likelihood = -341.60817 LR test of rho=0: chibar2(01) = 5.0e-05 Probability >= chibar2 = 0.497 Number of observations = 1,493 Number of groups = 167						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 2: Subsample with submission	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.08	0.07	-1.24	0.22	-0.21	0.05
T2-T1, quarters	-0.06	0.06	-1.03	0.30	-0.18	0.06
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	0.47	0.32	1.49	0.14	-0.15	1.10
Local manufacturer headquarter or sales representative (Estonia), baseline (no local headquarter/representative)						
-Local headquarter/representative	1.17***	0.38	3.07	0.00	0.42	1.91
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	0.15	0.50	0.30	0.76	-0.83	1.14
-L01C Plant alkaloids and other natural products	-1.19*	0.53	-2.25	0.02	-2.22	-0.15
-L01D Cytotoxic antibiotics and related substances						
-L02B Hormone antagonists and related agents	0.35	0.40	0.87	0.38	-0.43	1.12
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.001	0.001	0.98	0.33	-0.001	0.004
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	0.0001	0.0003	0.25	0.80	-0.001	0.001

Model 2: Subsample with submission	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.67	0.50	1.35	0.18	-0.31	1.64
-Priority review only	0.72*	0.34	2.11	0.04	0.05	1.39
-Combination	1.04***	0.32	3.20	0.00	0.40	1.68
Year of marketing authorisation	-0.01	0.04	-0.24	0.81	-0.08	0.06
Belgium	0.79	0.46	1.71	0.09	-0.12	1.70
Scotland	1.84***	0.48	3.79	0	0.89	2.79
Sweden	3.35***	0.57	5.86	0	2.23	4.47
Time since EU-wide approval (quarters)	0.45***	0.08	6.03	0	0.31	0.60
Time since EU-wide approval (quarters), squared	-0.01***	0.00	-4.16	0	-0.02	-0.01
Constant	-5.18	0.92	-5.64	0	-6.98	-3.38
Log likelihood = -266.21368						
LR test of rho=0: chibar2(01) = 3.7e-05 Probability >= chibar2 = 0.498						
Number of observations = 797						
Number of groups = 128						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 3: Subsample with Prescrire rating	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.10***	0.01	-6.62	0.00	-0.13	-0.07
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	0.21	0.29	0.74	0.46	-0.35	0.78
Local manufacturer headquarter or sales representative (Estonia), baseline (no local headquarter/representative)						
-Local headquarter/representative	0.85*	0.33	2.54	0.01	0.20	1.50
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	0.35	0.47	0.74	0.46	-0.57	1.26
-L01C Plant alkaloids and other natural products	-0.27	0.45	-0.60	0.55	-1.15	0.61
-L01D Cytotoxic antibiotics and related substances	-0.24	0.85	-0.29	0.78	-1.90	1.42
-L02B Hormone antagonists and related agents	0.43	0.41	1.04	0.30	-0.38	1.23
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.002	0.001	1.55	0.12	-0.001	0.004
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	0.0000001	0.0000003	0.20	0.84	-0.0000005	0.000001
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.81	0.50	1.60	0.11	-0.18	1.80

Model 3: Subsample with Prescrire rating	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
-Priority review only	0.77*	0.33	2.34	0.02	0.12	1.41
-Combination	1.05***	0.32	3.29	0.00	0.42	1.67
Year of marketing authorisation	-0.01	0.03	-0.35	0.72	-0.08	0.06
Belgium	0.65	0.37	1.77	0.08	-0.07	1.36
Scotland	1.57***	0.34	4.60	0.00	0.90	2.24
Sweden	3.16***	0.43	7.44	0.00	2.33	4.00
Time since EU-wide approval (quarters)	0.36***	0.06	5.60	0.00	0.23	0.49
Time since EU-wide approval (quarters), squared	-0.01***	0.00	-4.35	0.00	-0.02	-0.01
Prescrire rating	-0.13	0.11	-1.19	0.23	-0.33	0.08
Constant	-4.21	0.86	-4.88	0.00	-5.89	-2.52
Log likelihood = -323.78502						
LR test of rho=0: chibar2(01) = 7.2e-05 Probability >= chibar2 = 0.497						
Number of observations = 1,440						
Number of groups = 155						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 4: Subsample with ESMO-MCBS	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.04	0.02	-1.90	0.06	-0.08	0.001
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	-0.18	0.39	-0.45	0.65	-0.94	0.59
Local manufacturer headquarter or sales representative (Estonia), baseline (no local headquarter/representative)						
-Local headquarter/representative	0.66	0.43	1.54	0.12	-0.18	1.49
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	0.09	0.77	0.12	0.90	-1.42	1.61
-L01C Plant alkaloids and other natural products	-1.06	0.62	-1.71	0.09	-2.28	0.16
-L01D Cytotoxic antibiotics and related substances						
-L02B Hormone antagonists and related agents	0.19	0.50	0.37	0.71	-0.79	1.16
Expected price in the therapeutic class (ATC-3), lagged one quarter	-0.003	0.002	-1.35	0.18	-0.01	0.001
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	-0.0000004	0.0000004	-0.99	0.32	-0.000001	0.0000004
FDA expedited approval programme (EAP, baseline: no EAP)						

-Fast track only	-0.06	0.64	-0.09	0.93	-1.30	1.19
-Priority review only	0.39	0.58	0.68	0.50	-0.74	1.53
-Combination	0.73	0.56	1.29	0.20	-0.38	1.83
Year of marketing authorisation	-0.04	0.05	-0.86	0.39	-0.14	0.05
Belgium	0.95*	0.44	2.16	0.03	0.09	1.82
Scotland	1.77***	0.42	4.24	0.00	0.95	2.59
Sweden	3.46***	0.54	6.38	0.00	2.40	4.53
Time since EU-wide approval (quarters)	0.40***	0.08	4.87	0.00	0.24	0.57
Time since EU-wide approval (quarters), squared	-0.01***	0.004	-3.02	0.00	-0.02	0.00
ESMO-MCBS rating	0.02	0.15	0.16	0.87	-0.27	0.32
Constant	-4.09	0.99	-4.13	0	-6.03	-2.15
Log likelihood = -208.15312						
LR test of rho=0: chibar2(01) = 0.00 Probability >= chibar2 = 1.000						
Number of observations = 524						
Number of groups = 102						

*p < 0.05, ** p < 0.01, *** p < 0.001

In the country level model 1 (full sample model), time to submission is significant in all countries (see Appendix 8). Manufacturers with a local sales representative are more likely to launch in Estonia. High expected prices increased the hazard of launch in Belgium and Sweden and decreased it Scotland. Expected volume was only significant in Estonia. FDA expedited approval programmes were significant in Scotland and Sweden.

In the country level model 3, time to submission is significant in Belgium, Estonia, and Sweden. Manufacturers with local sales representative is significant in Estonia. Expected price was significant in Belgium, Scotland and Sweden while expected volume was only significant in Estonia. Use of FDA expedited approval programmes increased the hazard of launch significant in Scotland and Sweden, while higher additional clinical value, as estimated post-launch by Prescrire, not significantly correlated with a higher hazard of launch in any country. In all country level models 1 and 3, longer times since EU-wide marketing authorisation initially correlate with higher hazard of launch, while in the longer term, they correlate with decreased hazard of lunch. The year of marketing authorisation, negatively correlated with the hazard of launch in Estonia. This means that medicines which received EU-wide marketing authorisation in recent years were less likely to be on the market. There was no correlation between the age of the medicine (year of EU-wide marketing authorisation) and the hazard of launch in the other countries.

4.5 Discussion

Shorter times from EU-wide marketing authorisation to submission for reimbursement were positively correlated with increased hazard of launch in most model specifications. The majority of the cancer medicines included are predominantly dispensed in hospitals, including day-units. In Belgium, Scotland, and Sweden, manufacturers submit applications to obtain national coverage for hospital medicines. An early submission for reimbursement suggests that the manufacturer has a strong interest in entering the market quickly. In Estonia, applications to the inpatient service list are made by clinicians therefore manufactures are in principle not able to influence this process. Potentially, manufacturers could try and influence clinicians to make a submission but there is no evidence on whether this is happening or not. Scotland does horizon scanning and actively invites manufacturers to submit newly approved indications to SMC for assessment. Belgium may also proactively invite manufacturers. However, the impact of these activities on the likelihood of submission and launch is unknown. In addition to the small market size, limited expenditure on health per capita and as

share of gross domestic product in Estonia is likely to impact the probability of early launch of new cancer medicines. Estonia is also the country where manufacturers seem to have fewer opportunities to promote early entry of new cancer medicines, through formal channels, since only clinicians can make a submission for reimbursement.

Conditional marketing authorisation was not associated with lower hazard of launch in any model specifications. A study on differences in HTA recommendations for oncology medicines which received a conditional marketing authorisation *vs.* standard marketing authorisation found no differences in HTA outcome between these two groups (Lipska et al. 2015). Taken together these findings suggest that for oncology medicines in Europe, receving a conditional marketing authorisation does not necessarily delay entry nor makes the medicine less likely to receive a positive reimbursement decision. In Estonia, manufacturers with a local sales representative are more likely to launch as confirmed by previous findings (Ferrario, Reinap, et al. 2016). We did not find any correlation between having a local manufacturer headquarters and the hazard of launch (a positive correlation was found in previous studies (Costa-Font, McGuire, and Varol 2015, Danzon, Wang, and Wang 2005, Kyle 2006, 2007, Danzon and Epstein 2012)). One reason may be the relatively small number of locally manufactured medicines in the sample.

In the all country model, expected prices do not affect the hazard of launch, this is likely to be due to limited price variation across the four study countries. In Belgium and Sweden, higher expected prices are correlated with shorter time to launch, while in Scotland, they correlate with longer time to launch. Confidential discounts through patient access schemes are common for cancer medicines in Scotland and may be the explanation for this finding since we could not adjust for them.

Only in Estonia was expected volume associated with higher hazard of launch. Results from previous studies are mixed, some did find a correlation with expected volume (Costa-Font, McGuire, and Varol 2015, Danzon, Wang, and Wang 2005), other did not (Danzon and Epstein 2012).

Expedited approval programmes by the FDA were associated with a higher hazard of early launch in Scotland and Sweden. Award of an expedited review programme relies on pre-market data which may not always be a good predictor or post-launch effectiveness. In a

study from Canada, pre-market priority review was not associated with post-market therapeutic value (Lexchin 2015). There was no correlation between Prescrire rating or the EMSO-MCBS rating and the hazard of launch in any country.

In line with previous findings (Costa-Font, McGuire, and Varol 2015) and in contrast with others (Danzon and Epstein 2012), we find that the hazard of launch first increases and then decreases as time from EU-wide marketing authorisation elapses.

4.5.1 Limitations

There are limitations in this study. For example, while analysis of time to first use gives an indication of the speed with which new medicines become available in a particular country, it does not say anything about the level of use, for which indication the medicine is used, i.e. there may be access for one indication but not for others, and whether this meets patients' needs and possible inequalities in access to medicines within a country. It is therefore important to analyse also actual utilisation levels, ideally by indication although available data on use of hospital medicines by indication are very limited. We did not have data on medicines utilisation by month prior 2007 for hospitals in Scotland and thus had to conduct part of the analysis based on a subsample of medicines for Scotland. Use of British National Formulary prices is likely to have led to an overestimation of the prices paid in the NHS Scotland as these do not include discounts which remain in commercial confidence. If the manufacturer headquarters or having a local sales representative (Estonia) changed from the time the medicine was approved for EU-wide use to the time the study was conducted, we would have considered the new headquarters or current status of having a sales representative in Estonia and not the one at the time of approval. Change of headquarters is unlikely to have affected many companies during the time period studied.

4.6 Conclusion

This study provides cross-country and country-level evidence on correlates of higher hazard of launch of new cancer medicines in selected European countries. In contrast to previous studies, we use a common benchmark (EU-wide marketing authorisation), when the medicine can potentially be marketed in all EU-countries and find that shorter time to submission for reimbursement, having a local sales representative, pre-launch evidence of added clinical value and need, and a short time gap since EU-wide marketing authorisation increase the hazard of launch in most model specifications. The effect of therapeutic group, expected

prices and volume varies across countries and model specifications. These findings suggest that more efforts are needed to ensure that launch of medicines with high clinical added value is prioritised over medicines with uncertain value and that limited expected volume in very small markets like Estonia, may cause delays in entry of new medicines. Horizon scanning and early dialogue with manufacturers through EMA channels and national initiatives are likely to help identifying medicines expected to bring high added clinical value. Strategic purchasing and joint procurement between regional groups (e.g. the Baltic countries) could help addressing issues of small volumes and various countries in Europe are already working in this direction with the aim of combining volume and securing competitive prices through joint negotiation and data sharing (Ferrario, Kanavos, et al. 2016b).

5 Determinants of utilisation differences for cancer medicines in Belgium, Scotland and Sweden (Paper 2)

5.1 Summary

Little comparative evidence is available on utilisation of cancer medicines in different countries and its determinants. In this chapter, I develop a statistical model to test the correlation between utilisation and possible determinants in selected European countries. I use a sample of 31 medicines for cancer treatment which obtained EU-wide marketing authorisation between 2000 and 2012. I obtained annual data on medicines' utilisation and expenditure covering in- and outpatient public sectors between 2008 and 2013 from national authorities in each country. I extracted information on the date of positive reimbursement decision for the first indication of a medicine, number of indications reimbursed in each year, co-payments, use of managed entry agreements, setting where the medicine was dispensed and price per defined daily dose from medicines' utilisation and expenditure data, health technology assessment reports, personal contacts with competent authorities and clinicians, the literature and assessment by the independent drug review organization Prescrire. I used these data to fit a longitudinal mixed effect model to test possible determinants of medicines utilisation in Belgium, Scotland and Sweden. In the all country model, I find that the number of indications reimbursed positively correlated with increased use of medicines (one indication=2.6, 95% CI [1.8-3.6]; two indications=2.4, 95% CI [1.4-4.3]; three indications=4.9, 95% CI [2.2-10.9]; all $p<0.01$), years since EU-wide marketing authorisation (1.2, 95% CI [1.02-1.4]; $p<0.05$), price per DDD (0.9, 95% CI [0.998-0.999], $p<0.01$), and Prescrire rating (0.5, 95% CI [0.3-0.9], $p<0.05$) after adjusting for time and other covariates. I conclude that the most important correlates of increased utilisation in a sample of cancer medicines introduced in the past 15 years in Belgium, Scotland and Sweden were medicines coverage and time since EU-wide marketing authorisation. Prices had a negative effect on utilisation in Belgium and Sweden suggesting that they represent a barrier to access. The positive impact of financial managed entry agreements in Scotland suggests that the use of confidential discounts removes the regressive effect of list prices on use.

5.2 Introduction

Managing the introduction of new high priced cancer medicines is a challenge for countries at all levels of development. On the one side payers want to provide access to new and potentially more effective medicines, while on the other they need to ensure the financial sustainability of their health care systems, value for money and an equitable distribution of the available resources.

In Europe, decisions regarding the reimbursement of new high cost medicines are increasingly made using health technology assessment (HTA). While important differences exist in the way individual countries implement HTA, they all include in their analysis and decision-making process information on the efficacy and effectiveness and, to different extents, information on the price of the new medicine. This technique does not only enable to determine the cost-effectiveness a medicine according to the licensed indication, it can also help identifying the patient subgroup in which the medicine is most cost-effective. Limiting access to such subgroup of patients is one tool countries are using to manage the introduction of new medicines.

Another way to manage entry is to delay the assessment of new medicines. This may be done with an explicit rationing objective, it may be caused by the time involved in conducting HTA but it may also be due to the lack of submission of a reimbursement dossier by the manufacturer. These factors can lead to a medicine not being reimbursed at all in a particular country or to reimbursement being limited to a subset of all licensed indications. Lack of a national level positive decision on reimbursement, or lack of a legal requirement to implement such decision at local level, can lead to disparities in availability of the medicine for patients within countries. In this context, local authorities or hospitals will decide whether or not to fund the medicine and it could possibly lead to no availability at all.

Increasingly, countries are using managed entry agreements (MEAs) to facilitate access while trying to limit budget impact and improve cost-effectiveness in a context of uncertainty (Ferrario and Kanavos 2013, Klemp et al. 2011, Ferrario and Kanavos 2014). The way medicines are financed has also an impact on access and can influence their uptake. Availability of top-up funding for new high cost medicines can incentivise prescribing and use over medicines which are funded by hospital budgets. The effect of prospective payment systems like diagnostic-related groups is most likely dependent on their design (Sorenson et

al. 2014). Special funds earmarked for particular products have been established in some countries. Examples include the cancer drugs fund in England (NHS England 2016a), the risk-share scheme for orphan medicines and the rare disease fund in Scotland (NSD NHS Scotland 2016, Scotland Government 2013) and the rare disease fund in Belgium (INAMI-RIZIV 2016a). The latter aim to increase availability of high cost medicines which may be otherwise not available or whose financing would put individual institutions in financial difficulties.

The setting, ambulatory or hospital, where the medicine is prescribed and dispensed can determine whether a co-payment applies or not and potentially influence levels of utilisation too. While co-payments for cancer medicines (particularly when these medicines are dispensed in hospitals) are not common in Western European countries, their use and the extent of cost-sharing may influence utilisation. In some countries, third party payers may require prescribing doctors to obtain prior authorisation by a physician designated by the payer, before the medicine can be prescribed.

Beyond pricing and reimbursement, disease burden, demographics, access to timely diagnosis, clinical practice, access to specialist care, whether the disease is a national priority and cultural factors including defensive medicine also have an impact on use of new high priced medicines and may lead to differential uptake across countries (Richards 2010, Nolte, Newbould, and Conklin 2010, Nolte and Corbett 2014, Lambrelli and O'Donnell 2009, Sullivan et al. 2011).

While the factors influencing access and use of cancer medicines have been to a certain extent identified and discussed in the literature, less evidence is available on the actual levels of cancer medicines use across different countries and most importantly their determinants.

Differences in the use of cancer medicines between selected high income countries have been investigated in an international study on medicines use in 2008/09 and its update in 2013/14 (Richards 2010, O'Neill and Sussex 2014). A study on endocrine therapies for breast cancer investigated patterns of use in eight Western European countries plus Australia over the period 2001-2012 (Kelly et al. 2015). A series of comparative longitudinal studies on patient access to cancer medicines in Europe have been conducted covering the time period from 1993 to 2014. These studies looked at differences in expenditure and, for selected medicines,

also milligrams (mg) per case and defined daily doses per case (Wilking and Jönsson 2005, Wilking, Jönsson, and Högberg 2009, Jönsson et al. 2016). Possible determinants of utilisation differences or lack of differences have been investigated using a qualitative approach (benchmarking possible determinants against quantitative data) (Richards 2010, Kelly et al. 2015, Groot, Huijgens, and Uyl-de Groot 2006, Kos, Obradovic, and Mrhar 2008). A study on utilisation of orphan medicines *vs.* non-orphan medicines used t-test to assess whether an association existed between orphan medicine status and variability in use across countries (Stolk et al. 2009). Some correlation analysis was conducted in the 2016 update of the study on uptake of oncology medicines in Europe which noted that uptake of innovative medicines largely depends on the country's gross domestic product and the level of health care spending per capita (Jönsson et al. 2016). However, the authors also noted that differences in use across countries with similar economic status exist (Jönsson et al. 2016).

Reasons for the limited number of studies including utilisation of cancer medicines data and using statistical methods are likely to include, but are not limited to, the difficulties in accessing data on medicines dispensed in hospitals from public sources and the cost of accessing from private ones. Further, the difficulty and sometimes impossibility of assigning a numerical value to all possible determinants of use to test as part of a statistical model. The aim of this study is therefore to test the correlation between utilisation of cancer medicines (mostly dispensed in hospital settings) and possible determinants of utilisation of cancer medicines in selected European countries. The study contributes to the existing literature by providing updated longitudinal evidence on use of cancer medicines in Europe and by developing a multilevel model to test the correlation between utilisation and likely determinants adjusting for important covariates.

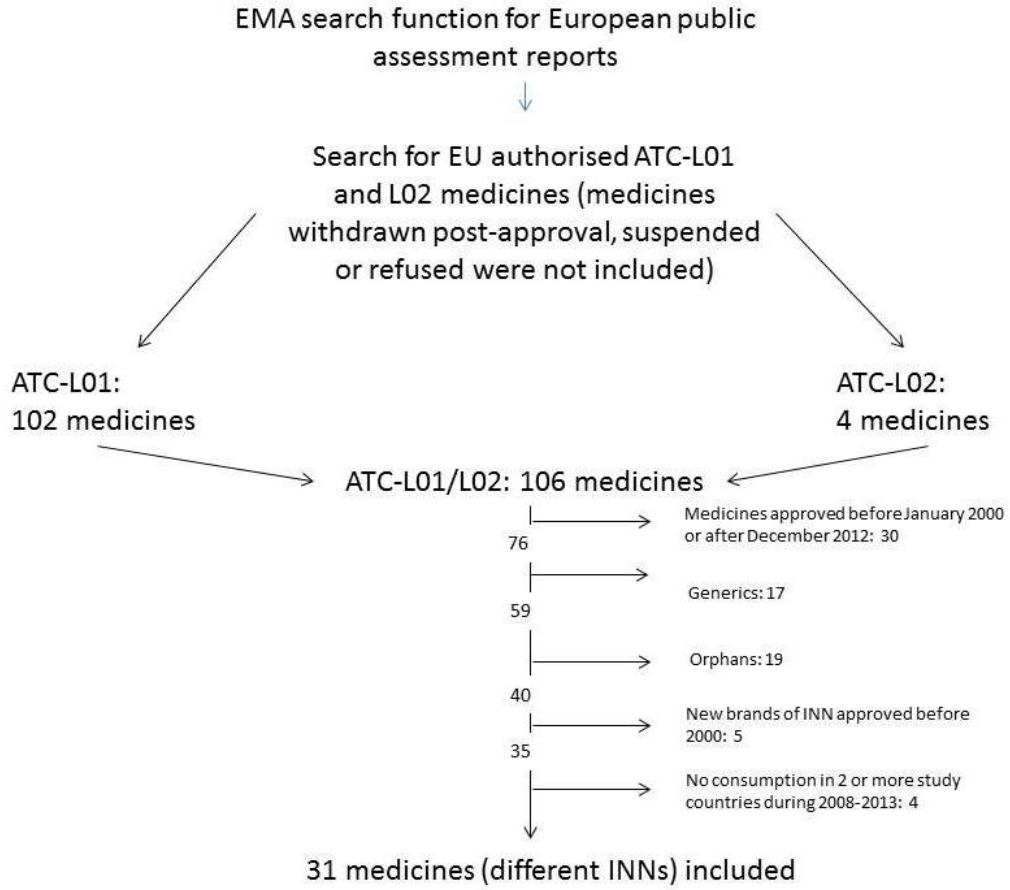
5.3 Methods

5.3.1 Sample selection and variable definition

Three countries were selected based on access to data from public sources: Belgium, Scotland and Sweden. Despite the convenience nature of the sample, the three countries represent a suitable study group, they are all part of the European Union, have comparable levels of gross domestic product per capita and spending on health per capita, benefit of a comprehensive system of universal health coverage and have a population size ranging from more than 5 to 11 million inhabitants in 2013 (Appendix 1).

Using the anatomic therapeutic chemical (ATC) search function for European Public Assessment Reports available from the website of the European Medicines Agency (EMA), I identified all antineoplastic (ATC-L01) and endocrine (ATC-L02) medicines authorised in the European Union (EU) and the European Economic Area countries (Iceland, Liechtenstein and Norway). I did not include medicines which were withdrawn post-approval, suspended or refused. The unified list (ATC-L01 and L02) contained 106 medicines (different brand names). I selected all medicines which obtained EU marketing authorisation between 2000 and 2012 (total: 76). In an attempt to have a homogenous, yet sufficiently large, sample (at least 30 medicines), we excluded generics (17), orphan medicines (as classified by EMA at the time of data extraction) (19), biosimilar medicines (zero) and medicines approved under exceptional circumstances (zero after excluding orphans), (Figure 6). Uptake of these medicines is likely to be influenced by different factors than for the majority of other medicines included and this would require a separate analysis for each of these three groups. There were five medicines approved with a conditional marketing authorisation in the remaining sample of 40 medicines. We excluded five medicines which were new brands of international non-proprietary names (INNs) approved before 2000. Finally, after extracting data on utilisation from the three study countries, we excluded four medicines for which there was no use during the study period (2008-2013) in two or more study countries. The final sample of medicines (different INNs) included in the analysis was 31 (Appendix 5).

Figure 6: Selection of cancer medicines to be included in the study



Although the subject matter of this study was cancer, I did not include immunostimulant medicines (ATC – L03) because only some of these medicines are indicated for cancer treatment. Further, even if a medicine is indicated for the treatment of cancer, the other indications may not be and my data did not allow to disaggregate medicines use by indication.

5.3.2 Data sources

Quantitative (e.g. mg of medicines dispensed, date of reimbursement for the first indication) and qualitative (e.g. positive *vs.* negative reimbursement decision, implementation of MEAs) data were used to build the statistical model. Data on medicines utilisation (pack size, number of packs, strength per quarter or month) in ambulatory and hospital settings by INN and brand (Belgium and Sweden) and by INN only (Scotland) between 2008 and 2013 was obtained from the National Institute for Health and Disability Insurance (INAMI-RIZIV) in Belgium, the Dental and Pharmaceutical Benefits Agency (TLV) and eHälsomyndigheten in Sweden and the National Health Service (NHS) in Scotland. The list of MEAs for each

country was sourced from a previous Chapter 7 for Belgium and Sweden and the Scottish Medicines Consortium website for Scotland (SMC 2015). Prices per defined daily dose (DDD) were estimated from expenditure data provided by INAMI-RIZIV in Belgium and TLV in Sweden and using historical prices from the British National Formulary in Scotland. DDDs from the Belgian Centre of Pharmacotherapeutic Information (CBIP 2016) were used since the ATC/DDD Index of the WHO Collaborating Centre for Drug Statistics Methodology does not define DDDs for most cancer medicines. Additional data on the study variables were extracted from the websites of national competent authorities (e.g. HTA reports and ministerial decisions) (INAMI-RIZIV 2015, TLV 2016c, SMC 2016a) and personal contacts with these authorities or clinicians and from the utilisation data provided by the countries.

The variables extracted included the date when a positive reimbursement decision (Belgium and Sweden) or positive recommendation for use (Scotland) for the first indication of a medicine was made, the number of indications (measured as different types of cancer) covered or recommended for use in each of the study years, use and type of a MEA, setting where the medicine was dispensed and patient co-payments. While decisions in Belgium and Sweden - relate to reimbursement and in Scotland they relate to use within the national health system, for the sake of simplicity the term used henceforth is 'reimbursement' or 'coverage'. In Sweden, a reimbursement decision is usually made by TLV for outpatient medicines and by the county councils (the latter, in recent years were increasingly made through the NT-council, a body representing all the county councils) for hospital medicines. Some medicines are not assessed by any of these two bodies but recommended as part of national guidelines. National guidelines aimed at supporting resource allocation decisions are developed by the National Board of Health and Welfare (NBHW), these are not clinical guidelines but can and are also used as clinical guidelines. Further, since 2011, national guidelines on breast, prostate, colorectal and lung cancer are developed by professional organisations under the regional cancer centre. Before 2011 each professional group was responsible for cancer care programmes. We therefore checked guidance by the NBHW, the regional cancer centre and contacted clinicians responsible for the cancer care programmes before 2011.

5.3.3 Data analysis

The study included a total of nine independent variables. This includes six continuous variables, notably (a) the number of years since a medicine obtained EU-wide marketing

authorisation for the first indication; (b) the number of years since a positive reimbursement decision was awarded for the first indication; (c) the median price per DDD; (d) time (year 1-6); (e) total pharmaceutical expenditure per capita and year (euros); and (f) the average rating of clinical added value across all indications assessed by the independent Drug Bulletin Prescrire (1-7 were 1 represents highest level of added clinical value, 6 the lowest level and 7 reserved judgment due to insufficient evidence) (2016). Three categorical variables are also included, namely (a) the number of reimbursed indications (zero to three); (b) the setting where the medicine was dispensed (1=hospital only, 2=ambulatory only, 3=both); and (c) use of a MEA (1=no MEA, 2=health outcome based MEA, 3=financial, 4=combination), which were modelled as dummies. The all country model included also dummy variables for countries and interaction terms between countries and time.

We used DDDs per 1,000 population to measure utilisation of cancer medicines. In order to compute the total number of DDDs consumed, we calculated the total mg of active ingredient dispensed for a particular INN. We used the DDD defined by the Belgian Centre of Pharmacotherapeutic Information (CBIP 2016) and divided the total mg by the Belgian DDDs.

The resulting longitudinal data set was analysed in Stata 13 using the mixed command to allow for random slopes (Rabe-Hesketh and Skrondal 2012). To allow for non-linear increase in utilisation over time we used a non-linear polynomial function with t^2 as an additional predictor (Hedeker and Gibbons 2006). The between-medicines variability is treated as a random effect (i.e. as a random-intercept term at the medicine level):

$$y_{ijk} = \alpha_{kj} + \beta_k X_{ijk} + t + t^2 + k + t*k + t^2*k + u_j + v_k + e_{ijk}$$

where i=year, j=medicine and k=country, X_{ijk} is a vector of all the independent variables included, u_j is the medicine specific random effect, v_k is the country specific fixed effect and e_{ijk} is the error term.

Random effects model unobserved between-subject (in this case medicines) variation as random, while fixed effects model unobserved variation between subjects (in this case countries) as constant (Rabe-Hesketh and Skrondal 2012). Interactions allow for differential increase (slope) between subjects. In this case they allow for time to have a different effect on

utilisation growth in each country. The logarithm of medicines use was modelled because of non-normal distribution of the non-transformed dependent variable.

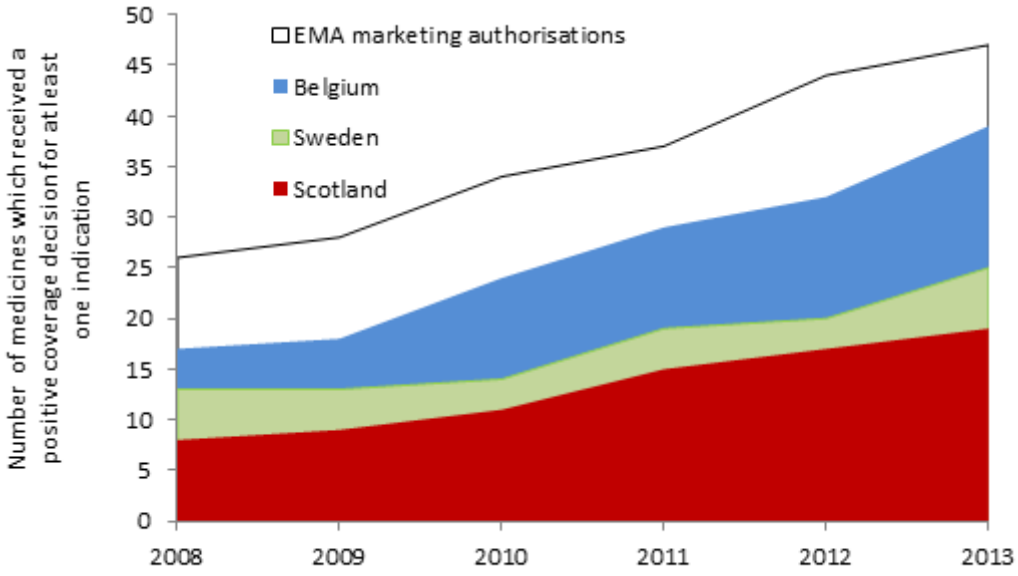
5.4 Results

5.4.1 Descriptive analysis

The median time since EU-wide marketing authorisation in the sample was 5.6 years (N=31 medicines, min=1.3 years, max=13.3 years) as of December 2013. At that time, the median time since a positive reimbursement for the first indication of the 31 medicines included was made was 3.9 years (N=30, min=0.45 years, max= 10.5 years) in Belgium, 3.7 years (N=16, min=0.23, max=11.2) in Scotland and 4.2 years (N=21, min=0.1, max=12.7) in Sweden. Some medicines had not been assessed by Scottish Medicines Consortium in Scotland (1) and either TLV or NT-council or NBHW or professional bodies in Sweden (9); other medicines were assessed and rejected (1 Belgium, 12 Scotland and 1 Sweden) as of December 2013. Until a few years ago, the adoption and utilisation of new cancer medicines in Sweden used to be at the discretion of the oncologists and their institutions. In the last few years, national guidance has increasingly become available through professional bodies, the NBHW, the NT-council and TLV. Out of the total 31 INNs studied, Belgium recommended at least one indication for 30 of them, Scotland 18 and Sweden 21.

Belgium had the highest number of indications covered (n=39, 83% of total indications with EU-wide approval, N=47) as of December 2013, followed by Sweden (n=25, 53% of total) and Scotland (n=19, 40% of total) (Figure 7). This does not mean that the other indications were only available if the patient paid out-of-pocket, but that there was no national level reimbursement decision. Individual hospitals or local authorities may then decide to make the medicine available to all or selected patients.

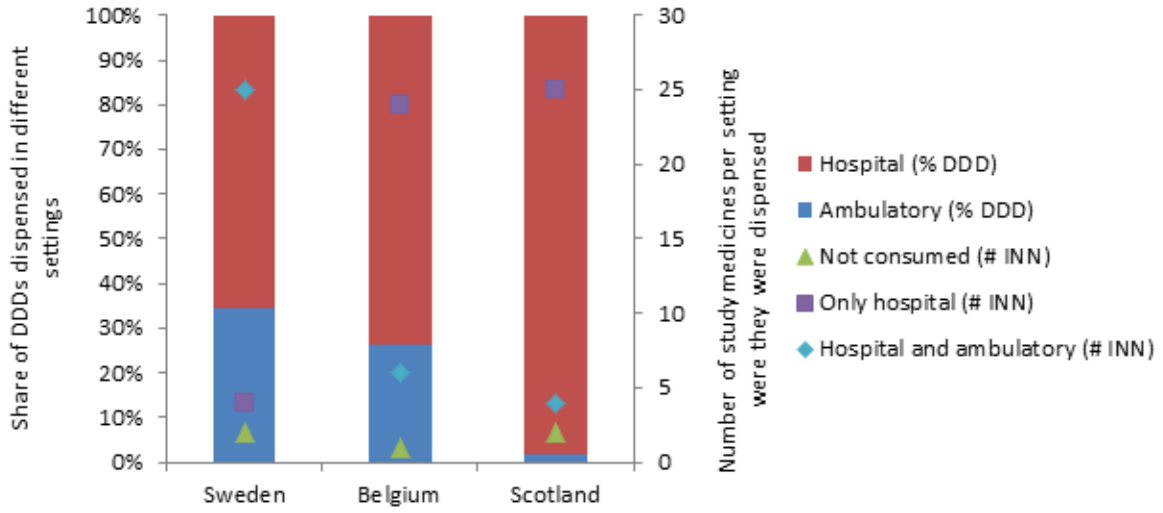
Figure 7: Cumulative number of indications covered *versus* approved EU indications (both measured as different types of cancer)



In Belgium, cancer medicines are fully reimbursed by compulsory health insurance. Similarly, but not limited to cancer medicines, there are no co-payments or charges on prescription medicines in Scotland. In Sweden, prescription medicines dispensed in hospitals are reimbursed at 100%, while prescription medicines dispensed in pharmacies are subject to a deductible plus a co-payment. Outpatient-orders, when for example the primary care unit has ordered a medicine and dispense it to the patient during the consultation, are not subject to co-payments. Since there were no co-payments in Belgium and Scotland and very minimal co-payments in Sweden (maximum annual co-payment for one year is about EUR 240 (SEK 2,200) for all medicines (TLV 2016a)), this variable was not included in the statistical model. Five, nice, four medicines were part of a MEA in Belgium, Scotland and Sweden, respectively. These included five combination agreements in Belgium, eight financial and one combination agreements in Scotland and three combination and one health outcome agreements in Sweden.

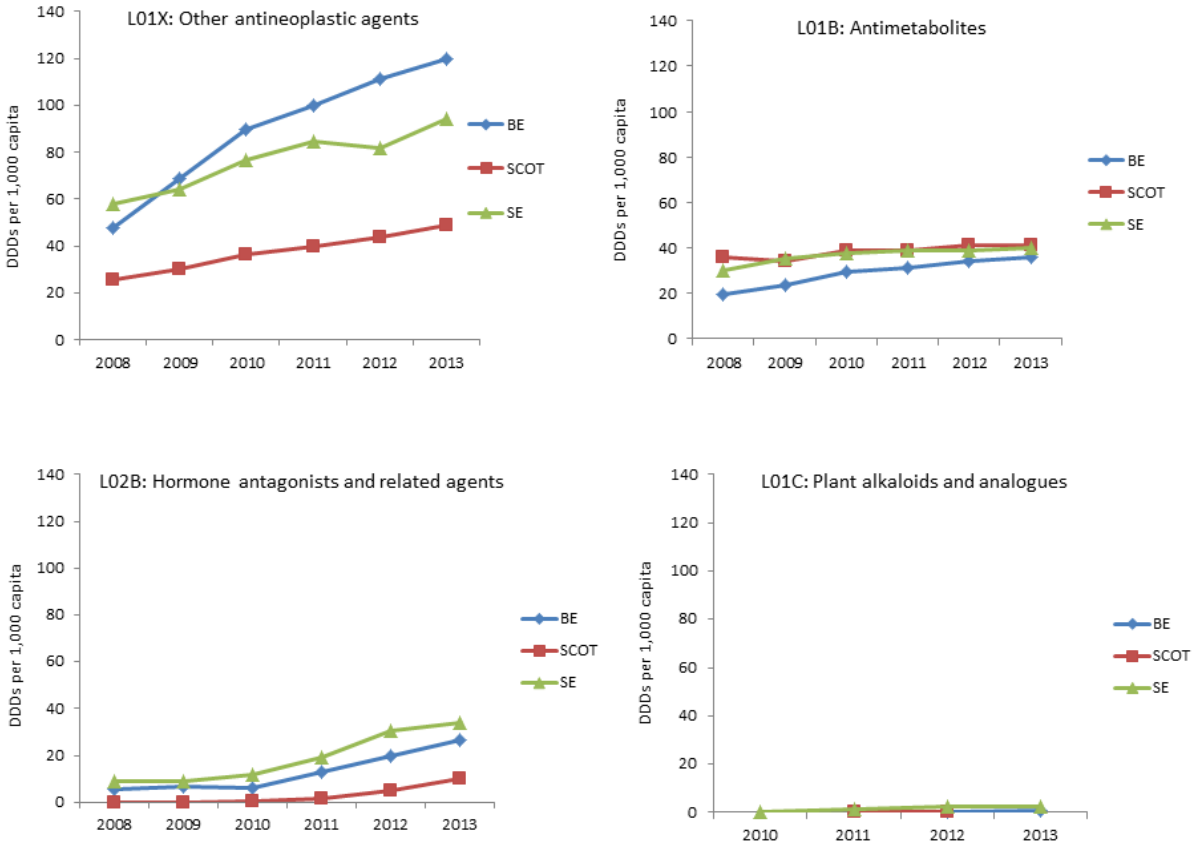
In all three countries, the largest volume share amongst the medicines in the sample (measured as total number of DDDs) was dispensed in hospital settings (including day care units) in all years (Figure 8). In 2013, this share was highest in Scotland (98%), followed by Belgium (74%) and Sweden (66%). Sweden had the highest number of medicines dispensed in both hospital and ambulatory settings (25) followed by Belgium (6) and Scotland (4).

Figure 8: Setting where medicines were dispensed by share of DDDs and number of medicines



The following figures (Figure 9) show medicines use as the number of DDDs dispensed per 1,000 population between 2008 (or the year when utilisation of the medicine was first recorded) and 2013 by ATC-level 3 pharmacological subgroup. Belgium had the highest per capita use of 'other antineoplastic agents' (L01X), the group to which most study medicines belong (N=23) in all years, while Sweden had the highest per capita use of 'hormone antagonist and related agents', (L02B) (N=3) and 'plant alkaloids and analogues' (L01C), (N=2). Scotland, closely followed by Sweden, had the highest per capita use of 'antimetabolites' (L01B) included in the study sample (N=3).

Figure 9: Number of DDD consumed per 1,000 capita



The median price per DDD was highest in Belgium (EUR 116.5, min= EUR 2.9, max= EUR 3966.6), followed by Sweden (EUR 90.3, min= EUR 2.4, max= EUR 2724.4) and lowest in Scotland (EUR 88.1, min=3.6, max=5030.2). The median Prescrire rating across all the 31 medicines included in the study was 5, which corresponds to 'nothing new'. The medicine with the highest rating was imatinib with a rating of 2, representing 'a real advantage', for four of the six indications evaluated. A number of medicines (11) had a Prescrire rating of 6, which stands for 'not acceptable'.

5.4.2 Statistical analysis: Longitudinal mixed-effects model

In the all country model, the number of indications reimbursed (1 indication=2.6,95% CI (1.8-3.6); 2 indications=2.4,95% CI (1.4-4.3); 3 indications=4.9, 95% CI (2.2-10.9); all $p<0.005$) and the number of years since marketing authorisation (1 year=1.2, 95% CI (1.1-1.4), p-value < 0.05) positively correlated with increased use of medicines after controlling for time and other covariates (Table 13). Price per DDD (0.9, 95% CI (0.998-0.999), p-value < 0.05) and the low added clinical value had a regressive effect on utilisation (0.5, 95% CI (0.3-0.9), p-value < 0.05). Having controlled for time and country effects, no correlation was

found with the number of years since a positive reimbursement decision for the first indication was given, the existence or not of managed entry agreements, or the level (or the log) of total pharmaceutical expenditure.

Table 13: All country model

	Exp(β)	[95% CI]		p-value
Years since EU-wide marketing authorization	1.202*	1.021	1.405	0.026
Years since positive reimbursement decision	0.998	0.980	1.015	0.795
Number of disease areas covered				
-1	2.599**	1.840	3.633	0.000
-2	2.425*	1.377	4.259	0.002
-3	4.904**	2.192	10.913	0.000
Use of managed entry agreements (baseline: no MEAs)				
-Health outcome MEA	0.962	0.393	2.627	0.933
-Combination MEA	1.590	0.693	3.653	0.274
-Financial MEA	1.539	0.831	2.852	0.171
Setting where the medicine is dispensed (baseline: Hospital)				
-Ambulatory	0.460	0.156	1.368	0.163
-Hospital and ambulatory	0.720	0.495	0.954	0.087
Price per DDD	0.999*	0.998	0.999	0.001
Prescrire rating	0.545*	0.337	0.881	0.013
Pharmaceutical expenditure per 1000 capita	1.000	1.000	1.000	0.837
Year	0.925	0.605	1.412	0.716
$Year^2$	1.019	0.945	1.098	0.626
Country (baseline: Scotland)				
Sweden	4.711*	0.343	57.111	0.034
Belgium	4.393	0.372	3.785	0.255
Sweden x Year	1.185	0.593	1.896	0.772
Belgium x Year	1.062	0.790	1.188	0.839
Sweden x $Year^2$	0.969	0.868	1.091	0.761

Belgium x Year^2	0.973	0.003	5469.815	0.642
constant	3.896	1.000	1.000	0.712

Results for the country level models showed that the following variables were positively correlated with increased utilisation: the number of disease areas covered in all countries, years since EU-wide marketing authorization in Scotland and Belgium, use of managed entry agreements in Scotland, the setting where the medicine was dispensed in Sweden (Table 14). The variables that negatively influenced use were: the price per DDD in Belgium and Sweden and the low value of a medicine in Scotland.

Table 14: Country models

a) Belgium

	Exp(β)	[95% CI]		p-value
Years since EU-wide marketing authorization	0.890	0.653	1.213	0.461
Years since positive reimbursement decision	1.284	0.900	1.833	0.168
Number of disease areas covered	1.000	1.000	1.000	
-1	2.648**	1.788	3.923	0.000
-2	3.876**	2.119	7.090	0.000
-3	6.802**	3.095	14.951	0.000
Use of managed entry agreements (baseline: no MEAs)				
-Combination MEA	1.043	0.389	2.797	0.934
Setting where the medicine is dispensed				
-Hospital and ambulatory	0.595	0.112	3.146	0.541
Price per DDD	0.998**	0.997	0.999	0.000
Prescrire rating	0.610	0.366	1.017	0.058
Pharmaceutical expenditure per 1000 capita	1.000	1.000	1.000	0.480
Year	1.049	0.744	1.481	0.784
Year^2	0.972	0.916	1.033	0.363
constant	1882.717	0.001	3399451731.077	0.305

b) Scotland

Scotland	Exp(β)	[95% CI]		p-value
Years since EU-wide marketing authorization	1.289*	1.115	1.490	0.001
Years since positive reimbursement decision	1.011	1.000	1.022	0.061
Number of disease areas covered				
-1	1.832	0.967	3.471	0.063
-2	1.180	0.322	4.329	0.803
-3	38.205**	2.395	609.506	0.010
Use of managed entry agreements (baseline: no MEAs)				
-Combination MEA	1.100	0.272	4.446	0.894
-Financial MEA	3.249*	1.554	6.791	0.002
Setting where the medicine is dispensed				
-Hospital and ambulatory	1.174	0.602	2.288	0.638
Price per DDD	0.998	0.995	1.001	0.193
Prescrire rating	0.552*	0.367	0.832	0.004
Pharmaceutical expenditure per 1000 capita	1.000	1.000	1.000	0.710
Year	1.066	0.788	1.440	0.679
$Year^2$	0.976	0.935	1.019	0.267
constant	2.598	0.028	240.853	0.679

c) Sweden

Sweden	Exp(β)	[95% CI]		p-value
Years since EU-wide marketing authorization	1.361**	1.139	1.616	0.000
Years since positive reimbursement decision	0.902	0.787	1.034	0.140
Number of disease areas covered				
-1	2.316*	1.279	4.221	0.006
-2	3.320	1.000	11.023	0.050
Use of managed entry agreements (baseline: no MEAs)				
-Health outcome MEA	3.287	0.826	13.197	0.091
-Combination MEA	0.888	0.326	2.411	0.816
Setting where the medicine is dispensed				
-Ambulatory	0.519	0.174	1.537	0.238
-Hospital and ambulatory	1.685*	1.048	2.713	0.031
Price per DDD	0.998**	0.954	2.691	0.000
Prescrire rating	0.784	0.522	1.174	0.242

Pharmaceutical expenditure per 1000 capita	1.000	1.000	1.000	0.103
Year	4.688	0.779	28.078	0.090
$Year^2$	0.788	0.595	1.045	0.090
constant	77652.576	0.044	140363314266.971	0.125

5.5 Discussion

Overall, Belgium and Sweden had the highest level of utilisation (measured as DDD/1000 capita) for non-orphan cancer medicines which obtained EU-wide marketing authorisation between 2000 and 2012. Belgium had the highest absolute number of DDDs consumed per 1000 capita in 2012 and 2012. This does not seem to be explained by the burden of disease since Sweden has generally a lower incidence rate than Belgium and Scotland (apart for melanoma) and that Scotland has the highest incidence among the three countries for a number of cancers (e.g. breast, bronchus and lung, liver, oesophagus, pancreas and stomach) (Appendix 6). In Sweden and Scotland medicines used in hospitals are financed through the hospital budget and may be used before a national level decision on reimbursement is made. In contrast in Belgium, with the exception of compassionate use, pricing and reimbursement have to be completed before doctors can prescribe a medicine in hospital settings. However, once this is completed, hospital medicines are reimbursed separately by INAMI and are not part of the fixed hospital budget. This may explain why Belgium has higher per capita use than Sweden between 2011 and 2013 and generally a higher use than Scotland despite the latter has often a higher disease burden.

The 2010 report to the United Kingdom (UK) Department of Health used rankings to compare use of selected medicines across various therapeutic areas among 14 OECD countries in 2008/09 (Richards 2010). An update of the 2010 report was released in 2014 providing data for 2012/13 (O'Neill and Sussex 2014). The two analyses included the UK and Sweden but not Belgium. Although I cannot really compare my results with the UK Department of Health study due to differences in the medicines included, countries studied and methods of analysis, I can at least observe that utilisation of cancer medicines in Sweden was usually higher than in Scotland in my sample. In the Department of Health study, Sweden ranked 9th in terms of cancer medicines use and the UK ranked 10th (with some differences within the cancer class, e.g. use of endocrine therapies was higher in the UK than Sweden). Further, I can confirm the importance of HTA outcomes, included in my model as years since a positive reimbursement decision was made and indications covered, in

determining levels of utilisation. I can also confirm the absence of correlation between, in my study pharmaceutical expenditure per capita, in the case of the UK Department of Health report health expenditure per capita, and utilisation.

The number of indications covered positively correlated with increased utilisation in all models although not all levels of increase were significant. The effect was smallest in Sweden possibly because before 2010, and to a certain extent still today, decisions on whether to fund or not a cancer medicine have been made by the respective county councils in the absence of national level guidance. Today there is increasing coordination in decision-making thanks to the centralisation of cancer in six centres of excellence and closer collaboration between TLV and NT- council. The likely impact of coverage decisions on prescribing and use was also mentioned in a longitudinal study on endocrine therapies (Vitry, Thai, and Lu 2011) and the role of reimbursement and funding arrangements for governing access to myeloma treatment in England has been highlighted (Mehta and Low 2007).

Time since EU-wide marketing authorisation had a positive effect in all countries but Belgium. One explanation could be that in Belgium, reimbursement is a more important factor than years since marketing authorisation. Use in both hospital and ambulatory settings *vs.* hospital only had a positive effect in Sweden where it applies to most medicines included in this study. Interestingly, the price per DDD had a regressive effect in Belgium and Sweden but not in Scotland where, in contrast, low value medicines had a regressive effect. One possible explanation for the lack of negative impact of prices in Scotland may be the implementation of MEAs (all with a financial component for the medicines with MEA in this sample) which off-set the high list price per DDD. The 2016 update of the study on the uptake of new cancer medicines in Europe observed a correlation between the ESMO-MCBS and actual uptake, however this was not statistically significant and the number of medicines represented for most non-curative score levels was very small (score 1, n=0; score 2, n=3; score 3; n=3, score 5, n=1), only score 4 had 10 medicines represented (Jönsson et al. 2016). Finally, it is worth noting that large differences between and within country in access are not just limited to medicines but as a recent analysis by the OECD showed, affect a number of medical procedures (OECD 2014).

Not all possible determinants of utilisation of cancer medicines are readily convertible into a numeric value that can be tested as part of a statistical model. Examples include cultural

factors and clinical practice. Other determinants may be measurable but not readily available at medicine level between 2008 and 2013. For example, inclusion of access to timely diagnosis could be measured by looking at the average stage at which patients are diagnosed. However, the required data are not simple to obtain for different countries and several medicine-indication combinations and would require utilisation data by indication. This study therefore had to limit the number of variables included to those for which data were available at the required level and frequency in the three study countries.

There are a number of limitations in our study. First, it was not possible to include incidence of different types of cancer in the model. The majority of the medicines included in the sample were approved for the treatment of different cancer indications which are associated with different incidence levels. Only availability of utilisation data by ICD-10 code would have therefore enabled to link, in a reliable way, use with incidence. Second, it is well-known that list prices (e.g. British National Formulary) and undiscounted expenditure figures do not reflect what health payers pay for medicines (Vogler et al. 2012). Nevertheless, list prices are still the starting point for negotiation and the presence of special pricing arrangements at national level is captured by the MEA variable. Further, it would have simply been impossible to access real discounted prices on 31 cancer medicines in three different countries. Third, again due to lack of data at indication level but also lack of cost-utility estimates for all the medicines in each country, I could not include in the model the incremental cost-effectiveness ratio estimated for different indications in each country. Fourth, the number of dispensed doses does not necessarily mean that they were all consumed. Considering the high cost of new cancer medicines and the severity of cancer, it is unlikely that wastage will have significantly affected the results. Fifth, I did not have access to dispensing data within countries and, therefore, could not control for differences in dispensing at that level, which may be significant.

5.6 Conclusions

Access to new medicines ought to be targeted to medicines which bring a meaningful added value to patients in comparison to existing therapies. Use of medicines with modest therapeutic improvement, mostly at higher prices than existing treatments, draws resources away from potentially more effective interventions. It is therefore important that competent authorities assess added therapeutic value and enable access to medicines with high value and limit access to those with low value. This study showed that the most important correlates of

increased medicines utilisation in a sample of cancer medicines introduced in the past 15 years were medicines coverage and time since EU marketing authorisation. Prices had a negative effect on use meaning that they can represent a barrier for access. The lack of a regressive effect of prices on utilisation in Scotland, and the positive impact of financial MEAs, suggests that the latter may remove the regressive effect of list prices on use. Scotland was also the only country where low clinical added value of a medicine was correlated with reduced utilisation suggesting that existing entry arrangements in place, particularly HTA and clinical guidelines, seem to guide towards use of high value products and limiting access to low value ones. However, it is also important to note that Scotland had the lowest level of use for most medicines raising the question as to whether the other two countries have too generous access requirements or whether the former has too restrictive ones. Only an analysis of patient level data including prescribing information would enable to answer this question.

6 A framework to understand differences in utilisation of HER-2 targeted medicines for breast cancer (Paper 3)

6.1 Summary

Differences in the level of utilisation of cancer medicines across Europe have been highlighted in various studies. However, there is limited evidence on their causes. In this study, I use the case of HER-2 targeted therapies for breast cancer to analyse cross-national differences in utilisation in Belgium, Estonia, Scotland and Sweden. I developed a framework to identify determinants of the use of HER-2 targeted therapies (trastuzumab, lapatinib, pertuzumab and trastuzumab emtansine) based on a literature review and treatment guidelines. I populated the framework with information from official country websites, complemented and validated it by conducting interviews with oncologists. I obtained data on use of HER-2 targeted therapies from national authorities. Differences in the use of lapatinib, pertuzumab and trastuzumab emtansine are driven by lack of reimbursement in some countries (Estonia and Scotland). Trastuzumab is reimbursed in all countries and all new breast cancer patients are tested for HER-2 overexpression and prescribed trastuzumab if the tumour is invasive and larger than 1 cm or smaller but with risk factors. Yet, important differences exist in the use of trastuzumab (DDD per new case) between countries with high consumption (Belgium and Sweden) and countries with low consumption (Estonia and Scotland). This seems to be driven by differences in the use of trastuzumab beyond progression (only used in Belgium and Sweden). Estonia has a comparatively low incidence of breast cancer, the least comprehensive national breast cancer screening programme, and, despite progress, patients are diagnosed relatively late. If it is the case that a number of breast cancer cases are not diagnosed, Estonian patients could be worst off in terms of access despite similar levels of usage per patient to Scotland.

6.2 Introduction

Variations in the level of utilisation of cancer medicines across Europe have been highlighted in various studies (Richards 2010, O'Neill and Sussex 2014, Kos, Obradovic, and Mrhar 2008, Groot, Huijgens, and Uyl-de Groot 2006, Kelly et al. 2015, Jönsson et al. 2016). However, there is limited evidence on the underlying reasons for this variation. Studies have sought to explain these differences by discussing likely factors that may drive the observed variations (Kos, Obradovic, and Mrhar 2008, Kelly et al. 2015, Benjamin et al. 2014, Wilking, Jönsson, and Högberg 2009), conducting simple correlation analyses (Jönsson et al. 2016), developing qualitative frameworks to analyse possible reasons for disparities (Groot, Huijgens, and Uyl-de Groot 2006), conducting literature reviews (Nolte and Corbett 2014, Nolte, Newbould, and Conklin 2010, Lublóy 2014, Chauhan and Mason 2008), and setting up an expert panel to identify possible determinants of variations (Richards 2010). While frameworks to analyse access to medicines exist, these have often been developed with a focus on low- and middle income countries (WHO 2004, Bigdeli, Jacobs, et al. 2013, Center for Pharmaceutical Management 2003). The primary objective of frameworks targeting developed countries (Cohen et al. 2007, Chauhan and Mason 2008), was not to identify determinants of access to cancer medicines. For this reason, they may miss some of the peculiarities affecting access to this pharmacotherapeutic group. Notable exceptions include a study which proposes a conceptual framework of factors influencing patients' access to oral anticancer medicines (Benjamin et al. 2014). However, this framework focuses variations at patient level rather than population level.

In this study, I use the case of HER-2[11] targeted therapies to analyse differences in utilisation of breast cancer medicines at the population level, using a qualitative framework. My choice was motivated by the fact that trastuzumab, the first HER-2 targeted therapy for breast cancer to market, is well established as an effective treatment in early breast cancer (O'Sullivan et al. 2015, Moja et al. 2012), though not necessarily cost-effective in all settings (Pichon-Riviere et al. 2015). This precludes the argument of poor or uncertain evidence on its effectiveness as the reason for disparities in use across countries. In the metastatic setting, trastuzumab was found to improve overall survival and progression-free survival in HER2-positive patients

[11] "HER2 (human epidermal growth factor) is a protein that can affect the growth of some cancer cells. It is found on the surface of normal breast cells. Some breast cancer cells have a very high number of HER2 receptors. The extra HER2 receptors stimulate the cancer cells to divide and grow. When there are higher levels of the HER2 protein in a breast cancer, it is called HER2 positive breast cancer." http://www.macmillan.org.uk/cancerinformation/cancertypes/breast/aboutbreastcancer/typesandrelatedconditions/her2%20positive.aspx (accessed 15 November 2016)

(Balduzzi et al. 2014). The cost-effectiveness of trastuzumab in metastatic patients in Europe was found to be mainly an issue of price until the first generic medicines would enter the market (Garattini, van de Vooren, and Curto 2015). I also included all follow-on HER-2 targeted therapies for breast cancer, as they may explain a reduction in utilisation of trastuzumab after they enter the market.

This study does not aim and is not designed to judge the quality of cancer care in the selected countries. While elements of quality of care like waiting times are explored, this is done in the context of understanding differences in utilisation of HER-2 targeted therapies. Further, higher utilisation does not necessarily mean better quality care. Quality of cancer care is a complex subject which is not determined solely by analysing utilisation of medicines alone.

6.3 Methods

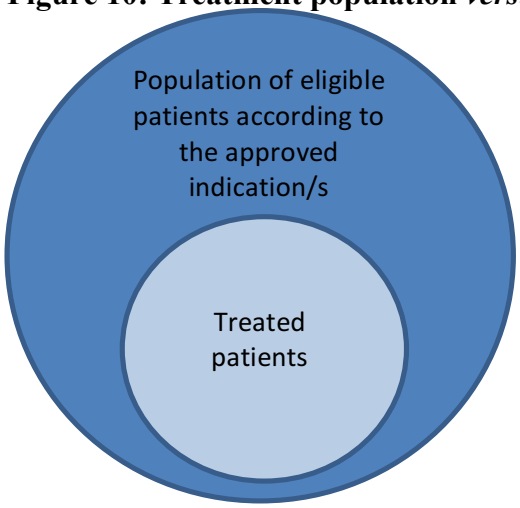
6.3.1 Literature review

A comprehensive review of the literature was conducted to identify studies on determinants of differences in use of cancer medicines across countries. Some of these determinants are also responsible for differences in use of cancer medicines at a subnational level. However, the focus of this study is on international differences in per capita utilisation, not on subnational or patient level differences, although these contribute to the overall level of utilisation at national level.

6.3.2 Development of the framework

A list of determinants was compiled and used to develop a framework to explore differences in use of HER-2 targeted therapies for breast cancer. The framework was built with the following logic in mind: there is a population of eligible patients according the EU-wide approved indication/s for these medicines. Within in this larger patient population there is a smaller group of patients who are eligible for treatment and actually receive it (Figure 10).

Figure 10: Treatment population *versus* eligible population



This reality leads to two questions relevant to the utilisation of medicines: 1) what determines the size of the eligible treatment population? And 2) what determines access to HER-2 targeted therapies among eligible patients?

6.3.3 Data sources

Annual data on utilisation of HER-2 targeted therapies (trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine) between 2008 and 2014 were obtained from the relevant public authority holding this information in each country. This was the National Institute for Health and Disability Insurance (RIZIV-INAMI) in Belgium, the State Medicines Agency in Estonia, the Information Services Division (ISD) of NHS Scotland and the eHealth Agency (eHälsomyndigheten) in Sweden. Data covered medicines dispensed in both outpatient and inpatient settings. Variables included INN, the number of packs, pack size and strength of medicines dispensed in the respective countries. Total mg consumed were estimated and divided by the defined daily dose (DDD) for the four HER-2 targeted therapies with EU-wide marketing authorisation as of December 2014. As there were no DDD by the WHO Collaborating Centre for these four medicines, I used the DDD by the German Institute of Medical Documentation and Information (trastuzumab: 20 mg for parenteral form, 29 mg for parenteral subcutaneous form, trastuzumab emtansine: 12 mg, lapatinib: 1375 mg, pertuzumab: 20 mg), (DIMDI 2016).

A number of data sources were used to populate the framework. These include the European Cancer Observatory (European Cancer Observatory (EUCAN) 2016); official websites of national competent authorities in pricing and reimbursement, national health insurers,

medicines regulatory authorities and ministries of health (TLV 2016c, INAMI-RIZIV 2015, Janusinfo 2016, SMC 2016a, Esti Haigekassa 2016b, Läkemedelsverkets 2016, Socialstyrelsen 2016); national health information system websites (ISD 2016b), health systems reviews of the European Observatory (Gerkens and Merkur 2010, Lai et al. 2013, Anell, Glenngård, and Merkur 2012, Steel and Cylus 2012); peer-reviewed literature (Ferlay et al. 2013, Slamon et al. 1987, Burstein 2005), further electronic correspondence with competent authorities, national statistic units, and interviews with oncologists in the countries studied for information clarification.

Up to two oncologists per country were interviewed (two in Belgium, Estonia, and Scotland; one in Sweden) using a semi-structured questionnaire based on the framework developed (Appendix 7). The oncologists interviewed were generally from the capital (Brussels, Edinburgh, and Tallinn) and another main oncological centre (Glasgow, Gothenburg, Leuven, and Tartu). Six of them were senior oncologists (i.e. head of Unit or Department) and one was a consultant oncologist; six were male and one was female. Given the difficulties in approaching oncologists (e.g. finding contacts and arranging the interviews), interviews were organised through contacts in the countries studied who introduced me to the interviewees. While I was introduced to three oncologists in Sweden, only one agreed to be interviewed. The objective of the interviews was to complement information from the desk review of national websites and the literature as well as update and validate some the information retrieved. The structure of the interview therefore varied according to the information gaps remaining in each country after conducting the desk review. The interviews were kept semi-structured to enable going deeper into topics worth further investigation. For example, additional questions were asked to the oncologist in Sweden about the special fund available in one county to fund new hospital medicines.

6.4 Results

6.4.1 Development of a framework to analyse differences in use of HER-2 targeted therapies

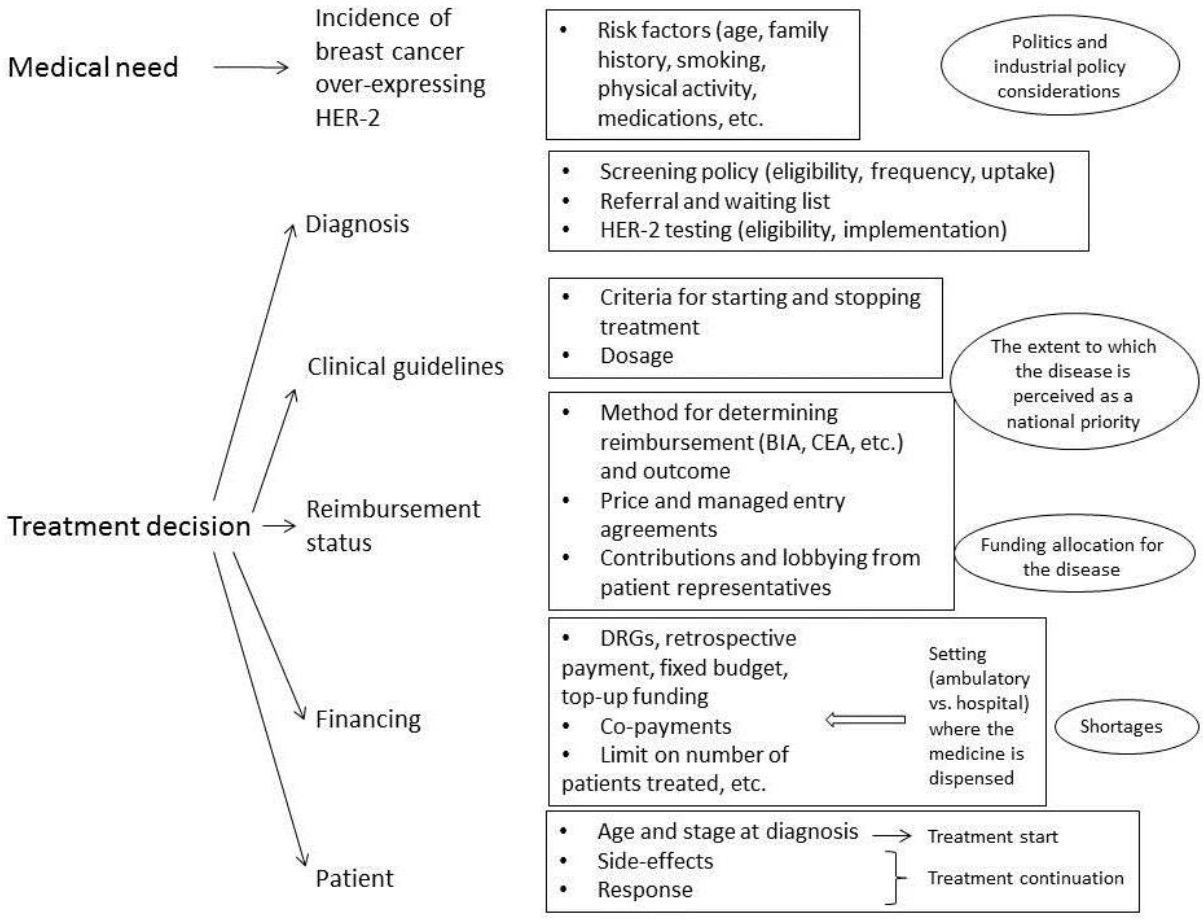
Use of HER-2 targeted therapies is determined by medical need (burden of disease) and a range of factors that can affect treatment decisions (Figure 11). The size of the eligible treatment population is determined by the incidence of breast cancer overexpressing HER-2. Incidence of breast is determined by genetic, demographic and life-style risk-factors (family history, age, smoking, physical activity, etc.). For a patient with breast cancer to start

treatment, a diagnosis has to be made. The extent to which breast cancer is diagnosed and the timing of diagnosis is influenced by the existence and nature of national screening policies (e.g. is there a national screening programme? Who is eligible for screening? How frequently is screening conducted? What is the actual uptake of screening programmes? Which screening method is used?). Referral practices and waiting lists can affect the time needed to access a specialist and start treatment. Finally, only breast cancers overexpressing HER-2 should be treated with the corresponding targeted medicines. Therefore the scope of screening for HER-2 overexpression in all new breast cancer patients, the method, and the quality of testing can further affect the number of eligible patients.

Patients diagnosed with breast cancer overexpressing HER-2do not automatically obtain a HER-2 targeted therapy prescription. A range of factors can influence oncologist's decisions. These include clinical guidelines, patient related factors like age and diagnosis stage, side-effects, and patient's response may affect treatment initiation and continuation. The reimbursement status of the medicine is another important factor which is in turn determined by the assessment method/s (e.g. budget impact analysis, cost-utility analysis), the interpretation of the evidence, the price of the medicine and any special pricing arrangements offered by the manufacturer (e.g. managed entry and risk-sharing schemes), industrial policy considerations, and the role of patient representatives. Additional factors which may influence a clinician's decisions relate to how medicines are financed (e.g. as part of diagnostic-related groups, hospital budget, retrospective reimbursement by health insurance, availability of earmarked funding or other special arrangements for high-cost medicines, whether patients are required to make a co-payment and whether there is a cap on the number of patients that can be treated or on total expenditure) and where the medicines are dispensed (different prices, co-payments and reimbursement arrangements may apply in hospital *vs.* ambulatory care). Different financial arrangements for medicines in hospitals *vs.* the community may affect where patients are treated and which formulation they are given. For example, there may be a disincentive to prescribe an oral cancer medicine to be taken at home instead of its intravenous equivalent to be administered in the hospital, if the hospital will make a financial loss due to reduced patient volume (per-case based system) (Benjamin et al. 2014). To avoid this, some countries have decided that independently of where the medicine is administered, some specialised medicine will always be funded by the hospital (Groot, Huijgens, and Uyl-de Groot 2006). This is the case for example in Denmark, Norway and Sweden. Finally, shortages of medicines can affect their availability for prescription and

may result in treatment delays or treatment switching (EAHP 2014). From a macro perspective, the extent to which the disease is perceived as a national priority and the budget allocation to health will determine the amount of resources available for breast cancer and enable or constrain funding allocation for medicines.

Figure 11: Framework to analyse access to HER-2 targeted therapies for breast cancer

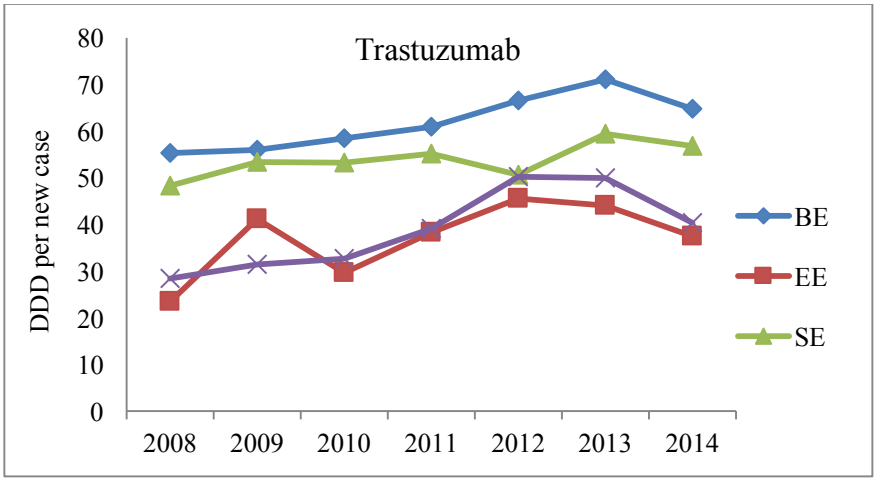


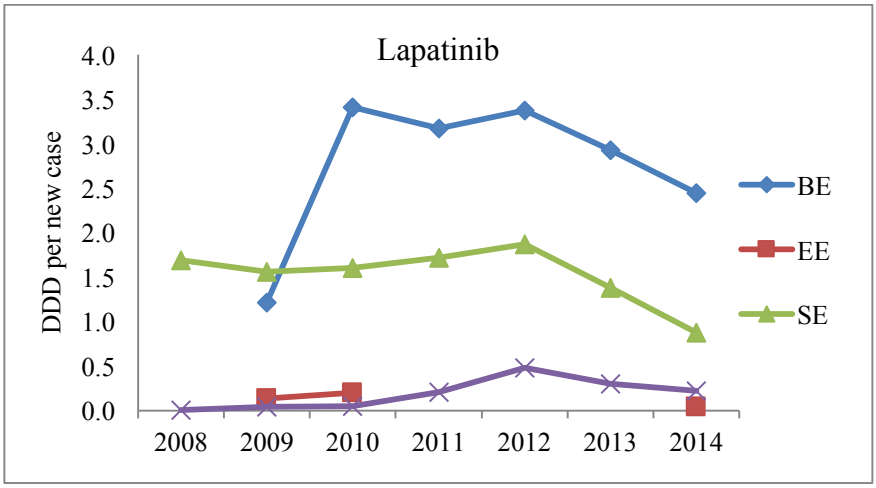
6.4.2 Utilisation of HER-2 targeted therapies in Europe

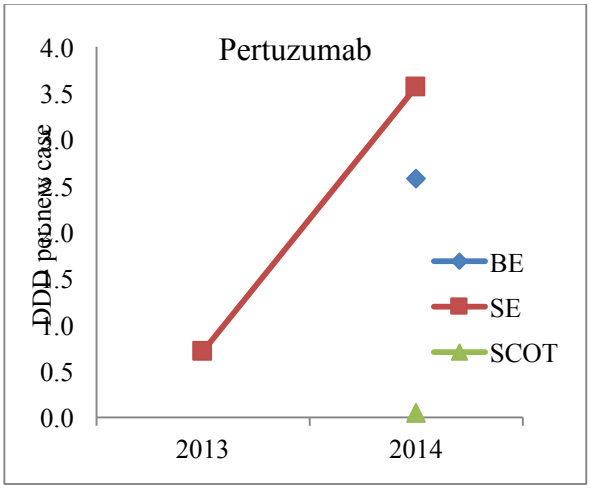
Trastuzumab was the first HER-2 targeted medicine to obtain EU-wide marketing authorisation in 2000 and as of December 2014 had 9 indications approved. In 2014, utilisation of trastuzumab was highest in Belgium (on average 65 DDD per new case), followed by Sweden (on average 57 DDD per new case), Scotland (on average 40 DDD per new case) and Estonia (on average 37.5 DDD per new case), (Figure 12). Lapatinib, pertuzumab and trastuzumab emtansine were approved in 2007, 2011 and 2012, respectively, and as of December 2014 had 3, 1 and 2 indications with EU-wide marketing authorisation,

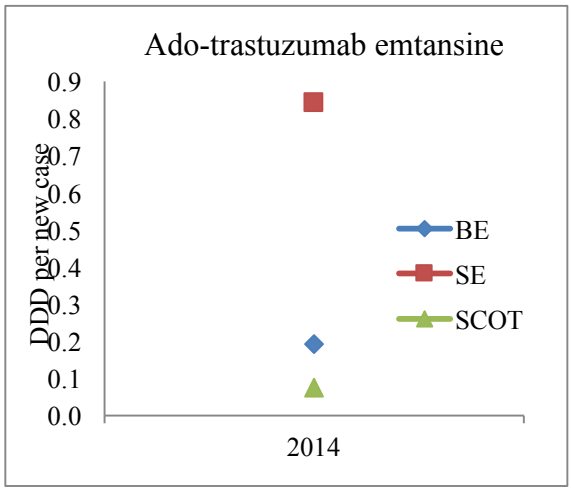
respectively. In 2014, use of lapatinib was highest in Belgium (on average 2.4 DDD per new case), followed by Sweden (on average 0.9 DDD per new case), Scotland (on average 0.2 DDD per new case) and Estonia (on average 0.04 DDD per new case). In Belgium, consumption of lapatinib after 2010 was probably displaced by pertuzumab and trastuzumab emtansine from 2010 onwards according to one of the interviewees. Lapatinib is now specifically used for brain metastasis. In 2014, utilisation of pertuzumab was highest in Sweden (on average 3.6 DDD per new case), followed by Belgium (on average 2.6 DDD per new case) and Scotland (0.05 DDD per new case), while for trastuzumab emtansine utilisation was highest in Sweden (on average 0.8 DDD per new case) followed by Belgium (0.2 DDD per new case) and Scotland (on average 0.08 DDD per new case). There was no utilisation of pertuzumab and trastuzumab emtansine in Estonia up to December 2014.

Figure 12: Utilisation of HER-2 targeted therapies









Notes: Belgium (BE), Estonia (EE), Scotland (SCOT), and Sweden (SE).

In all countries, trastuzumab remained dominant in the HER-2 targeted market as of 2014 (nearly 100% market share in Estonia, 99% in Scotland, 96% Belgium and 91.5% Sweden).

Penetration of follow-on HER-2 therapies in 2014 was highest in Sweden (5.7% pertuzumab, 1.4% lapatinib and 1.4% trastuzumab emtansine) and lowest in Estonia.

6.4.3 Testing of the framework

6.4.3.1 Incidence of breast cancer over-expressing HER-2

In 2012, incidence of breast cancer was highest in Scotland (169 per 100,000) followed by Belgium (148 per 100,000), Sweden (108 per 100,000) and Estonia (69 per 100,000) (Ferlay et al. 2013). The percentage of breast cancer overexpressing HER-2 has been estimated to be around 15-30% of primary (node-negative) breast cancer cases depending on the source (SMC 2006, EMA 2004, Slamon et al. 1987, Burstein 2005). Indicative estimates during the interviews suggested that the percentage of all newly diagnosed breast cancer cases that overexpress HER-2 is approximately 15-18% in Belgium (unofficial data), about 15-20% in Estonia (unofficial data), and 15% in Greater Glasgow and Clyde (official data), which should be representative of the prevalence in Scotland.

6.4.3.2 Diagnosis

All countries have free national screening policies in place but their coverage differs. Sweden covers the widest age group of women from 40 to 74 years old whereas Estonia covers the narrowest age group of women from 50 to 62 years old every two years and does only cover insured patients (6% estimated uninsured patients (Esti Haigekassa 2016a), unemployed men aged 30 to 50 and individuals from households with the lowest expenditure quintile are more likely to be uninsured (Vork et al. 2010, Koppel et al. 2008)). Uptake among invited women (with health insurance, registered in the population registry, with correct address and no previous mammography in past 12 months) was 62% in 2014 (estimated based on (Esti Haigekassa 2015)). European guidelines recommend screening women aged 50-69 with mammography every two years (Health & Consumer Protection Directorate-General 2006) and this is currently practiced in Belgium (50-60 years old with insurance) and Scotland (50-70 years old) (The Scottish Government 2016). In Belgium, 60% of eligible women were screened in 2009-10 (Agence Intermutualiste 2014). Some Belgian regions offer screening also to younger women down to age 40, this service is partially reimbursed by health insurance (Belgian Health Care Knowledge Centre (KCE) 2014) while the programme for women aged 50-69 years old is fully reimbursed. In 2010/11, 74.7% of eligible women had a mammography in Scotland (The Scottish Government 2016). Sweden has the most generous screening programme covering the widest age range (40 to 74 years old) and mammography

every 18-24 months (Socialstyrelsen 2016). Overall, 80% of invited women participate in the screening programme but coverage varies between geographical areas (Sveriges Kommuner och Landsting 2013).

In all countries studied, all patients diagnosed with breast cancer are tested for HER-2 overexpression, all cases are discussed during multidisciplinary consultations, and all countries have breast cancer units. In Estonia, all metastatic and early breast cancer patients have been tested since 2006 (although some hospitals may have started before). In Scotland testing of early breast cancer patient started following the positive recommendation by SMC in September 2006. Some time was required to reach nationwide coverage, due to more remote areas of Scotland. Licensing of trastuzumab for use in metastatic breast cancer preceded SMC's establishment and as such it was not clear when nationwide testing for metastatic cancer was reached. In Sweden all patients diagnosed with breast cancer are tested for HER-2 overexpression no later than 2007 (for nationwide coverage of all patients early and metastatic). According to international guidelines, breast cancer patients are first tested with ImmunoHistoChemistry (IHC) to measure the level of HER-2 receptor protein expression (on a scale from 0 to 3+). Patients are considered HER-2 positive if the result of IHC is 3+. For patients with HER-2 levels 2+, a fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) is conducted to measure the level of gene HER-2/neu gene which is responsible for the overproduction of HER protein. A study comparing the performance of FISH and CISH differences between the two tests do not affect the analytical performance of these genetic assays (Poulsen et al. 2013). The main difference between the tests was in the scanning speed (superior in CISH) (Poulsen et al. 2013). In Belgium all metastatic patients have been tested since at least 2000 and early breast cancer patients since 2004/5 with IHC followed by FISH for patients with 2+ and 3+ , and in several centres even for 1+ and 0 cases. This is an important difference in testing practices leading to a high number of FISH tests being conducted in Belgium as 3+ patients are not automatically classified as HER-2 positive based on IHC results, despite recommendations by the American Society of Clinical Oncology (Colpaert and Salgado 2007). The reason for this is that treatment with trastuzumab is only reimbursed if the HER-2 gene amplification is proved by FISH (Colpaert and Salgado 2007).

In Sweden most suspected cases are detected during regular screening as part of the national programme (49% of breast cancers in the population, 64% of breast cancer for women aged

40 to 74 years old (Regionala Cancercentrum I Samverkan 2016)). These patients are sent to the specialized breast unit (they are located in each larger hospital) where a biopsy is performed. If the diagnosis is confirmed the patient is given an appointment with the oncologist. A treatment decision is usually made after surgery unless a decision to start with neoadjuvant treatment was taken at the meeting prior to the surgery. Long waiting times to access cancer care services have been report in Sweden, these affect mainly the time from disease suspicion to treatment initiation (Wilkens et al. 2016). Reducing these waiting times and standardising care delivered across different regions of Sweden are the aims of the 2015 national cancer programme in Sweden (Wilkens et al. 2016). In Estonia, patients may be diagnosed through the national screening programme, referred for investigation by primary care doctors or gynaecologists (including women's clinics in Tallinn which perform mammography outside the national screening programme) or diagnosed within hospital breast cancer units in the capital which patients can access without referral. Cancer care is concentrated in the North Estonia Medical Centre (Tallinn, capital) and in Tartu University Hospital. Tallinn Children's Hospital and the East Tallinn Central Hospital also provide cancer care though in a smaller scale. Waiting times in oncology are shorter than for other speciality areas (Esti Haigekassa 2016a). There are national quality guidelines specifying the maximum waiting time (e.g. the maximum waiting time from registration to the first visit to the specialist should be less than 4 weeks, the same from diagnosis to treatment) and generally oncology waiting times are within these limits (Esti Haigekassa 2016a). In Belgium, waiting times do not seem to be an issue and patient do not need to see a family doctor to be referred to a specialist (Gerkens and Merkur 2010). There are national waiting targets for breast cancer, two weeks from diagnosis to treatment decision and two weeks from treatment decision to treatment initiation. In Scotland, while official data are not available, a large number of patients tend to be diagnosed through national screening, others with symptoms are sent by general practitioners. According to one interviewee, HER-2 positive patients are mostly referred by general practitioners since these breast cancers are more aggressive and more likely to have a palpable lump. Screening on the other hand is more likely to detect smaller breast cancer cases which are HER-2 negative. The NHS Scotland has set two standards for waiting times in cancer care, the 62 day standard and 31 day standard. The first target is that 95% of patients with a suspicion of cancer wait a maximum of 62 days from referral to first cancer treatment (ISD 2016a). This was met for 96.9% of all breast cancer (all cancer types 89.7%) during the time period 1 April to 20 June 2016 (ISD 2016a). The second target is that 95% of all patients should not wait more than 31 days from the time

a treatment decision is made to actual treatment start (ISD 2016a). During the time period 1 April to 20 June 2016, this target was met for 96.9% of all breast cancer patients (all cancer types 95.7%) (ISD 2016a).

6.4.3.3 Clinical guidelines

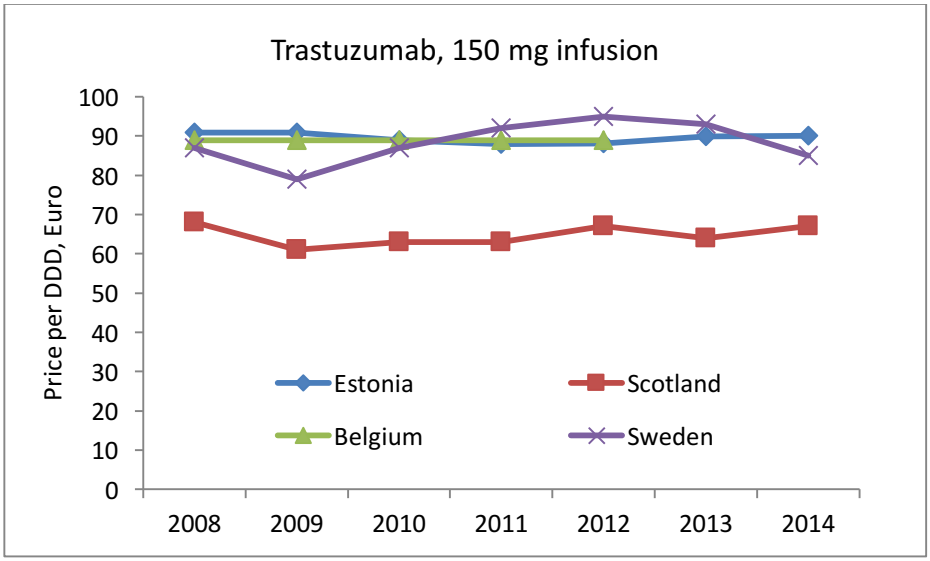
All countries apart from Estonia have national treatment guidelines in place (Wildiers et al. 2013, Scottish Intercollegiate Guidelines Network (SIGN) 2013, National Board for Health and Welfare 2014). In Belgium and Scotland these are clinical guidelines whereas in Sweden they are meant for managerial purposes particularly to guide resource allocation decisions. However, they may be used to guide clinical decision too. All six regions of Sweden have developed their own adaptation of the national guidelines (e.g. Regional adaptation Southern Sweden (Sydsvenska Bröstcancergruppen 2016)). These contain more details in terms of clinically relevant information for administering treatment and are expected be in line with the national guideline. Regional guidelines are also more often updated than the national guideline to reflect introduction of new treatments. The national clinical guidelines contain detailed information on early breast cancer and early metastatic breast cancer but are less detailed about the treatment of late metastatic breast cancer. As a result, there is more variation across the country in the treatment of late metastatic breast cancer while treatment of early breast cancer is much more uniform. Estonia follows the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines whose implementation is adapted to meet local budgetary requirements. For example, in Tallinn there is hospital level consensus practice on when to perform examinations, when to administer adjuvant treatment as well as initiation and discontinuation criteria for chemotherapy which may differ from NCCN or EMSO guidelines. Tartu has developed its own hospital guidelines based on ESMO and NCCN and adapted to the local context and budgetary possibilities (e.g. number of therapy regimens). In Belgium hospitals also develop their own guidelines based on the national guidelines and reimbursement status of medicines. Similar to Sweden, this is done to keep in line with the entry of new medicines as national guidelines are updated less frequently. Due to limited international consensus on treatment of metastatic breast cancer and the number of possible treatment options available, treatment practice varies across the country. Overall, it is common practice to start with the most effective therapeutic option available. If there is more than one option, the treatment causing fewer side effects is the preferred choice. All treatment decisions take into account the patient's age, any co-morbidities, and patient's preferences. There are three cancer

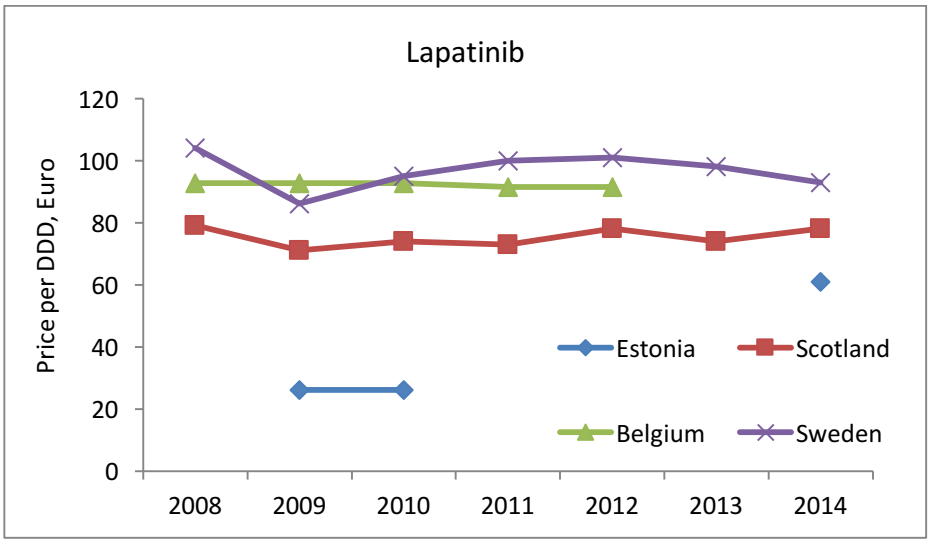
networks covering different geographical areas of Scotland. Hospitals use their regional cancer network guidelines which are based on national and international guidelines and local clinical practice.

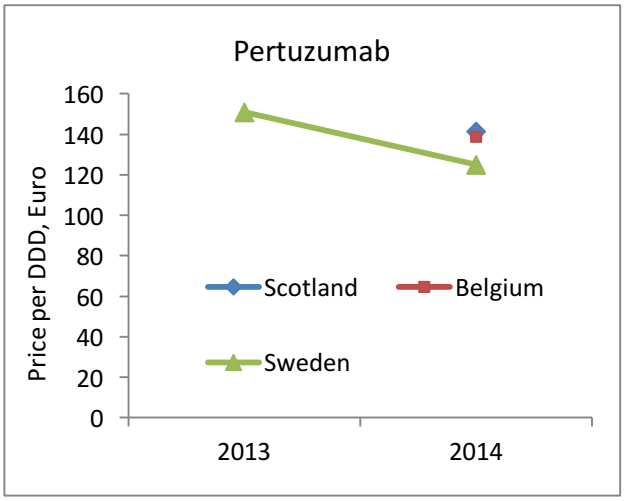
6.4.3.4 Pricing and reimbursement

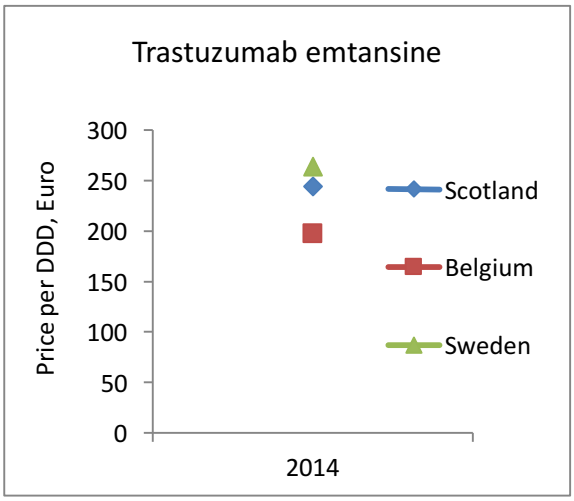
Belgium and Estonia use external reference pricing to inform pricing decisions, while Sweden uses value-based pricing. Free pricing applied in the United Kingdom until 2014 subject to Pharmaceutical Price and Regulation Scheme restrictions including a 40% return on capital limit (Department of Health 2008). Figure 13 shows the prices for HER-2 medicines in the four study countries. These are based on expenditure and volume (DDDs) information in Belgium, Estonia, and Sweden. For Scotland, these figures reflect list prices from the British National Formulary and as such, not include confidential discounts which may be offered by manufactures. Further, both pertuzumab and trastuzumab emtansine were part of confidential price agreements in Belgium and Sweden but further confidential discounts could potentially be offered to hospitals in all countries.

Figure 13: Relative prices









All countries use health technology assessment (HTA) and budget impact analysis to determine the reimbursement status of new medicines. There were nine indications of trastuzumab with EU-wide approval as of December 2014, four for early breast cancer, four for metastatic breast cancer and one for metastatic stomach cancer. Eight were accepted for reimbursement in Sweden (in Sweden, these were included in national treatment guidelines and widely used), seven in Scotland, five in Belgium and two in Estonia as of December 2014 (Table 15). There were three indications of lapatinib with EU-wide approval as of December 2014. Three were reimbursed in Sweden, two in Belgium and zero in Estonia and Scotland as of December 2014. One indication of pertuzumab for metastatic or locally recurrent breast cancer had EU-wide approval and was reimbursed only in Belgium and Sweden as of December 2014. One indication of trastuzumab emtansine had EU-wide approval and was reimbursed only in Belgium and Sweden as of December 2014.

In Scotland, the views of patient representatives were included through the Patient and Clinician Engagement (PACE) process during the appraisal of trastuzumab in combination with capecitabine or fluorouracil and cisplatin for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. This ultra-rare indication (SMC uses this term for medicines used to treat conditions with a prevalence of 1 in 50,000, or less, or a maximum of 100 people in Scotland (SMC 2016b)) was recommendation for restricted use. In contrast pertuzumab and trastuzumab emtansine were not recommended even though the views of PACE group were taken into account (SMC 2014a, b). Another example of how patient have influenced access to HER-2 targeted therapies in Scotland is the case of a Scottish nurse, who, after being denied access through an individual patient request, wrote a letter to the Scottish First Minister asking for access to trastuzumab emtansine in 2016 (BBC 2016). The case was picked up the media and the former nurse was eventually granted access. Meanwhile the Government reported to have requested the manufacturer to resubmit an application to the SMC at ‘a fair price’ (BBC 2016). The hope is that the new price will improve the cost-effectiveness of the medicine to a level that SMC can make a positive recommendation for use and enable access to all eligible patients (BBC 2016).

Table 15: Recommended indications for use based on reimbursement recommendations and clinical practice

Stage	EU-wide approved indications	In combination with	Reimbursement as of December 2014				Clinical guidelines / practice			
Trastuzumab (Herceptin®)			BE	EE	SCOT	SE	BE	EE	SCOT	SE
early	following adjuvant chemotherapy with doxorubicin and cyclophosphamide	paclitaxel or docetaxel	x	√	√	√	x	√	√	√
	following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)	-	x	√	√	√	x	√	√	√
	in combination with adjuvant chemotherapy	docetaxel and carboplatin	x	√	√	√	x	√	√	√
	in combination followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter	neoadjuvant chemotherapy	√	√	√	√	√	√	√	√
metastatic	for the treatment of those patients who have received at least two chemotherapy regimens including at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone-receptor-positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments;	-	√	√	√	√	√	√	√	√
	in combination for the treatment of those patients who have not received chemotherapy and for whom an anthracycline is not suitable	paclitaxel	√	√	√	√	√	√	√	√
	in combination for the treatment of those patients who have not received chemotherapy	docetaxel	√	√	√	x	√	√	√	√

Stage	EU-wide approved indications	In combination with	Reimbursement as of December 2014				Clinical guidelines / practice			
	in combination for the treatment of postmenopausal patients with hormone-receptor-positive metastatic breast cancer, not previously treated with trastuzumab	an aromatase inhibitor	x	x	x	√	x	x	x	√
metastatic stomach	only used in combination	cisplatin and either capecitabine or 5-fluorouracil (other anticancer medicines)	√	√	x		√	√	√	√
lapatinib (Tyverb®)			BE	EE	SCOT	SE	BE	EE	SCOT	SE
advanced or metastatic	in combination for patients with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting	capecitabine	√	x	x	√	√	x	x	√
metastatic	in combination for post-menopausal women with hormone-receptor-positive metastatic disease, not currently intended for chemotherapy	with an aromatase inhibitor	√	x	x	√	√	x	x	√
	in combination for patients with hormone-receptor-negative metastatic disease that has progressed on prior trastuzumab therapy or therapies in combination with chemotherapy	trastuzumab	x (may be reimbursed in very special situatio	x	x	√	x (may be used in very special situations)	x	x	√

Stage	EU-wide approved indications	In combination with	Reimbursement as of December 2014				Clinical guidelines / practice			
			ns)							
pertuzumab (Perjeta®)			BE	EE	SCOT	SE	BE	EE	SCOT	SE
metastatic or locally recurrent	Only used in combination	trastuzumab and docetaxel (other cancer medicines)	√	x	x	√	√	x	x	√
locally advanced, inflammatory, or early stage	Neoadjuvant, only used in combination	trastuzumab and chemotherapy	x	x	x	√	x	x	x	√
ado-trastuzumab emtansine (Kadcyla®)			BE	EE	SCOT	SE	BE	EE	SCOT	SE
locally advanced or metastatic	the patient received prior therapy for locally advanced or metastatic disease	-	√	x	x	√	√	x	x	√
	the patient developed disease recurrence during or within six months of completing adjuvant therapy	-	√	x	x	x	√	x	x	√

Notes: recommended/used (√), not recommended/not routinely used (x); Belgium (BE), Estonia (EE), Scotland (SCOT), and Sweden (SE). In Estonia, no negative decisions are made for hospital medicines, either a positive decision is made or no decision at al

6.4.3.5 Financing

In Sweden the 21 county councils are responsible for funding medicines used in hospitals. The budget for hospitals is set each year. Medicines recommended for use by the NT-council (a body representing all the Swedish county councils) are generally funded by the county councils which, through the six regions they belong to, are represented in the NT-council. After a positive decision by the NT-council, the time new medicines are made available to patients differs across county councils. Generally within a maximum of one year the new medicine is made available in all counties. So far, the NT-council has released its first recommendation for a cancer medicine in 2012, the exact oncology indications recommended by the NT-council are funded by the county councils without imposition of additional restrictions. In the Västra Götaland region a special budget was set up to fund new cost-effective medicines for the first two years after they have been introduced (Cancerfonden 2015). At the end of the two years the hospitals are expected to take over the financing of these medicines. By the end of this time period, the new medicine is expected to have either replaced another treatment, generated savings on other procedures, reduced its use from when it was first introduced due to side effects and/or reduced effectiveness in clinical practice, or justified an increase in the hospital budget for medicines. Hospitals in the Västra Götaland region can apply twice per year for additional budget although the NT-council releases new recommendations more frequently. Options are currently discussed to align funding applications with the release of positive NT-council recommendations to avoid delays due to financial constraints in introducing new medicines. Before additional funding is made available for new medicines, a period of less than six months, if the hospital cannot otherwise fund the new medicine it may be necessary to prioritise access to the new cancer medicine for patients which, based on clinical criteria, are most likely to benefit from the treatment. In Sweden, co-payments only apply to medicines dispensed in the outpatient sector up to a limit of SEK 2,200 (approximately EUR 233) per year for all medicines purchased (TLV 2016b). Until September 2013, only lapatinib was available in a formulation suitable for community use (tablets). As of September 2013, trastuzumab is available as subcutaneous injection. Nevertheless, dispensing in the community for subcutaneous trastuzumab was negligible between September 2013 and December 2014 (32 DDD community pharmacies *vs.* 42,928 DDD hospitals). In Sweden, most cancer medicines are paid by hospitals independently of where they are dispensed and administered.

In Estonia, Scotland and Sweden, medicines are paid from fixed hospital budgets, while in Belgium cancer medicines are retrospectively reimbursed. No co-payments for cancer medicines apply in Belgium, Estonia and Scotland. In Estonia, hospitals have annual contracts with the Estonian Health Insurance Fund for a certain volume of services to be provided, including cancer care. If hospitals overspend, there is negotiation with the Insurance Fund who may, depending on budget availability, cover part of the excess spending the remaining to be covered by the hospital. A prospective payment with tariffs for different types of oncology treatments (e.g. a course of breast cancer chemotherapy) - which also specifies the treatment regimens which can be used – is in place in Estonia. There is currently a unique tariff for breast cancer chemotherapy. The introduction of two payment tariffs, one for HER-2 positive patients and one for HER-negative patients is envisaged for next year to reflect their different costs. The current average reimbursement price works well for breast cancer chemotherapy, in other areas (e.g. colorectal cancer) it is more challenging to provide treatment within existing tariff due to the high cost of biologic medicines in this therapeutic area. These tariffs are updated as applications for inclusion of new medicines to the inpatient service list are made. However, assessment usually takes several months so there can be a delay in updating tariffs to reflect the entry of new medicines. In the interim, hospitals need to manage within existing budgets and reallocate savings from one cancer area to another where possible. It is not common for hospitals to fund medicines that are not reimbursed by the health insurance. That said there is some flexibility to reallocate patients between different indications of a reimbursed medicine as long as hospitals stay within the overall budget. If a medicine is not reimbursed the only other options for patients access is via occasional special early access programmes based on donations from the pharmaceutical industry (e.g. there was such programme in place for lapatinib but only covering a limited number of patients for a specific timeframe), through the support of a private Estonian foundation which covers the cost of non-reimbursed medicines for a limited number of patients or by paying out-of-pocket. When dealing with limited financial resources to make new medicines available, including trastuzumab, clinicians try, to the extent possible, to allocate treatment according medical criteria and the ability to benefit (considering for example the age of the patient and existing co-morbidities). These decisions are always taken as part of multidisciplinary group meetings.

In Belgium, cancer medicines fall under ‘Category A” of vital medicines together with diabetes and HIV/AIDS medicines (INAMI-RIZIV 2016b). As such they are excluded from

prospective funding (75% prospective budget and 25% retrospective reimbursement), which other hospital medicines are subject to. There are therefore no budget limits on prescribing of hospital cancer medicines as long as they are prescribed for reimbursed indications. If a medicine is not yet reimbursed patients may access it through compassionate access programmes funded by the pharmaceutical industry (until a reimbursement decision is made), or, more rarely, due to timelines and uncertainty about the percentage of reimbursement, through a public solidarity fund for patients with high medical need (partial funding, the patient needs to co-pay). Hospitals do not fund not reimbursed medicines out of their own budget. A system of prior-authorisation is in place in Belgium whereby the hospital pharmacist has to confirm that the medicine is given for a reimbursed indication.

In Scotland, medicines approved by the SMC are automatically included in the hospital formulary for the approved indication/s. If a medicine has not yet received a recommendation by the SMC or has received a negative recommendation, the treating oncologist can submit an individual patient request for access. A committee within the hospital will then decide whether or not to grant access on an individual patient basis. There are no limits to prescribe medicines-indications included in the hospital formulary but for individual patient requests funding considerations may play a role.

No HER-2 targeted therapies were dispensed in the community in Belgium, Estonia and Scotland as of December 2014. While pertuzumab and trastuzumab emtansine require intravenous infusion, there are two EMA approved formulations of trastuzumab for subcutaneous use (approved 23 June 2013), one of which comes as cartridge, to the other as intravenous injection, and lapatinib comes in tables for oral use. There was no use of subcutaneous injections in Estonia as of December 2014, use of this formulation started in January 2014 in Scotland (hospital only), in 2014 in Belgium and in September 2013 in Sweden.

6.4.3.6 Patient

I did not find any study comparing age and stage at diagnosis across the study countries so I relied on statistics produced by each country. As a result, the interval used to monitor time trends as well as the metric for staging differs. Nevertheless, some common trends can be observed across countries. All countries experienced a reduction in late stage detection and an increase in early stage detection. In Belgium between 2004 and 2013, there was an average

annual 0.5% decrease in the number of patients diagnosed at stage IV and a 12.5% decrease in the number of unclassified cases (Belgian Cancer Registry 2015). At the same time, the number of cancer cases detected at stage I increased by 2.3% on average per annum (Belgian Cancer Registry 2015). In Estonia, during the period 1995-1999, 12% of cases were diagnosed with distant spread, 8% were unclassified and 34% were localised (Baburin et al. 2014). In 2005-2007, 8% of newly diagnosed cases showed distant spread, 3% were unclassified and 43% were localised (Baburin et al. 2014). In Scotland, during the period the 2-year period 2011-2012, 6% of patients were diagnosed at stage IV, 5% were unclassified and 39% were diagnosed at stage I (ISD 2016b). During the 2-year period 2013-2014, there was a small reduction in the percentage of patients diagnosed at stage IV, to 5% of all new cases and of the percentage of unclassified cases, 4% (ISD 2016b). There was also a small increase in the percentage of patients diagnosed at stage I to 40% of all new diagnosed cases (ISD 2016b). Side-effects and treatment response can affect treatment continuation. The frequency with which such events occurred in the study countries was not available to me.

6.5 Discussion

This study tried to shed some light on factors affecting access to cancer medicines in Europe using the example of HER-2 targeted therapies for breast cancer in four European countries. While focusing on breast cancer, the proposed framework can be easily adapted to other therapeutic areas. The study demonstrates that a positive reimbursement decision is a necessary but not sufficient condition to ensure equitable access to cancer medicines. The following factors were found to be equally important: the ability to identify suspected cases early, promptly refer them for diagnosis, and then provide treatment; the way cancer is treated and financed.

In particular, this study identified the following key determinants of differences in use of HER-2 targeted therapies in Belgium, Estonia, Scotland, and Sweden. These include whether a particular medicine-indication is covered by the national health care system, flexibilities in prescribing non-reimbursed indications of a medicine for which some other indications are reimbursed, financing of medicines at hospital level, availability of alternative access options of non-reimbursed medicines, and the ability of the health care system to identify breast cancer cases and promptly treat them.

Use of trastuzumab beyond progression seems to be the key driver of the variation in utilisation observed between Belgium and Sweden at the high end and Estonia and Scotland at the low end. The patent for Herceptin® in Europe expired on July 2014 (Derbyshire 2015). Yet, no biosimilar medicine has yet appeared on the market in the countries studied. A biosimilar is currently marketed by the South Korean biotechnology company Celltrion in South Korea and the company has filed marketing authorisation request to the EMA in October 2016 (GaBi 2016). This was preceded by the application of Biocon and partner Mylan to the EMA in August 2016 (Taylor 2016). When the first biosimilar medicines of trastuzumab will enter the European market, and, if barriers limiting their use are lifted or at least reduced (e.g. limitations affecting substitution), there will be competition in a previously monopoly market. This will ultimately reduce the price of trastuzumab. This price reduction will improve the cost-effectiveness of the medicine and make it more affordable. At the moment, what limits the use beyond progression in Estonia and Scotland are financial constraints (fixed payment system per case in Estonia which does not cover for continuation of treatment beyond progression) and lack of cost-effectiveness in Scotland. As such, it is reasonable to expect that in the light of the evidence supporting use of trastuzumab beyond progression (Waddell et al. 2011, Von Minckwitz et al. 2009, Stemmler et al. 2005, Bartsch et al. 2007, Ménard and on behalf of the Demetra Group 2008), Estonia and Scotland may start to use the medicine in this indication following a price decrease for trastuzumab due to biosimilars entry.

Screening is an essential component of national cancer strategies and plays an important role in reducing the burden of cancer mortality. A meta-analysis of 11 randomised controlled trials with 13 years of follow-up estimated a 20% reduction in breast cancer mortality in women over 50 years old invited for screening (Marmot et al. 2013). Key factors affecting this estimate were participation and rescreening rates (Marmot et al. 2013). Although in recent years, the burden of breast cancer in Estonia has transitioned towards the high incidence–low mortality type model, overall breast cancer incidence is much lower in Estonia than in more affluent European countries and mortality from breast cancer is still relatively high, particularly among elderly women (Baburin et al. 2016). While stage and tumour size at diagnosis have improved over time, still breast cancer is diagnosed relatively later in Estonia (Baburin et al. 2014). Low coverage (only insured women aged 50-62 years old) and uptake (62% of invited women) of the national screening programme and limited awareness (public campaigns for screening targeting the age group 50-62 years old send them message that it is

only this age group who is at risk) are likely to be important contributing factors to low incidence rates and late stage at diagnosis. Of course low incidence could also be, in part, explained by differences in genetic background, a risk factor for cancer. However, if a number of breast cancer patients remain underdiagnosed, Estonian patients could be worst off in terms of access despite consumption of trastuzumab per new case in Estonia is very similar to Scotland. Hence improving survival in Estonia will need to look beyond, without neglecting, access to new cancer medicines and take measures to increase the number of breast cancer cases which are diagnosed and focusing on improving early diagnosis.

Currently there are no budgetary limitations of prescribing of cancer medicines in Belgium. Things are likely to change in the future as budgetary pressure keeps growing due to entry of new and expensive medicines, particularly biologics. A study projected that by 2020, the budget for oncology will need to more than double – from 454 million in 2014 to 1.124 billion in 2020 - to enable access to innovative targeted and immunotherapies (Van Dyck et al. 2016). Existing price reductions can only fund 24% of the needed additional budget over the next five years calling for urgent measures to address this funding gap (Van Dyck et al. 2016). Unless measures are taken to generate efficiencies (e.g. disinvestment, greater use of generic and biosimilar medicines) and the total budget for oncology medicines is increased (Van Dyck et al. 2016), current levels of access may not be guaranteed anymore. However, Belgium has already taken a number of steps towards ensuring continued high level of access. For example, a payback system is in place since 2006 to promote responsible use of medicines and prevent unexpected expenditure due to higher than forecasted volume, contracting between the INAMI-RIVIZ and industry to deal with issues of uncertainty around therapeutic value and budget impact which ensures reimbursement at the conditions agreed in the contract for a period of 1-3 year, and reassessment of clinical evidence and/or budget which could lead to a change in the reimbursement modalities after revision. Further, together with the Netherlands, Belgium is one of the founding members of Belenuxa, a voluntary collaboration between competent authorities in the area of horizon scanning, HTA and procurement, including pricing negotiation for new medicines (Ferrario, Kanavos, et al. 2016a). Sweden is part of a similar voluntary collaboration called the Nordic Pharmaceutical Forum. These represent opportunities to work with other countries towards sustaining high levels of access, and improving access where needed, to new medicines. In the United Kingdom, a newer addition to the 2014 Pharmaceutical Pricing Regulation Scheme (PPRS) - a voluntary agreement between the pharmaceutical industry and the Department of Health -

was the branded medicines spend cap (sometimes referred to as pay back policy). In Scotland, the money paid back from companies via the PPRS is being put into the New Medicines Fund (set up in 2013 as the Rare Conditions Medicines Fund) that is helping fund treatments for end-of-life and rare conditions.

This study has various limitations. For example, I adjusted utilisation (measured in DDDs) by the number of new cases in a particular year. Ideally, I would have wanted to adjust utilisation by the number of patients treated but this was not possible due to lack of data. Further, due to lack of data on prescribing by indication, I could not account for utilisation of trastuzumab for the treatment of stomach cancer. However, this is unlikely to be substantial due to the lower incidence of metastatic stomach cancer. Due to lack of data on patient diagnosis and prescribing decision, this study could not make any inferences on the appropriateness of prescribing. However, this was not the aim of the study, neither to judge quality of care. Instead, it aimed to identify possible determinants for variations in use of HER-2 targeted therapies.

6.6 Conclusions

Differences in use of lapatinib, pertuzumab and trastuzumab emtansine are driven by various factors including, but not limited to, lack of reimbursement in some countries (Estonia and Scotland). Trastuzumab is reimbursed in all countries and all new breast cancer patients are tested for HER-2 overexpression and prescribed trastuzumab if the tumour is invasive and larger than 1 cm or smaller but with risk factors. Yet, important differences exist in use of trastuzumab (DDD per new case) between countries with higher consumption (Belgium and Sweden) and countries with lower consumption (Estonia and Scotland). This seems to be driven by differences in the use of trastuzumab beyond progression (only used in Belgium and Sweden). Estonia has a comparatively low incidence of breast cancer, the least comprehensive national breast cancer screening programme and, despite progress, patients are diagnosed relatively late. If indeed a number of breast cancer cases are not diagnosed, Estonian patients could be worst off in terms of access despite similar levels of usage per patient to Scotland.

7 Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden (Paper 4)

7.1 Summary

Managed entry agreements are a set of instruments used to reduce the impact of uncertainty and high prices when introducing new medicines. In this chapter I develop a conceptual framework for these agreements and test it by exploring variations in their implementation in Belgium, England, the Netherlands and Sweden and over time as well as their governance structures. Using publicly available data from health technology assessment bodies and a survey I conducted with the European Medicines Information Network, I develop a database of agreements implemented between 2003 and 2012. I also conduct a review of governance structures for these agreements. In December 2012 there were 133 active MEAs for different medicine-indications across the four countries. These corresponded to 110 unique medicine-indications. Over time there has been a steady growth in the number of agreements implemented, with the highest number in the Netherlands in 2012. The number of new agreements introduced each year followed a different pattern. In Belgium and England it increased over time, while it decreased in the Netherlands and fluctuated in Sweden. Only 19 (17%) of the unique medicine-indication pairs identified were part of an agreement in two or more countries. England uses mainly discounts and free doses to influence prices. The Netherlands and Sweden have focused more on addressing uncertainties through coverage with evidence development and, in Sweden, on monitoring use and compliance with restrictions through registries. Belgium uses a combination of the above. Despite similar reasons being cited for managed entry agreements implementation, only in a minority of cases have countries implemented an agreement for the same medicine-indication; when they do, a different agreement type is often implemented. Differences in governance across countries partly explain such variations. However, more research is needed to understand whether e.g. risk-perception and/or notion of what constitutes a high price differ between these countries.

7.2 Introduction

A combination of high prices of new patented medicines, uncertainties relating to their clinical effectiveness and use in real life represent a dilemma for decision-makers and a potential barrier to access. These challenges, complemented by patients' demand for fast access to new medicines, have prompted countries to find ways to manage the introduction of new medicines and limit the impact of high prices and uncertainty. One way decision-makers are trying achieve this, is by implementing a heterogeneous group of instruments known as 'managed entry agreements' (MEAs) (Klemp et al. 2011).

The nature of MEAs can be very different between and within countries; some are conditional reimbursement decisions subject to reassessment of the relevant technology. Coverage with evidence development (CED) agreements require the manufacturer to provide additional data on a medicine's performance in real-life. This is common requirement of the Swedish Dental and Pharmaceutical Benefits Agency (TLV). For ropinirole (a medicine for the treatment of moderate to severe idiopathic restless legs syndrome) for example, the available data on the long-term effects and side-effects of the medicine when it was first assessed were deemed insufficient because of large uncertainty around the cost per QALY. The medicine was therefore provisionally listed, on condition that the manufacturer would provide an updated economic model with real-life evidence (TLV 2006). The review showed that the medicine was not cost-effective at the current price and a small price reduction was implemented to keep the medicine on the reimbursement list (TLV 2012).

Other agreements represent a final coverage decision conditional on the provision of a MEA. When bortezomib (a medicine for multiple myeloma) was first assessed by the National Institute for Health and Care Excellence (NICE) in England, it was found to be effective but not cost-effective with an estimated incremental cost-effectiveness ratio (ICER) of GBP 38,000 per quality adjusted life year (QALY)(NICE 2006). The willingness to pay for a QALY in England is broadly known to be up to GBP 30,000 unless end-of-life criteria apply. Following a reassessment of the medicine and the proposal of a payment by result agreement by the manufacturer including treatment interruption if the medicine does not achieve the expected response after four treatment cycles and reimbursement for failure, the ICER declined to GBP 20,700 and the medicine was recommended for use within the national health service (NICE 2007).

Agreements are often divided into financial and health-outcome based agreements. The previous two examples would fall under the latter group although they both can have financial consequences. Purely financial agreements include price-volume agreements (PVAs) and dose/time capping schemes. PVAs define a threshold of expenditure after which a rebate is triggered and aim to limit budget impact or introduce certainty about a budget not being overrun. Capping schemes involve the establishment of either a time or dose cap after which the manufacturer pays for any additional doses required. This was the case for ranibizumab (for age-related macular degeneration) for which the manufacturer agreed to pay for any patients requiring more than 14 doses per affected eye (the scheme has now changed into a simple discount scheme following the introduction of a discount-based MEA for the diabetic macular oedema indication of ranibizumab) (NICE 2008).

Defining MEAs is often complicated by the use of country-specific terms to define them, the context in which they operate and the different views as to what constitutes a MEA. In the United Kingdom (UK) they are known as patient access schemes (PAS), Belgium uses the term conventions, while they are not known under a specific name in Sweden. In the Netherlands they were initially part of funding policies to improve access to expensive hospital and orphan medicines (2006-2011) and referred to as 'conditionally allowed specialist medicines' (CVZ 2012b). Despite their diversity, MEAs have a common denominator, namely to facilitate access to new medicines in a context of uncertainty and high prices.

The body of evidence on MEA implementation to date is weak. Apart from exploring the impact of MEA from a theoretical economic perspective (Gandjour 2009, Zaric and O'Brien B 2005, Zaric and Xie 2009, Barros 2011), few studies presenting cross-sectional evidence across settings exist (Carlson et al. 2010, Stafinski, McCabe, and Menon 2010, Adamski et al. 2010, Carbonneil et al. 2009, Ferrario and Kanavos 2013); only one attempts an analysis of the therapeutic focus (Ferrario and Kanavos 2013), while another presents longitudinal data on MEAs for orphan medicines (Morel et al. 2013). Further, there are very few studies on the impact of MEAs (Willis et al. 2010, Pickin et al. 2009, Russo et al. 2010). Finally, there has been no published evidence comparing the different approaches used by countries to improve access and no comparison of governance structures around MEAs with the aim of explaining their implementation patterns.

A number of taxonomies have been proposed for their classification and some of them include only performance based risk-sharing agreements (Carlson et al. 2010, Casado et al. 2009, Jaroslawski and Toumi 2011, Garrison et al. 2013, Towse and Garrison 2010, Launois and Ethgen 2013, Ferrario and Kanavos 2013), as well as evaluation frameworks (McCabe et al. 2010, Garrison et al. 2013, Towse and Garrison 2010). However, there is lack of an analytical framework that enables an understanding of how MEAs modulate key decision-making variables.

The aim of this study is to develop a conceptual framework for MEAs and to test it by exploring variations in MEAs implementation across countries and over time as well as their governance structures.

7.3 Methods

7.3.1 Data sources

Data on the medicine-indication pairs subject to a MEA, the types of MEAs implemented and their governance structures (relevant legislation, policies, guidelines and submission templates) were sourced from websites of HTA agencies, health insurers and governments (NICE 2014b, TLV 2016c, INAMI-RIZIV 2015, Dutch National Health Care Institute 2014). Additional material based on primary data collection on MEA was used from a European survey of MEAs (Ferrario and Kanavos 2013), supplemented by personal contacts with competent health authorities mainly to clarify or complement information retrieved from the data sources described. All MEAs reported by countries, from the date the first official MEA was implemented in each country, up to December 2012, were included in the analysis.

7.3.2 Study design

The study countries include Belgium, England, the Netherlands and Sweden. These were selected because they implement MEAs, have either a publicly available list of MEAs or participated in a recent survey on MEAs (Ferrario and Kanavos 2013), use health technology assessment (HTA) to guide their coverage decisions and have publicly available HTA reports, reflect a diversity in health system organisational structure (tax-based single purchaser systems (NHS) *vs.* social health insurance systems) and different perspective of HTA analysis (health system *vs.* societal perspective). Countries such as Poland or Italy which are well known to implement MEAs could not be included because in the first all

agreements are in commercial confidence and in the second because complete up-to-date data on all MEAs implemented and HTA reports were not available.

I only included MEAs for medicines with nationwide implementation or, in the case of England, MEAs with implementation within the entire devolved administration. For England, we included all PAS listed on NICE's website but we did not include information on PAS for medicines which had either not been reviewed by NICE or for medicines which had been rejected by NICE. Such cases exist (NHS Northern 2013) but may not be implemented across the country. For Sweden, in addition to MEAs concluded by the Dental and Pharmaceutical Benefit Agency (TLV) at national level, we also included agreements concluded by the New Medicinal Therapies group (NLT) at regional level because these have nationwide implementation. I did not consider, as some other studies did (Carlson et al. 2010, Carbonneil et al. 2009), 'only in research' recommendations by NICE to be CED schemes because use of medicines with such recommendation is limited to clinical trials.

7.3.3 Analysis

A database of MEAs in the four study countries was compiled using these data sources. The database includes information on: a) medicines involved in a MEA (brand name, international non-proprietary name (INN), anatomical therapeutic chemical (ATC) classification , therapeutic indication); b) type of MEA (e.g. coverage with evidence development, discount, dose/time-capping, payment by result, PVA and registry if linked to a specific data collection request by the public counterpart on which reimbursement was dependent) based on the European context tailored taxonomy proposed in the EMINet report (Ferrario and Kanavos 2013); c) MEA year of introduction of the MEA and expected year of completion. These data were used to analyse time trends in the number of MEAs implemented over time, the number of new MEAs introduced each year and their therapeutic focus.

The development of the conceptual framework started with a review of the different types of MEAs implemented and the criteria for reimbursement decisions in the four study countries. After identifying the common elements between these two and decomposing the latter in their elements (clinical effectiveness, price and use), the mechanism of action of MEAs was established. The framework was then applied in the four study countries to explore differences in MEAs implementation.

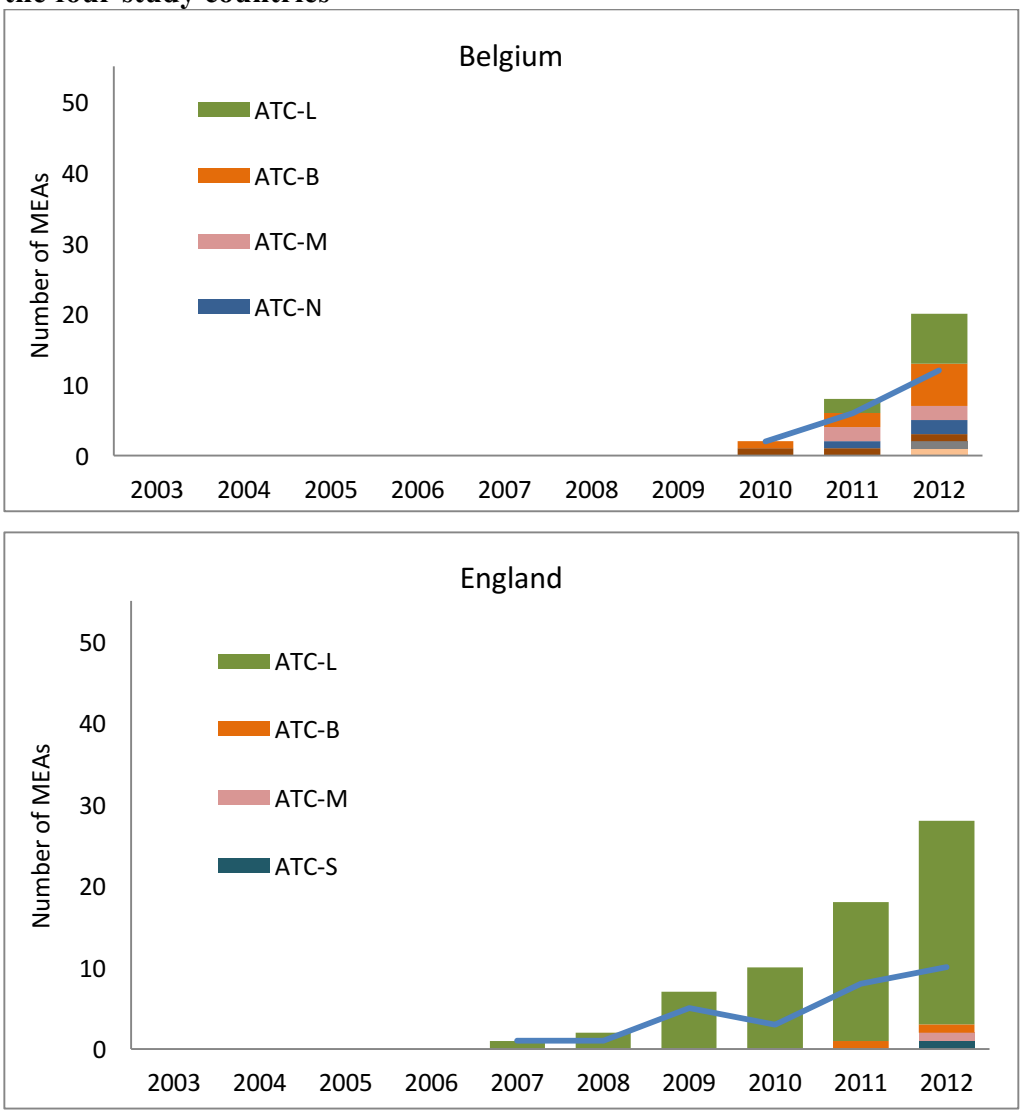
The review of governance structures focused on the objectives countries are pursuing by introducing MEAs, the process for introducing MEAs and the stakeholders involved. This information was then related to the number, types and therapeutic focus of agreements implemented in the study countries to explore possible links.

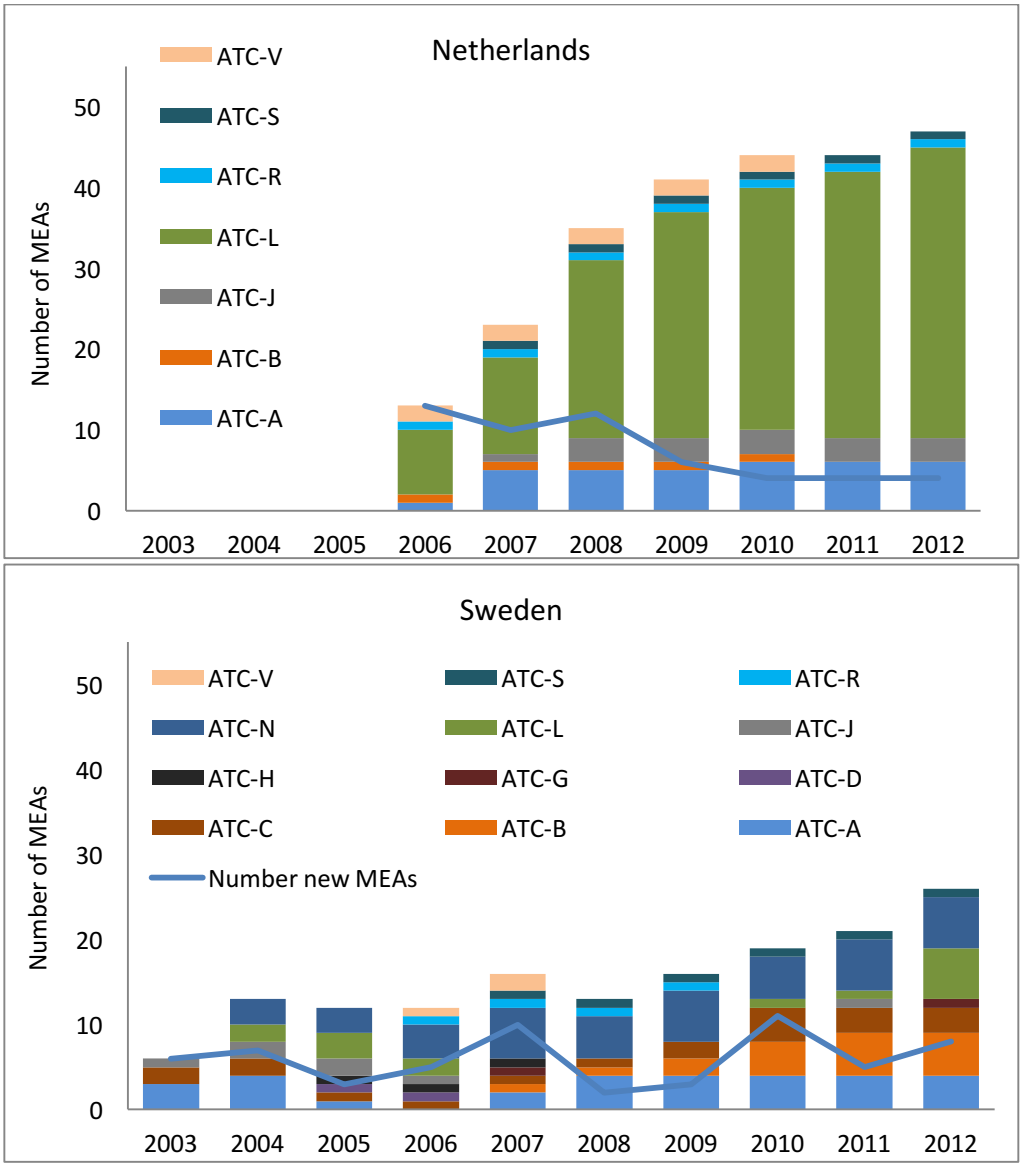
7.4 Results

7.4.1 Trends in MEA implementation over time

Among the four study countries, Sweden was the first to introduce MEAs in 2003 followed by the Netherlands in 2006, England in 2007 and Belgium in 2010. The number of MEAs has grown steadily over time across all countries reaching a peak of 53 active agreements in the Netherlands in 2012 (Figure 14). If we look at the number of new agreements introduced each year we can observe a different pattern. The number of MEAs introduced in the Netherlands has declined between 2008 and 2011, while it has kept increasing in Belgium and England between 2010 and 2012. MEA introduction follows a more irregular pattern in Sweden where peak years (e.g. 2007 and 2010) are followed by a sharp decline in subsequent years.

Figure 14: Trends in MEA implementation since the introduction of the first MEA in the four study countries





Notes: ATC classification: A: Alimentary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Anti-infectives for systemic use; L: Antineoplastic and immuno-modulating agents; M: Musculo-skeletal system; N: Nervous system; R: Respiratory system; S: Sensory organs; V: Various. Source: WHO Collaborating Centre, Oslo, ATC-index 2012.

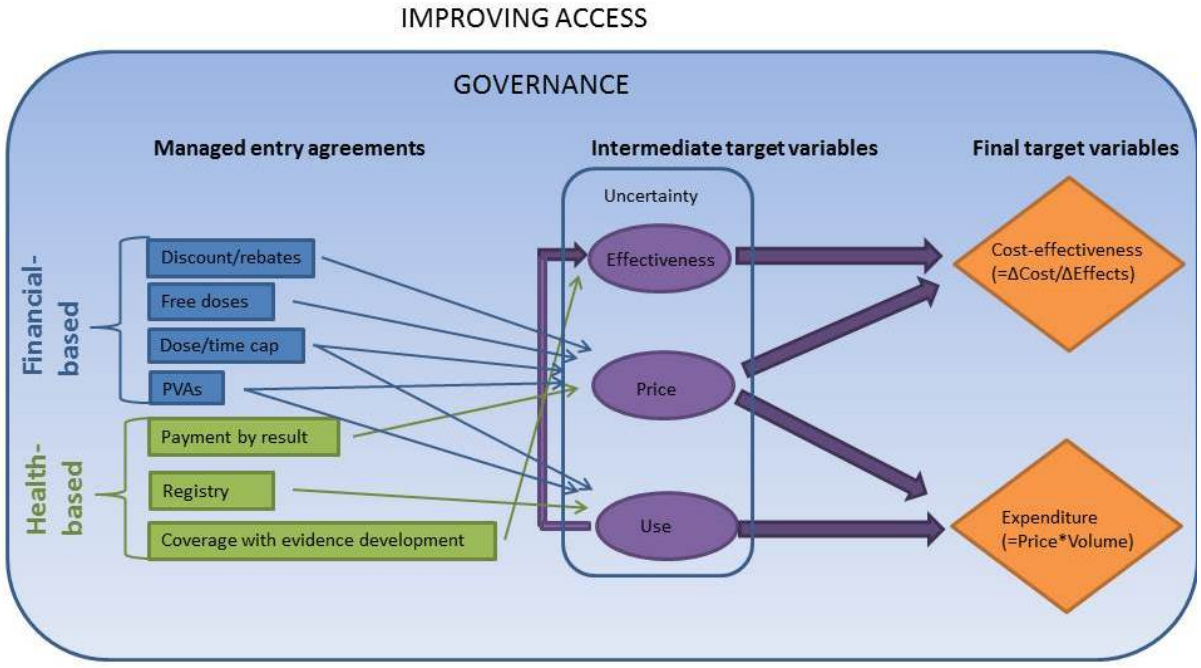
There is a clear focus on MEAs involving antineoplastic and immunomodulating medicines (ATC-L) in England and the Netherlands (89% and 74% of all agreements in 2012 respectively). In Belgium and Sweden, while this preference is less strong, ATC-L is still the therapeutic group with most MEAs in place (35% in Belgium followed by 30% for blood and blood forming organs (ATC-B) and 23% in Sweden for each of ATC-L and nervous system

(ATC-N)). Countries are also implementing MEAs for orphan medicines (5 in Belgium, 7 in England and Wales, 13 in the Netherlands (three of these medicines have lost their orphan status by now but were initially included in the policy on orphan medicines) and in 5 Sweden).

7.4.2 Conceptual framework

Countries mentioned different reasons to engage in MEAs. These include improving access, reducing uncertainty and prices, improving cost-effectiveness and personalising treatment. Access can be seen as the ultimate goal while reducing uncertainty and high prices and personalising treatment as the means to achieve this. The latter can be ascribed to two main policy objectives: improving cost-effectiveness (micro-efficiency) and limiting budget impact (macro-efficiency). To achieve these objectives, countries use a variety of MEAs to influence a set of target variables (effectiveness, price and use), which, in turn, have an impact on cost-effectiveness and budget impact (Figure 15).

Figure 15: Conceptual framework for managed entry agreements



Source: The author

7.4.3 Application of the conceptual framework

The conceptual framework highlights the various ways the four countries studies have used MEAs to influence the three intermediate target variables to improve the two final target variables of cost-effectiveness and/or budget impact.

England uses mainly discounts (16) and free doses (7) to influence one single target variable, price. The stated goal is to improve cost-effectiveness and access but in practice, modulating prices helps at the same time to contain budget impact. In the Netherlands, CED (52 agreements) is extensively used to modulate effectiveness by generating real-life data on the medicine's effectiveness and use. These data will be used to produce a final cost-effectiveness estimate at the end of the agreement's life-time and make a final reimbursement decision. As some of these agreements come to an end, one of these medicines has become part of a payment by result agreement (as of December 2012) (CVZ 2012a) while others are still under evaluation. A limited number of financial pilot arrangements have been concluded by the Ministry of Health and CVZ, thus hinting to a potentially new direction for MEAs in the Netherlands. Similar to the Netherlands, Sweden has a strong focus on reducing uncertainty around cost-effectiveness. This is achieved by implementing CED (20 CED agreements), complemented by monitoring use and compliance with restrictions (9 registries). As a result, some of these agreements also target budget impact although the stated aim is only to address uncertainty affecting cost-effectiveness. The 29 agreements just described were all concluded at national level by TLV. In 2012, three agreements for cancer medicines were brokered by NLT on behalf of the county councils (which then signed individual contracts with the manufacturer). Belgium tends to adopt a combination of financial and health-outcomes based MEAs to limit budget impact and address uncertainty. Different combinations of PVAs, rebates, time cap, CED and registries are employed to target price, use and effectiveness and ultimately budget impact and cost-effectiveness.

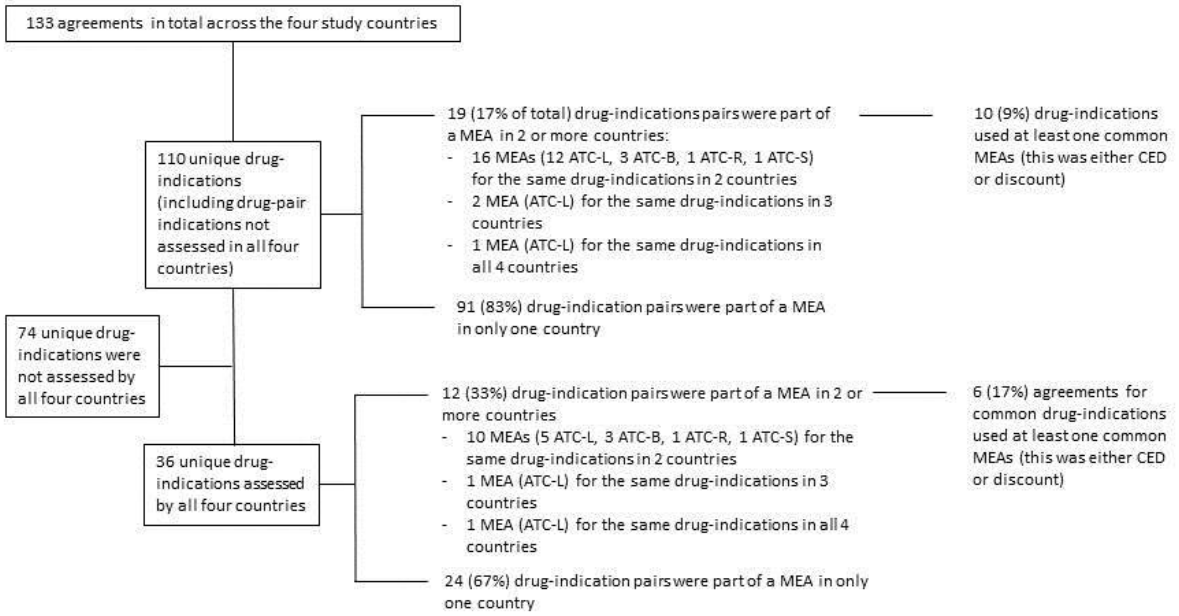
Some of the goals stated by countries may differ from the goals obtained by the application of the conceptual framework. This is because countries will tend to state their main goal for introducing MEAs but not always mention the secondary effects that their action on intermediate target variables can have. For example, the rationale for introducing MEAs in England is to improve a medicine's cost-effectiveness and therefore enable patients to access new medicines (UK Department of Health and ABPI 2008). To achieve this, they mostly introduce discounts, which improve a medicine's cost-effectiveness (i.e. the ICER) bringing it to a value which is within NICE's willingness to pay threshold. However, introducing a

discount will also lead to lower expenditure in comparison to the full price originally asked by the manufacturer. So although not stated in national policy documents, this is an additional impact of introducing discounts.

7.4.4 Differences in the ways countries engage in MEAs for the same medicine

As of December 2012 we identified 133 active MEAs for different medicine-indications across the four countries (Figure 16). These corresponded to 110 unique medicine-indications. Nineteen of these were part of a MEA in two countries, two in three countries and one in all four countries. Reflecting the higher number of agreements for ATC-L in the sample, twelve of the common agreements were for ATC-L, three for ATC-B, one for ATC-R and another for ATC-S. However, not all the 110 medicine-indication pairs identified as part of a MEA in at least one of the four countries underwent HTA in all four countries. If we exclude the seventy-four medicine-indication pairs which did not undergo national HTA in one or more country, the remaining 36 medicine-indication pairs, which were assessed in all four countries, were part of a MEA in one (n=24), two (n=10), three (n=1) and four (n=1) countries.

Figure 16: MEAs for the same medicine-indication across the four study countries



Source: The author

7.4.5 Governance of MEAs and process

The rationale for introducing MEAs features common objectives in the four study countries (Table 16). These include improving access, addressing uncertainty and in some cases improving cost-effectiveness (England) or reducing prices and personalising treatment (county councils in Sweden). In the following tables (Table 16, Table 17), some of the key governance features of MEAs as implemented in the study countries will be reviewed.

Table 16: Objectives pursued by introducing MEAs and legal basis of policy

	Objectives	Legal or policy basis
Belgium	○ Address unmet medical need ○ Provide patient access to promising new medicines ○ To provide manufacturer with an additional option to access the market ○ Manage risk and uncertainties ○ Limit budget impact	○ Law on compulsory health insurance (Royaume de Belgique 21 décembre 2001) and the Royal Decree (RD) (14 juillet 1994).
England	○ Improve cost-effectiveness ○ Facilitate patient access to medicines	○ The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (UK Department of Health and ABPI 2008)
Netherlands	*2006-2011 (expensive hospital and orphan medicine policy[1])* ○ Improve access to expensive hospital and orphan medicines ○ Reduce inequalities *2012-2013 (add-ons policy[2])* ○ Prevent geographical inequalities in availability of DRGs[3] reimbursed medicines between different hospitals *2014 onwards* ○ Ensure fast access by assessing only medicines with budget impact greater than EUR 2.5 million per year	*2006-2011* ○ Expensive medicines and orphan medicines provided the policy framework for introducing CED schemes (Nederlandse Zorgautoriteit) *2012-2013* ○ Add-ons policy (Nederlandse Zorgautoriteit 2012) *2014 onwards* ○ As of December 2013, a new policy specialist medicines is in place (Dupree and Pasman 2013).
Sweden	*TLV* ○ Alleviate uncertainties regarding cost-effectiveness at the point of decision *Country councils* ○ Reduce costs ○ Ensure that treatment is targeted to patients who are most likely to respond to a new medicine	○ In Sweden there is no specific policy or framework for MEAs, however, the possibility of granting reimbursement subject to special reimbursement conditions is described in very generic terms in the Swedish reimbursement system (TLV 2013).

Notes: [1]As part of this policy hospitals received additional funding to cover for 80% and 100% of the cost of expensive hospital and orphan medicines (included in the policy) from the Dutch Healthcare Authority (NZa) respectively. [2]As part of this new interim policy hospitals receive extra funding (add-on) for medicines costing more than EUR 10,000 per patient per year). [3]Diagnostic-related groups (DRGs)

Source: The author based on EMINet survey and personal contacts with competent health authorities

Table 17: The process of implementing MEAs

	Rational for introducing a MEA	Who can propose	Who takes the final decision on whether to approve or reject a proposed MEA
Belgium	Negative reimbursement decision by the commission for reimbursement of medicines (CRM) or no decision by the CRM due to lack of 2/3 majority	The CRM or manufacturer	Minister of Social Affairs and Public Health provided the Minister of Budget approves the MEA
England	The drug is not cost-effective at the current price	Only the manufacturer	The Department of Health
Netherlands	Prior 2012: Expensive hospital and orphan drugs were eligible for additional funding (80% and 100% respectively)	Organisations entitled to submit a medicine for inclusion in one of these two policies could send a request to the Supervisory Boards for Healthcare Insurance (CTZ) and the Healthcare Authority (ZAio)	The Pharmaceutical Assistance Commission (CFH) within the CVZ reviews the medicine and makes a recommendation for inclusion to the CVZ who advises the CTG/ZAio.
Sweden	A MEA can be introduced as part of a conditional reimbursement decision by TLV (CED or registry only) or by the NLT (both financial and health-outcome based)	TLV/NLT and the manufacturer can propose a MEA (though at TLV level is it generally requested by TLV)	TLV or the NLT

Source: The author based on EMINet survey and personal contacts with competent health authorities

An important difference in the way MEAs are implemented in different countries relates to the type of decision and whether it is transitory and, therefore, subject to re-evaluation or permanent, and therefore lasts throughout the period during which a medicine is recommended. In Belgium, the Netherlands (CED) and in Sweden (for MEAs concluded by

TLV), MEAs lead to a temporarily decision to reimburse and the inclusion of a medicine in the reimbursement list is subject to re-evaluation at the end of the agreement's lifetime. This means that if the medicine does not achieve the expected endpoints on e.g. effectiveness, reimbursement could be potentially withdrawn. In England and Sweden (for MEAs concluded by the county councils), MEAs are not linked to a conditional reimbursement decision but are still subject to reassessment as part of the regular re-evaluations conducted by NICE or the county councils.

7.4.6 Do governance elements help explain variations in MEA uptake across countries?

In England there is an explicit focus on improving cost-effectiveness more than addressing uncertainty. This is reflected by the instruments used, predominantly discounts and free doses rather than CED. Belgium mentions limiting budget impact complemented by addressing uncertainty as their main objectives. In an attempt to achieve that, PVAs, rebates and time cap schemes together with CED are implemented. Improving access to expensive hospital and orphan medicines and reducing geographical inequalities in access to these medicines is the main objective in the Netherlands. This was mainly achieved by the additional funding provided as part of the policies on expensive hospital and orphan medicines rather than on the use of CED. However, CED agreements are introduced for medicines with an initial added therapeutic value but an uncertain ICER, which explains the use of CED. In the case of Sweden, the objective of TLV to alleviate uncertainties around cost-effectiveness is clearly reflected in the use of CED and registries (it is worth noting that in Sweden registries are often the enabling factor to implement a MEA, i.e. they were already in place before a MEA was introduced). The use of discounts and registries for agreements concluded by the county councils is also reflected in the objectives the latter are pursuing.

It is difficult to make any links between the rationale of introducing MEAs and the number of existing and new MEAs and the therapeutic focus as the objectives are rather generic and difficult to translate into expected numbers or therapeutic preferences. However, at least in the Netherlands, the objective of reducing inequalities in access to high-cost and orphan medicines made all such medicines eligible for inclusion in the related funding policies. To be included in these policies and receive extra-funding, a medicine had to be subject to outcome research (CED) thus explaining the large number of CED implemented in the Netherlands. Regarding the types of MEAs and their therapeutic focus, they seem more likely to be linked with the rationale for introducing MEAs and the types of MEAs foreseen in the

law and policies on MEAs in the respective countries, rather than on the process for introducing MEAs.

7.5 Discussion

The conceptual framework for MEAs we developed enabled us to highlight differences in the types of MEAs implemented in four European countries. Our comparison of medicine-indication revealed that only in a minority of cases two or more countries engaged in a MEA for the same medicine- indication. When comparing the MEA used for the same medicine-indication, only 10 agreements used at least one common MEA across the two or more countries. Our findings are supported by a study on orphan medicines which found that only nine of the twenty-six orphan medicines part of MEA in either Belgium, England and Wales, Italy, the Netherlands or Sweden were part of a MEA in more than two countries (Morel et al. 2013).

A number of conclusions can be drawn from this analysis. First, while the total number of MEAs implemented in each country has increased over time, the number of new agreements introduced each year has followed a different trend in some countries. Further, we showed how in some countries there is a strong focus on introducing MEAs for antineoplastic and immunomodulating medicines. Second, whereas countries have similar objectives when introducing MEAs, only in a minority of cases are MEAs introduced for the same medicine-indication; and even when this is the case, different MEA types are used. Third, there is generally no clear link between governance around MEAs and the number, types and therapeutic focus of the agreements implemented.

The first finding raises questions about the drivers behind these trends in MEA implementation. Policy changes are unlikely to have played a role. There were no policy changes in Sweden which could have impacted MEA introduction over the time period studied. In England there were two events of relevance. The first was the release in 2009 of a report on the uptake of PAS highlighting the burden on front line health workers in administering these schemes (Williamson 2009). This led to changes in the types of schemes implemented from ex-post rebates to ex-ante price discounts and avoidance of schemes which require performance monitoring. The second was the creation of the Cancer Drugs Fund in 2010 which could have potentially led to a greater propensity not to recommend a medicine if uncertainty was high (since access could still be granted on an individual basis provided the

medicine-indication was to be included in the Cancer Drugs Fund). The policy on expensive hospital and orphan medicines in the Netherlands came to an end in 2011, yet the decline in the number of new MEAs introduced each year commenced after 2008.

In terms of therapeutic focus, the largest proportion of MEAs across all countries is on antineoplastic and immunomodulating products (ATC-L). In Sweden this percentage was only 23% in 2012 which is probably explained by the fact that most of the MEAs currently implemented until 2012 had been concluded at national level by TLV (which makes decisions only for outpatient medicines). However, since the introduction of a national review process for inpatient medicines led by the NLT, three MEAs have been concluded for cancer medicines (out of a total of 9 medicines reviewed between 2010 and 2012) foreshadowing a possible new trend. Another important factor in determining numbers and therapeutic groups is the scope of the MEA policy. This is evident in the Netherlands where the highest number of agreements was observed. To obtain additional funding as part of the Dutch policies on expensive hospital and orphan medicines, manufacturers had to engage in CED. This provided an incentive to manufacturers of expensive hospital products (often belonging to ATC-L group) and orphan medicines, to engage in CED to be included in these policies. In Belgium the focus on ATC-L and ATC-B seems also to be linked with the scope of MEAs, which includes only class I medicines (innovative medicines) for which the manufacturer has claimed an added therapeutic value.

The second finding raises questions as to why significant differences arise across countries for the same medicine. Even acknowledging that different types of MEAs can be used to achieve either better cost-effectiveness or limiting budget impact, this does not explain why they so often implement MEAs for different medicine-indications. Common medicines, assessed by all countries, for MEAs included antineoplastic agents (cabazitaxel, bortezomib, pazopanib, ipilimumab), immunosuppressants (tocilizumab), antithrombotic agents (dabigatran and rivaroxaban), endocrine therapies (abiraterone), immunostimulants (mifamurtide), antihaemorrhagics (romiplostim), antiasthmatics (omalizumab) and ophthalmologics (ranibizumab). More similarities would have been likely to arise if more countries were included. While complete information on MEAs implemented in France is not available, the French Transparency Commission has asked for postlaunch studies to verify whether the medicine performance in real-life in the light of a potential future rebate if this was lower than expected for risperidone (schizophrenia), dipeptidyl peptidase-4 (DPP4)

inhibitors and glitazones (diabetes) (Garrison et al. 2013). DPP4 inhibitors and risperidone were also part of CED Sweden and DDP4 of monitoring registries in Italy (Siviero 2014, Arnberg 2014).

MEAs are not the only instrument to facilitate access to new high cost medicines and this may help explaining some of the identified differences in MEA engagement across countries. In England, the Cancer Drug Fund provides Government funding for medicines which have either not yet been reviewed by NICE or have received a negative recommendation. Belgium also has a special fund to reimburse medicines for rare conditions which would otherwise not be reimbursed (INAMI-RIZIV 2016a). The English Cancer Drugs Fund provides a list of medicines and indications for which clinicians can apply on behalf of their patient. Between April 2013 and March 2014, 21% of all notifications were for non-approved or not reviewed indications of bevacizumab, 16% abiraterone (1st line use, 2nd line is recommended as part of a PAS), 8% bendamustine, 8% for cetuximab (1st line treatment of head and neck cancer, the colorectal cancer indication is part of a PAS) and 5% for everolismus (NHS England 2014). So while in England these medicines-indications were made accessible through the Cancer Drugs Fund, in the Netherlands different indications of bevacizumab and cetuximab are part of CED schemes.

Another way to make medicines available which would not be normally considered as cost-effective is through end-of-life criteria. NICE has specific end-of-life guidance (NICE 2009) and if a medicine is considered eligible to be reviewed under these criteria, higher cost per QALY than the usual willingness to pay threshold would prescribe may be accepted. One example is vemurafenib which was accepted and an ICER between GBP 44, 000- 51,800 (after the application of a confidential discount through PAS) under end-of-life criteria (NICE 2012). If one country applied end-of-life criteria for a medicine while another opts for a MEA, this may also be a reason for the differences identified. However, at least in the case of vemurafenib in England, end-of-life criteria were applied in conjunction with a PAS.
The third finding suggests that the regulatory frameworks around MEAs may partly explain variations in therapeutic focus and overall numbers, but there must be other factors influencing their existence and implementation. One such factor is definitely the time since the first MEA was introduced as indicated by the catch-up effect in (Figure 14). Whether only one party (either the manufacturer or the competent health authority and which authority) is able to propose a MEA could potentially have an impact on the number of MEAs in place.

However, the process of developing a MEA and the benefits for the parties involved are likely to play a more important role. In the Netherlands for example, the manufacturer had a strong incentive to engage in CED to obtain additional funding as part of the 2006-2011 expensive hospital or orphan medicine policy.

Depending on the stakeholders involved and their roles, the process of introducing a MEA varies substantially across countries. In Belgium, the Netherlands and Sweden for example, the introduction of MEAs is a more reactive process. This can only be initiated after the initial assessment as a result of uncertainty or high prices. In England, in addition to the reactive approach, PAS can also be proposed proactively by manufacturers when they make their first submission to NICE. They can also be proposed at the end of the appraisal process although the current trend seems to be for manufacturers to propose them in a proactive way. This is likely due to the fact that NICE decisions are to a certain extent predictable (the willingness to pay threshold is well known to the applicant), meaning that the manufacturer is in a position of judging whether its submission is likely to be successful or not given the cost-effectiveness ratio. The applicant can therefore decide to proactively propose a PAS, which will bring the ICER to a level considered acceptable by NICE, with the obvious advantage of introducing the medicine more quickly into the market than if they had opted for a more reactive approach.

The analysis on the links between governance elements and engagement in MEAs was only of explorative nature given the limited sample size. Despite this limitation, it did permit us to highlight important features of MEAs across the four study countries, such as the similarities of their objectives and conversely, the diversity in the ways countries employ MEAs. This analysis did not include MEAs implemented in only one or a few regions due to the lack of data on most of these agreements. Nevertheless, the analysis did include all MEAs (according to definition presented in the methods section) with nationwide application and which are linked to a HTA.

One issue related to MEA which has not received much attention to-date is the impact of price confidentiality on priority setting and the development of clinical guidelines. In countries such as the UK, where priority setting as part of clinical guidelines is based on the ICER and, while discounts are confidential, the published ICER does incorporate the confidential discount, this does not distort priority setting. However, if these decisions are

based on an ICER which does not incorporate the discount given on the list price, this can have a distortionary effect. Further, even in countries where the ICER does incorporate the confidential discount, the problem remains for comparator medicines as the competitor manufacturer does not officially know the amount of the discount and can only submit a best estimate (usually including some sensitivity analysis with different prices) of the ICER of the new medicine. A survey among policy makers in Canada highlighted the various potential threats in countries in which MEAs are negotiated at subnational level and rebates are confidential (Morgan et al. 2013b) . These include inequities in medicines pricing and coverage across regions and, where pharmaceutical coverage is not universal, the issue of uninsured or underinsured patients not being able to benefit of the lower price negotiated by the health insurance plan (Morgan et al. 2013b). Similarly, price confidentiality means it is not possible to assess the impact of financial agreements on price and budget impact as highlighted for the case of post-launch studies in France (Garrison et al. 2013). This issue of price confidentiality is part of broader debate on implementing differential pricing to facilitate access to new high cost medicines in less wealthy countries. Opinions on how this should be best achieved, particularly on the need, strongly advocated by industry, for price confidentiality are currently divided (Kalo, Annemans, and Garrison 2013, Ridley 2005, EFPIA 2014, Danzon, Towse, and Mestre-Ferrandiz 2015).

Finally, another issue is the use of different pricing and/or reimbursement arrangements for different indications of the same medicine. In England and Scotland there has been an attempt to minimise this problem by requiring manufacturers offering a simple discount for a particular indication, to apply the same pricing conditions to all current and future indications of that particular medicine. This applies, irrespective of whether these other indications are recommended or not by NICE or SMC, including NICE not recommended indications available through the CDF, as long as the medicine is purchased by the NHS. Different approaches across indications may arise for medicines with PAS other than simple discounts which are a minority. For example, bortezomib for multiple myeloma in patients at first relapse is part of a response scheme in England. However, other indications are not part of scheme and only available through the Cancer Drugs Fund (e.g. treatment of relapsed/refractory mantle cell lymphoma, treatment of naïve relapsed multiple myeloma and treatment of Waldenstrom's Macroglobulinaemia).

7.6 Conclusion

This chapter has shed light on patterns in MEAs implementation across countries and identified some factors which may explain the identified variations using a new conceptual framework. I find that despite citing similar reasons for using MEAs, countries employ MEAs for the same medicines in a minority of cases, and even in such cases countries often implement different MEAs. This raises questions as to the reasons for such variations. My analysis showed that health system specific features relating to governance (the scope of the MEA policy and the mandate of the agency assessing medicines) explain some of the identified variations. However, more research is needed to understand whether for example, different weight assigned to uncertainty, difference willingness to pay and/or the relative importance of cost-effectiveness *vs.* budget impact could play a role. As countries worldwide are dealing with the same issue and increasingly look at MEA to manage the introduction of new and expensive medicines, there is definitely scope for sharing lessons.

8 The role of strategic procurement in increasing access to cancer medicines (Paper 5)

8.1 Summary

Strategic procurement encompasses all activities aimed at increasing the efficiency of procurement. The aim of this chapter is to identify procurement practices that can improve availability of affordable cancer medicines for patients. I conducted a comprehensive literature review on the impact of pharmaceutical procurement on price, volume, expenditure, stock-outs, and quality use of medicines using the PICOST framework. I identified a number of good practices which, if more widely applied to cancer medicines, could lead to better procurement outcomes. These include preparing the market for entry of new on-patent medicines, leveraging on horizon scanning to inform pricing negotiations with the pharmaceutical industry, implementing procurement practices and policies to enhance or create competition (in the case of originator markets), promoting rapid entry and uptake of generic and biosimilar medicines, and using therapeutic equivalence based formularies to inform prescribing and procurement decisions. Several challenges remain to be addressed to be able to reap the full potential of strategic procurement, most importantly greater implementation of procurement practices which have shown to deliver good procurement outcomes.

8.2 Introduction

High prices of new medicines have long been a worry for the public, payers and policy makers (Leopold, Chambers, and Wagner 2016) but in recent years these concerns have escalated due to the release of a number of medicines which are unaffordable to treat patients in low-income as well as high-income countries (Iyengar, Tay-Teo, et al. 2016b). While the international and national debates have focused on pricing and reimbursement methods, less attention has been given to how different models of strategic procurement can contribute to lower prices for medicines, reaching more patients, sustainable supply and quality of care. Strategic procurement encompasses all efforts to increase the efficiency of procurement by for example reducing the number of repetitive orders, generating economies of scale, etc. (WHO 2000).

In this Chapter, I review the literature on the impact of different procurement methods on price, availability and responsible use of medicines in high-income countries. I use this information to identify lessons learned which could be applicable to the procurement of cancer medicines.

An affordable price (affordable according to the definition of affordability as the "ability to purchase a necessary quantity of a product or level of a service without suffering undue financial hardship" (Kessides et al. 2009)) is a mean towards an end which is access to medicines to improve patients' health outcomes and quality of life. If affordably priced medicines cannot be used due to regulations against substitutions (e.g. biosimilar medicines) or because products are not available (e.g. shortages), having an affordable price is not achieving its purpose. In this Chapter I will therefore look beyond prices and the procurement life-cycle to identify factors which, through procurement, affect the availability of affordable medicines for patients.

8.3 Methods

Using the PICOST framework presented in Chapter 3 (Table 8), I conducted a comprehensive literature review on the impact of different pharmaceutical procurement methods on the following procurement outcomes: price, volume, expenditure, stock-outs and quality use of medicines. I searched the following search engines: PubMed, Web of Science, and Google Scholar. Relevant peer-reviewed and grey literatures were included. This was complemented by information on relevant examples from a survey conducted by the World Health

Organization (WHO) Regional Office for Europe in 2016 (Ferrario, Kanavos, et al. 2016a) and personal contacts with representatives of competent authorities in pricing and reimbursement or procurement who participated to one of the following consultations organised by WHO (the consultation on strategic procurement of medicines in Copenhagen on 22-24 September 2016 or consultation on fair pricing 22-24 November 2016 in Geneva).

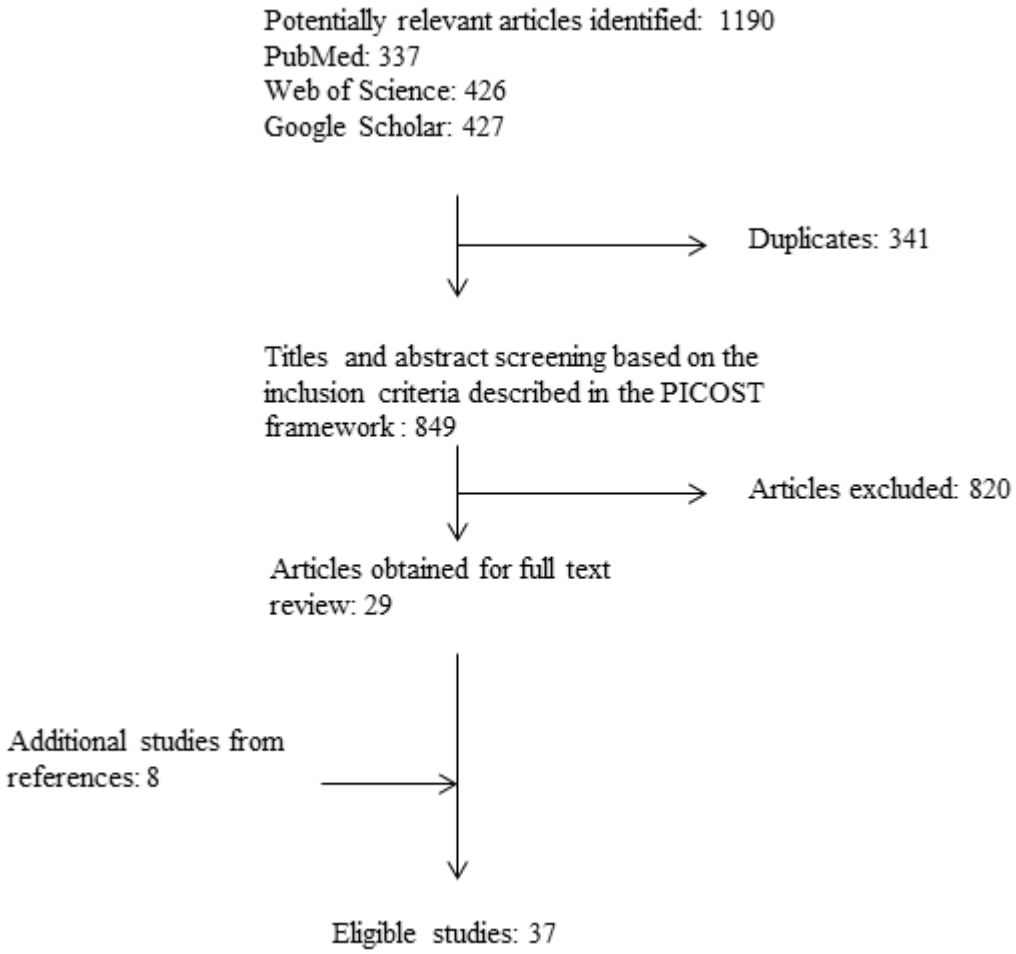
The following keywords were used for the literature review: (tender OR tendering OR procurement OR “preference policy” OR "rebate contracts" OR rabattvertäge OR rabattvertraege OR negotiation OR "reverse auction") AND (pharmaceuticals OR drugs OR medicines) AND (price OR prices OR expenditure OR availability OR “sustainable supply” OR “stock-outs” OR shortage OR “quality use” OR “rational use” OR “quality of care” OR “appropriateness of care”). The literature review included papers published between January 2000 and September 2016 published in English, German, Italian or French.

Inclusion criteria are presented in the PICOST framework, studies not meeting these inclusion criteria (e.g. focus on low- and middle-income countries) were excluded. Although the aim of this paper is to provide recommendations to improve procurement of cancer medicines, the scope of the literature review was not limited to cancer medicines.

8.4 Results

I retrieved 1190 papers and reports across three databases (PubMed, Web of Science and Google Scholar). 341 were excluded because duplicates. Following title and abstract screening to exclude papers that did not meet the inclusion criteria outlined in the PICOST framework, another 820 articles were excluded. A total of 29 papers were selected for inclusion. Follow-up of references let to the inclusion of another 8 papers. The final number of articles and reports included was 37 (Figure 17).

Figure 17: Prisma diagram



A variety of procurement methods are used worldwide. These can be summarised into three main groups: competitive tenders (open or restricted), negotiation (competitive and non-competitive) and direct purchasing. In the following subchapters I will describe these different experiences with the aim of highlighting lessons learned which could be applicable in other settings. As I did not find any examples of direct purchasing, I will focus on the first two by providing a short description of studies reviewed and their main conclusions.

8.4.1 Competitive tenders

Economic theory suggests that creating economies of scale can bring prices of products down. The application of this principle in the pharmaceutical sector is confirmed by a number of studies on the impact of pulling volume across health facilities and/or administrative areas (Baldi and Vannoni 2015, Castellblanch 2003, Tordoff, Norris, and Reith 2005, Vogler et al. 2013). Many variations of centralised (at national or subnational level) have been

implemented with positive results. When trying to identify success factors, one should consider the specific features of these centralised tendering systems. Further, it is important to notice that in most of the cases when centralised tendering was introduced, this was done as part of broader set of reforms than just pulling volume. Analysing country's experiences with centralised or joint tenders in the context of these broader changes is essential to understand any positive as well as negative outcomes.

8.4.1.1 Centralised tenders in the hospital sector

The requirement for all hospitals and health programmes in Chile to use the national electronic platform for procurement resulted in direct savings of 8.3% for medicines procurement and indirect saving of 2.8% through greater aggregation and 0.4% through better rules (Raventós and Zolezzi 2015).

Cyprus uses tendering in the inpatient and outpatient sectors covering both branded and generic medicines (Petrou and Talias 2014). An evaluation of the savings generated in 2011 for 178 products in comparison to pharmacy purchasing prices found an overall 60.6% reduction in expenditure. Reduction in expenditure was greatest for generics (94.8% reduction in comparison to pharmacy purchasing prices). Savings achieved for branded products were 33.4% of the equivalent volume purchased at pharmacy purchasing prices. These findings were confirmed by a long-term study on price reduction of branded medicines in Cyprus (Petrou 2016).

In 2008 the national Health Procurement Committee was re-established in Greece. It is responsible to formulate a plan to reduce procurement costs, shorten payment time, make uniform medical requests, transfer redundant materials from one hospital to another and improve management of expired products and the introduction of e-procurement (Kastanioti et al. 2013). The work of the national Committee resulted in 80% savings on 4 active ingredient purchased on behalf of three hospitals and 57% savings on 23 active ingredient purchased on behalf of all Greek hospitals in 2011 (Kastanioti et al. 2013).

In Denmark two initiatives have been key for the good procurement outcomes in the hospital sector: a centralised procurement organisation, Amgros, conducting procurement for all Danish hospitals and the Danish Council for the Use of Expensive Hospital Medicines. The latter assesses the cost-effectiveness of these medicines and provides guidance in the

selection process by Amgros and clinicians (Bartels 2016). Through these two process, 314 million euro savings were achieved in 2015 (Bartels 2016).

Both Denmark and Norway conduct tenders are therapeutic class level. In Norway, for specialised medicines tenders are conducted at condition level (e.g. rheumatoid arthritis, psoriasis, Crohn's disease, melanoma, prostate cancer, hepatitis C). All tender offers for specialised medicines are accepted since all medicines will be used (on-patent sector), the volume consumed of each medicine will depend on the recommendations by the national procurement body LIS. There is high compliance with LIS recommendations among clinicians which is why manufacturers are willing to provide discounts to obtain a better position in LIS guidelines (i.e. to achieve a higher sales volume).

In Norway switching to biosimilar infliximab enabled to increase the number of patients treated and even generated savings on total spending on this medicine. Very positive results were also achieved in Denmark where by the end of 2015, the biosimilar version of infliximab, had 99% market share, generating 2.6 million Euros (DKK 20 millions) savings (Amgros 2016a). In both countries, information was key to overcome initial scepticism among doctors and patients. In Denmark, information leaflets were developed and distributed to doctors and patients early in the process, further, the Danish Council for the Use of Expensive Hospital Medicines recommended switching new and existing patients to the biosimilar (Amgros 2016a). In Norway, an annual conference on anti-TNF alpha is organized every year since 2007. This conference is well attended by specialists and offered an opportunity to familiarize doctors early on with biosimilar medicines and discuss any concerns. Most importantly, the NOR-SWITCH study confirmed the safety of switching patients from the reference biologic to its currently marketed biosimilars (Moe 2016).Savings generated in other health system areas should be taken into account when conducting procurement as well as quality of care.

Greater price reductions in Italian regions with higher levels of corruption or lower levels of institutional quality suggesting that centralisation contributes to reduce favouritism and corruption leading to higher prices (Baldi and Vannoni 2015),.

8.4.1.2 Tender like system in the ambulatory sector

The examples above mostly focused on hospital procurement. Some countries are applying tendering-like procedures in the outpatient sector. These include for example Cyprus, Denmark, Germany, Malta, the Netherlands, Romania, Slovenia and Sweden (Dylst, Vulto, and Simoens 2011). Some evidence on the impact of tenders is available for Germany, the Netherlands and Sweden. The impact of these tendering-like procedures on shortages is unclear, in particular whether the very low prices achieved may cause manufacturers exit and supply problems.

Rebate contracts were introduced in Germany in 2003 and since 2007 pharmacists are required to dispensed the medicine with which the insurance company has a rebate in place unless the prescriber has explicitly asked to dispense a specific brand on medical grounds (German Ministry of Health 2016). These rebate contracts are another variation of preferred supplier contracts and can be negotiated at active ingredient level or for a portfolio of products. A study on preferred supplier contracts in post-patent market in Germany finds that – from a manufacturer's perspective - these contracts are a powerful strategic instrument for generic manufacturers in a highly competitive environment (Blankart and Stargardt 2016). Signing such contracts has a positive effect on a brand's own market share and a negative effect on the market shares of competitors (Blankart and Stargardt 2016). Further, the authors find that the time period between signing the first and the following preferred supplier contracts positively affects market share gained in the short-term while in the medium-long term this advantage disappears (Blankart and Stargardt 2016). No information on shortages was found in the literature. Since pharmacists are allowed to dispense a non-preferred medicine if the preferred one is not available and that different health insurers have different preferred medicines, this may prevent any shortages of the preferred medicine to impact on access. In principle this seems to be the case also in The Netherlands but it seems that substitution options are limited by the insurers' preferences and first search for an alternative wholesaler who may supply the preferred medicine.

In The Netherlands the preference policy has been introduced mid-2008 whereby health insurers design a preferred product, usually the least expensive, for each molecule included in the policy, to be the product of choice to their insurees for the duration of the contract. Substantial price reductions (more than 90%) for high volume generics like on omeprazole, simvastatin and amlodipine were observed between May 2008 and February 2012 (Kanavos,

Seeley, and Vandoros 2009, Kanavos 2012). During the first year savings well above Euro 300 million were achieved (Kanavos, Seeley, and Vandoros 2009, Kanavos 2012). However, complaints from pharmacies who lost the income generated through discounts (now benefitting the health insurers who directly contract with manufacturers) led to an increase in the pharmacy fee which cost an excess of Euro 225 million (Kanavos, Seeley, and Vandoros 2009, Kanavos 2012). Still there is a positive saving margin for health insurers. The seize of the savings has grown over time and totalled to nearly 680 million Euro in 2014 (Zorginstituut Nederland 2015). Supply problems affecting preferred medicines have been documented. A case of a local manufacturer withdrawing several products due to tender pressure as well as individual cases of shortages of preferred medicines were reported (Carradinha 2009). According to data from the Dutch Foundation of Pharmaceutical Statistics, on average, the preferred medicine was not available in 4.3% prescription cases in 2013 (SFK 2015). This means that the pharmacist has to find another wholesaler or another medicine, bearing in mind the preferred alternatives specified by the health insurer (SFK 2015). Overall the long-term impact of the preference policy in the Netherlands is positive. Individual products may occasionally not be available in all pharmacies but this is a negligible issue if compared with the size of the savings generated and the contained nature of shortages.

The short-term nature of the savings accrued is highlighted by a study on the effect of being the exclusive supplier for a generic product in Sweden. The study finds that while increasing the market share of the lowest-cost product beyond about 50% of the market generates significant short-term savings, these savings are lost relatively quickly over time, due to exit of competitors and the associated reduced price competition (Bergman, Granlund, and Rudholm 2015). Their findings also suggest that increasing the number of sellers from two to three reduces average prices by about one third (Bergman, Granlund, and Rudholm 2015).

8.4.2 Negotiation

Price negotiation is used in a number of countries in an attempt to obtain lower prices for on-patent medicines. Notable exceptions include Medicare in the United States (US). Lack of price negotiation and the requirement for most Government programmes to cover most new medicines are widely thought to be some of the key issues why Medicare Part D pays higher prices than other Federal programmes (De Lott et al. 2016, Kesselheim, Avorn, and Sarpatwari 2016, Outterson and Kesselheim 2009).

In 2010, the pan-Canadian Pharmaceutical Alliance (pCPA, formerly known as the pan-Canadian Pricing Alliance) was established for the joint negotiation of brand name medicines between Canadian Provinces and Territories and industry. The aims of the Alliance are to reduce differences in coverage decisions across the country and improve access to new medicines by increase purchasing power (IBM 2014). As of 30 September 2016, 118[12] joint negotiations for brand name medicines have been completed (Canada's Premiers 2016c) and 37 were underway (Canada's Premiers 2016b). In January 2013 the Value Price Initiative was established to reduce the cost of generic medicines (now collectively referred as pCPA). In the first three years of work up to April 2015, a price reference for commonly prescribed medicines at 18% of the equivalent brand name product was established for 14 medicines (Canada's Premiers 2016a). An independent review of the functioning of the pCPA was conducted in 2013 and some of the recommendations made, including greater transparency and standardisation (IBM 2014), have been implemented. Available evidence on the impact of the Alliance shows that there was no overall change in the proportion of new medicines listed across jurisdictions and a varied impact on time-to-listing across provinces and territories (Milliken et al. 2015). These conclusions are based on a limited number of medicines reviewed at the time of the study. Further evaluations are needed to establish whether the pCPA is meeting its objectives.

Australia uses information from horizon scanning to inform its pricing negotiations with manufacturers. This information is particularly important to prepare for the entry of new high cost medicines. In the case of Hepatitis C, it was also used to negotiate a favourable agreement for the treatment of all patients due to knowledge of competitors coming to the market in the near future.

A study on factors influencing the size of the discount obtained during closed doors pricing negotiations in Germany found that medicines without additional benefit and non-orphan medicines correlated with higher discounts (Theidel and von der Schulenburg 2016). On the

[12] "A completed pan-Canadian negotiation refers to those for which a Letter of Intent (document which outlines the agreed upon terms and conditions for listing) has been signed between the lead jurisdiction for the negotiation and the manufacturer OR negotiations have been closed without a Letter of Intent." p.3 (Canada's Premiers 2016c)

contrary, small population size, no deviation from recommended appropriate comparative therapy and inclusion of quality of life data correlated with lower discounts on the list price (Theidel and von der Schulenburg 2016). Despite these factors were associated with smaller or greater discounts, they were not sufficient to predict the final price. The authors concluded that other factors such as negotiation tactics, the political climate and other soft factors are likely to play a more influential role in the determining the final discount (Theidel and von der Schulenburg 2016).

8.4.3 Other factors that affect procurement outcomes

A number of factors outside the procurement cycle can affect its outcomes. These include pricing and reimbursement regulations like the impact of Medicare reimbursement rules on prices of generics in the US (Alpert, Duggan, and Hellerstein 2013), the influence of 70/90 reimbursement regulation on the price of generics in Ontario (Anis, Guh, and Woolcott 2003), the implementation of a reimbursement price cap for high-cost medicines in French hospitals (Degrassat-Théas et al. 2012); clinical guidelines and clinicians' involvement in the procurement process (Amgros 2016b, Bartels 2016); the ability to substitute for generics, biosimilar medicines or to implement therapeutic substitution[13] (Outterson and Kesselheim 2009, Kesselheim, Avorn, and Sarpatwari 2016, Bocquet et al. 2014, European Biopharmaceutical Enterprises 2015); the implementation of managed entry agreements (Ferrario and Kanavos 2013, Russo et al. 2010); the ability to parallel import products from lower-priced markets (Chaumont et al. 2015); shortages and their causes (Iyengar, Hedman, et al. 2016) including parallel exports (Kawalec et al. 2016) and existing policies (Tan, Moles, and Chaar 2016b); knowledge of prices in other markets (Hinsch, Kaddar, and Schmitt 2014); ability to collaborate with other countries to share information and experiences (Blau et al. 2015); and potentially joint negotiation of prices and managed entry agreements (Morgan et al. 2013a). Below a few examples are illustrated in more details.

A collaborative approach to procurement, consensus guidelines and regular audit were the key ingredients for maintaining access to cost-effective ARV medicines in London in the midst of budgetary pressures (Foreman et al. 2012). While antiretroviral collaborative

[13] "Therapeutic substitution is the replacement of the originally-prescribed drug [medicine] with an alternative molecule with assumed equivalent therapeutic effect" p. 728 (Johnston et al. 2011). "The alternative drug [medicine] may be within the same class or from another class with assumed therapeutic equivalence" p. 728 (Johnston et al. 2011).

procurement across London had been in place for a number of years and successfully delivering competitive prices, financial constraints required to achieve further price reductions (Foreman et al. 2012). To achieve these, the London HIV Drugs and Treatment Sub Group - a clinically led engagement structure bringing together commissioners, clinicians and patient representatives to plan, deliver and evaluate HIV care and treatment services - agreed to include therapeutic tender[14] in the procurement for 2011/2 (Foreman et al. 2012). First-line medicines options were identified with the aim of stimulating volume growth and securing lower prices without negatively impacting on efficacy or tolerability of treatment (Foreman et al. 2012). This, for the UK, novel approach to tendering has been characterised by greater clinical leadership and involvement of patient representatives to ensure its successful implementation and acceptance. From 2011 to 2014, at least GBP 10.5 million (recurring full year savings) were achieved through therapeutic tendering for branded ARV medicines in London, equivalent to about 5.2% annual reduction in ARV expenditure (i-base 2014).

8.5 Discussion

Managing entry of new medicines includes pre-launch activities (e.g. horizon scanning), peri-launch activities (e.g. HTA, pricing and reimbursement) and post-launch activities (e.g. updating of formularies and clinical guidelines, disinvestment) (WHO 2015a). Findings from this study highlighted the role of these different activities on procurement outcomes.

Preparing for entry of new on-patent medicines through horizon scanning was instrumental in negotiating a competitive deal for the procurement of medicines for the treatment of Hepatitis C in Australia. Once a product is on the market it is important to choose an efficient procurement method which leverages on economies of scale and takes into account the product characteristics (on-patent *vs.* off-patent, in-patient *vs.* out-patient, etc.). In the on-patent market, examples from Denmark and Norway showed that it is possible to create a competitive market through tenders at therapeutic class level. Voluntary collaborations in pricing negotiations have started among various European countries (Ferrario, Kanavos, et al. 2016a). While the impact of these initiatives in improving access needs yet to be evaluated, combining intelligence, skills and market power is likely to put participating countries in a stronger negotiation position. Examples from Germany, the Netherlands, and (in the short-

[14] Tenders usually conducted at ATC-4 (chemical subgroup) level instead of ATC-5 (substance) level to enhance competition

term) Sweden, showed that preferred supplier contracts can generate savings in the post-patent market. Careful monitoring of supply issues and product exit is needed to avoid interruption in treatment and decreased competition. Further, it is crucial to prepare the system for entry of off-patent products. A number of barriers exist in some countries preventing fast generic entry and uptake. These include data exclusivity provisions, limited generic substitution, very limited therapeutic and biosimilar substitution. Finally, disinvestment in low-value medicines can generate some financial space for entry of new and more cost-effective ones (Parkinson et al. 2015). Disinvestment can also be seen from the perspective of disinvesting in branded medicines following generic entry (Hughes and Ferner 2010). In this case, disinvestment can generate both savings and increased access (Elek et al. 2017).

Studies on the impact of different procurement methods on prices, volume, supply security, etc. have used a variety of methods and due to the diversity in the way the same procurement methods are implemented in different countries, caution is needed when aggregating conclusions from different studies. Another limitation is that a certain number of evaluation studies were conducted by those in charge of procurement and therefore potentially biased towards showcasing mainly positive results.

8.6 Conclusions

This chapter set out to identify ways in which strategic procurement can contribute to improve access to cancer medicines. I identified a number of examples where countries, through smart procurement practices aimed at generating efficiencies, can improve availability, reduce prices and expenditure and improve quality use of medicines. These include leverage on horizon scanning to inform pricing negotiations with the pharmaceutical industry, the implementation of procurement practices and policies to enhance or create competition (in the case of originator markets) and promote uptake of biosimilar medicines.

I also identify a number of challenges which are currently hampering efforts to take full advantage of strategic procurement. Based on these findings, I conclude that national regulatory changes should be identified which, if introduced at country level, can improve access to medicines (e.g. provisions to speed-up generic entry post-patent expiry and substitution for biosimilar medicines where the risk-benefit is positive). There is a need to create a competitive market, which can be achieved in different ways depending on the

product life-cycle (on-patent through therapeutic tendering and negotiation; post-patent: tendering either INN or therapeutic group level).

The following factors can contribute to more competitive prices, greater access and quality use of medicines: greater use of horizon scanning to inform strategies to manage entry of new medicines and negotiations with manufacturers, leveraging on economies of scale (at national and international level), being proactive in improving the efficiency of procurement, preparing the system for entry of off-patent medicines, minimise barriers to entry of off-patent medicines (both generic and biosimilar medicines), and use of evidence-based clinical guidelines to inform procurement. It is important that countries perform well on all components in order to improve their procurement outcomes and ultimately access to cancer medicines.

9 Conclusions, policy implications, limitations, future research

9.1 Findings from this thesis

Access to new and potentially more effective cancer medicines is challenged by very high entry prices and uncertainty around their effectiveness in routine clinical practice as opposed to the controlled conditions of clinical trials. Studies on access to cancer medicines have tended to focus on reimbursement decisions as these are more readily available than data on the use of cancer medicines. In this thesis, I aimed to determine whether access to cancer medicines varies across a sample of European countries/administrative areas (Belgium, Estonia, Scotland, and Sweden), why it varies and what countries are doing to improve access. To this end, I analysed data on the use of cancer medicines in the hospital and outpatient sectors and the use of managed entry agreements and strategic procurement to improve access.

I used a variety of quantitative and qualitative methods to address the research questions of this thesis. Survival analysis and the complementary log-log transformation of the Cox proportional hazard model were used to study times to launch of new cancer medicines and their determinants across and within the countries studied. I used longitudinal multilevel models to analyse determinants of differences in utilisation across and within the study countries. Based on the literature I reviewed, I developed a framework to identify determinants of the use of cancer medicines. I populated the framework by conducting a documentary review and interviews with oncologists. I conducted a comparative longitudinal analysis of the implementation of MEAs on managed entry agreements and developed a conceptual framework to understand their impact on key end-points for decision-makers. Finally, I reviewed the literature to identify good practices and challenges of different procurement methods in improving access to medicines.

In the following sub-sections, I will revisit the hypotheses outlined in Chapter 2 in the light of the findings of this thesis.

9.1.1 Hypothesis 1: Variations exist in access to cancer medicines across European countries and these can be substantial

This hypothesis was tested in Chapter 4, 5 and 6. This thesis used two main indicators, time to entry of new cancer medicines and the levels of use of cancer medicines, to study access to cancer medicines. These indicators were also the basis against which determinants of access were tested. Chapter 4 analysed time to entry of 46 new cancer medicines and its determinants in Belgium, Estonia, Scotland and Sweden. There were large differences in time to entry of new cancer medicines between Belgium, Scotland and Sweden. On average, the expected time from EU-wide marketing authorisation, to first use of a medicine, was shortest in Sweden, with an average of 14.3 months (43 launches, 3 non-launches), and Belgium, with an average of 26.8 months (39 launches, 7 non-launches). For medicines which obtained EU-wide marketing authorisation after April 2007, the average time to launch in Scotland was 12.7 months (29 launches, 2 non-launches). In the full sample of 46 medicines (including medicines launched before April 2007 whose date of first use was not known), only two medicines were not used between April 2007 and June 2015 in Scotland. Differences in time to access and number of launches were even larger when comparing these three countries with Estonia where the average time to launch was 63.9 months (27 launches, 19 non-launches).

Chapter 5 analysed the use of 31 cancer medicines in Belgium, Scotland and Sweden. It showed that marked differences in the use of cancer medicines exists across this sample of western European countries with comparable income levels and spending on health per capita. Belgium had the highest utilisation of other antineoplastic agents in 2013 (120 DDD per 1000 capita in Belgium *vs.* 94 DDD per 1000 capita in Sweden *vs.* 49 DDD per 1000 capita in Scotland), the group to which most study medicines belong. Sweden had the highest utilisation of alkylating agents, plant alkaloids and analogues, and hormone antagonist and related agents (34 DDD per 1000 capita in Sweden *vs.* 27 DDD per 1000 capita in Belgium *vs.* 10 DDD per 1000 capita in Scotland). Scotland, closely followed by Sweden, had the highest utilisation of antimetabolites included in the study sample (41 DDD per 1000 capita in Scotland *vs.* 40 DDD per 1000 capita in Sweden *vs.* 36 DDD per 1000 capita in Belgium).

In Chapter 6, I analysed the use of HER-2 targeted therapies for breast cancer in Belgium, Estonia, Scotland and Sweden. I found that utilisation of HER-2 targeted therapies per new breast cancer case was higher in Sweden and Belgium compared to Scotland and Estonia. 65 DDD of trastuzumab per new breast cancer case were consumed in Belgium, 57 in Sweden, 40 in Scotland and 37 in Estonia in 2014. While trastuzumab was widely used in all four

countries (more than 91% market share among HER-2 targeted medicines in all countries), lapatinib, pertuzumab and trastuzumab emtansine were not routinely available in Scotland and Estonia as of December 2014 (and not even as of 2016). Sweden was the first of study countries to introduce newer HER-2 targeted therapies following trastuzumab, confirming findings from Chapter 4 that Sweden is an early launch country and adopter of new medicines.

Empirical evidence from this PhD thesis confirmed that marked differences exist in access to cancer medicines in a sample of European countries.

9.1.2 Hypothesis 2: Differences in access are determined by HTA recommendations, which influences the reimbursement status, prices of medicines, how medicines are financed including special funding arrangements and limitations on the number of patients treated, and the sector/s where they dispensed

This hypothesis was tested in Chapters 4, 5 and 6. In Chapter 4, I found that medicines with shorter times to submission for reimbursement, local manufacturers headquarter (or local sales representative), an FDA priority review or a combination of expedited approval programmes, and medicines launched in Scotland and Sweden, were associated with higher a hazard of launch (probability of launch). Longer times since EU-wide approval initially correlated with an increased hazard of launch but as time further elapses they negatively affected the hazard of launch. The added clinical value of medicines explained shorter time to launch in Estonia but not in the other countries.

In Chapter 5, I found that in Belgium, Scotland and Sweden, the most important correlates of increased utilisation in a sample of 31 cancer medicines which received EU-wide marketing authorisation between 2000 and 2012 were medicines coverage and time since EU-wide marketing authorisation. Medicines dispensed in both hospital and ambulatory sectors in Sweden were correlated with higher use than medicines dispensed in hospital settings only. Sweden was the country with the highest number of medicines used in both hospital and ambulatory sectors (N=26), followed by Belgium (N=6) and Scotland (N=2). Prices had a negative effect on utilisation in Belgium and Sweden but not in Scotland. Instead, financial managed entry agreements, in the form of confidential discounts, were positively correlated with increased utilisation of cancer medicines in Scotland. One possible interpretation is that

the financial managed entry agreements in Scotland remove the regressive effect of high list prices on utilisation.

In Chapter 6, I found that trastuzumab was reimbursed in all countries and all new breast cancer patients are tested for HER-2 overexpression and prescribed trastuzumab if the tumour was invasive and larger than 1 cm or smaller but with risk factors. Yet, important differences existed in use of trastuzumab (DDD per new case) between Belgium and Sweden at the high end and Estonia and Sweden at the lower end. This seemed to be driven by differences in the use of trastuzumab beyond progression (only used in Belgium and Sweden). In Estonia hospital medicines were funded as part of a diagnostic related group type of system which prospectively paid the hospital based on a fixed cost per breast cancer patient. This system did not distinguish between HER-2 positive patients (higher treatment cost) and HER-2 negative patients (lower treatment cost). The level at which the payment for breast cancer was set did not seem to be sufficient to cover for treatment with trastuzumab beyond progression which explained why it was not used despite common practice in other countries. In Scotland, use of trastuzumab beyond progression was not considered cost-effective and therefore not recommended for routing use. Estonia had a comparatively low incidence of breast cancer, the least comprehensive national breast cancer screening programme and, despite progress, patients were diagnosed relatively late. If indeed a number of breast cancer cases were not diagnosed, Estonia could be worse off in terms of access despite similar levels of usage per patient in Estonia and Scotland.

Lapatinib, pertuzumab and trastuzumab emtansine were not routinely used in Estonia and Scotland as of 2016) due to the lack of a positive reimbursement decision. This confirmed the findings from Chapter 5 that the number of reimbursed indications affected the use of medicines. Alternative access options for non-reimbursed medicines included individual patient request in Scotland, special access programmes funded by the pharmaceutical industry (one such programme was in place for a limited amount of time for lapatinib in Estonia for example), and funding through a private foundation or out-of-pocket payment in Estonia. However, the limited coverage in terms of number of patients benefiting from these alternative access options limited their impact on access to non-reimbursed medicines as confirmed by utilisation data.

The findings of this thesis thus confirmed the importance of positive reimbursement decisions and HTA recommendations, as well as different financing methods for medicines, in enabling access. The thesis also highlighted the regressive effect of prices on access which was offset by confidential pricing arrangements, and the need to consider the whole spectrum of patients who would potentially be eligible for treatment when evaluating the level of access. Utilisation of the cancer medicines included in this study largely occurred in hospitals (including day-units). The effect of the dispensing channel (hospital only or hospital and ambulatory sectors) was thus limited and only significant in Sweden the country with the largest number of medicines dispensed in both sectors. Further, this thesis found that time to entry of new cancer medicines was affected by time to submission, whether the manufacturer had a local headquarter or sales representative, whether the medicine was granted an expedited review by the FDA and the added clinical value based on the rating by Prescrire (the latter only in Estonia).

9.1.3 Hypothesis 3: Differences in access to medicines do not always reflect the added clinical value of new medicines

This hypothesis was tested in Chapter 4 and 5. In Chapter 4, four models were developed to study time to entry of new cancer medicines. In the all country model 1 (full sample, 46 medicines, four countries) and model 3 (subsample of medicines with added clinical value rating by the independent drug bulletin Prescrire, 43 medicines, four countries), medicines granted an FDA priority review or a combination of expedited approval programmes were associated with higher hazard of launch (probability of launch) but not with added clinical value measured by the rating assigned by Prescrire (model 3). This means that higher ratings of clinical added value – in comparison to previously approved medicines - by Prescrire were not associated with higher hazard of launch. Model 4 (subsample of medicines with ESMO-MCBS rating), the hazard of launch was not affected by the ESMO-MCBS rating but this model had also the smallest sample given that ESMO-MCBS ratings were only defined for solid tumours at the time the study was conducted.

In the country level model 1 (full sample, 46 medicines, individual country) and model 3 (subsample of medicines with Prescrire rating, 43 medicines, individual country), FDA expedited approval programmes increased the hazard of launch in Scotland and Sweden.

Higher additional clinical value, as estimated post-launch by Prescrire, was only significantly correlated with a higher hazard of launch in Estonia.

This thesis thus found limited correlation between time to launch and added clinical value on one hand and levels of use and added clinical value on the other hand.

9.1.4 Hypothesis 4: Managed entry and risk-sharing agreements are increasingly used to facilitate entry of new medicines however their impact on time to entry, use and reduction of uncertainty is still largely unknown

This hypothesis was tested in Chapter 7 which analysed the use of managed entry and risk-sharing agreements in Belgium, England, the Netherlands and Sweden. The countries' studied implement managed entry agreements in an attempt to introduce new medicines which may have otherwise not been introduced because of their high cost and/or uncertainty regarding their performance in real-life. I found an increased use of managed entry and risk-sharing agreements between 2003 and 2012 with a focus on oncology and immune-modulating treatments and the implementation of financial agreements. However, very little was known on their impact in reducing prices and containing budget impact, improving cost-effectiveness and quality use of medicines and facilitating access to new medicines. This was due to the confidential nature of most pricing arrangements and difficulties in accessing patient-level data to evaluate the patient response and use according to recommended indications. Two issues can limit access to these data: data storage systems and restrictions in access to the data. For example, I contacted several hospitals in England to access data on patient response to bortezomib for multiple myeloma. The medicine was part of a health outcome based agreement whereby the manufacturer refunds or provides equivalent free stock for patients not achieving a minimal response – defined as a reduction of at least 50% in serum M protein after 4 cycles of chemotherapy (NICE 2007) – but because a number of hospitals were still using non-electronic prescription systems, this would have required a rather laborious review of paper records which only NHS staff can perform. Further, one hospital commented that they do not use the medicine because the scheme was too burdensome to implement and they only treated a very limited number of patients with multiple myeloma. Another hospital had introduced a system of vial-sharing (the size of the single does vial does not correspond to the standard treatment dose for one patient leading to wastage (Bach et al. 2016)) which they concluded was more cost-saving and simpler to

implement than the NICE-approved patient access scheme (Hills et al. 2010). Additional barriers were likely to have been the time required for the hospital pharmacist to extract these data even if electronically available, the possibilities that some hospitals may not have wanted to provide data which could show that they did not submit the refund request on time and therefore missed the opportunity to recoup treatment costs for patients in whom the medicine did not elicit the expected response and unclear governance regarding access to anonymised patient level data. Hypothesis 4 was thus confirmed by evidence from this thesis.

9.1.5 Hypothesis 5: A number of countries have used elements of strategic procurement to increase access to medicines. However, more efforts are needed at national and international levels to increase the efficiency of procurement and ensure sustainable access to medicines at affordable prices

This hypothesis was tested in Chapter 8 which conducted a literature review, complemented by information from key informants, on the impact of different procurement methods on price, volume, sustainable supply, and responsible use of medicines. Good practices identified included the use of horizon scanning to inform negotiation with manufacturers of on-patent products and budgeting at hospital level; measures to promote rapid uptake of generic and biosimilar medicines post-patent expiry; focus on prescribing and procurement on high value and cost-effective medicines through the implementation of clinical guidelines and formularies; and the creation a competitive market where this would otherwise not exist, due to active patents, through therapeutic tenders among others.

This thesis confirmed that a number of challenges in implementing strategic procurement (which includes all efforts aimed at increasing efficiency in the procurement process). These included restrictions on switching to generic and biosimilar medicines, non-evidence based concerns on their safety and efficacy leading to their low uptake; short budgeting processes; and non-inclusion of information from horizon scanning in budget negotiation for hospitals. Pharmaceutical procurement was an important lever towards better access to cancer medicines. Increased evaluation of existing procurement and negotiation practices and sharing of best practices among countries represents an opportunity to improve procurement outcomes and increase access to medicines.

9.2 Contribution of this thesis

This thesis has made various methodological and empirical contributions to the literature. These include: (1) the analysis of access to cancer medicines in Europe from a quantitative and qualitative perspective which provides a blueprint for similar analyses in other countries; (2) the identification of likely determinants of differences in access to cancer medicines which can guide policy-makers efforts in managing access to new therapies; (3) the development of a conceptual framework for managed entry agreements which can guide their design and evaluation; (4) the development of a framework to study determinants of access to cancer medicines.

These findings have a number of practical and policy implications.

9.3 Policy implications: What do these findings mean for policy and practice?

1) *The need for better data to identify disparities in access and monitor efforts to address them*

First of all, in order to study access to cancer medicines, data on medicines utilisation covering both inpatient and outpatient sectors are needed. At the moment this information is not readily available and accessible - from non-commercial sources - in most countries. The Organization for Economic Development and Cooperation (OECD) publishes data on defined daily doses (DDDs) per 1,000 individuals per day for selected therapeutic groups including alimentary tract and metabolism (ATC-A), blood and blood forming organs (ATC-B), cardiovascular system (ATC-C), genito-urinary system and sex hormones (ATC-G), systemic hormonal preparations, excluding sex hormons and insulins (ATC-H), anti-infectives for systemic use (ATC-J), musculo-skeletal system (ATC-M), nervous system (ATC-N) and respiratory system (ATC-R) (OECD 2016b). In 2016, no utilisation data were available for cancer medicines. Out of 34 OECD countries, 12 had data on medicines dispensed in hospitals in 2016. Comparative data on medicines utilisation across and within countries are important to identify disparities and investigate reasons behind them. In the 1990s for example, use of prescription-only medicines (measured in DDDs) in Estonia was found to be one third of that reported in the Nordic countries (WHO 2003). Further investigation revealed that this was due to underutilisation of chronic disease medicines, in particular hypertension and schizophrenia (WHO 2003). With this information, it was therefore possible to take steps to increase availability and use of cardiovascular and antipsychotic medicines (WHO 2003). Data on medicines utilisation can also be benchmarked against other interventions to study

the impact of introducing new medicines on use of other services. Another example from Estonia showed overuse of ulcer surgery due to limited availability of anti-ulcer medicines during Soviet times (WHO 2003). Comparative utilisation statistics are a key component of the European Surveillance of Antimicrobial Consumption Network's efforts to improve use of antimicrobials in Europe and beyond (Versporten et al. 2014, ECDC 2016). Indicators of antimicrobial utilisation (DDD per 1000 capita per day) are collected annually from countries and used to provide feedback and monitor countries' progress in reducing inappropriate use of antibiotics (ECDC 2016). Lack of routinely collected data on utilisation of cancer medicines at national and subnational level severely limits efforts to improve access to cancer medicines as it prevents monitoring the impact of interventions to improve patient access. This information is important to identify interventions that are working, those that work but need to be improved and those that are not working.

When available, utilisation data are usually aggregated with no information on the treatment indication and treatment intention (e.g. curative *vs.* palliative), or if used in combination with other medicines. Further, available data on utilisation often needs substantial cleaning before they can be used for analysis. Another issue is which metric of comparison to use. For most medicines, DDDs per 1000 capita are used to compare medicines use across and within countries. Due to highly individualised treatment regimens and wide differences in dosages used in chemotherapy, DDDs are mostly not defined by the WHO Collaborating Centre on Drug Statistics (WHO Collaborating Centre for Drug Statistics Methodology 2016). Some countries have established their own (e.g. Belgium (2016) and Germany (DIMDI 2016)), other countries express their utilisation of cancer medicines in grams of active ingredient (e.g. Denmark and Norway). These data limitations hinder the conduction of cross-country studies on use of cancer medicines. Some initiatives are starting to address this issue. The systemic anti-cancer therapies (SACT) dataset in England for example claims to be the first national database collecting comprehensive information on systemic oncological therapies (SACT 2016). For each patient, information on clinical status (primary diagnosis and stage grouping), programme and regimen (regimen, treatment intent, performance status, etc.), treatment cycle, medicine's details (medicines name and dosage) and outcome (dose reduction, delayed start or reduced duration, etc.) are collected (NHS 2016). Despite existing limitations in available data, more value could be extracted from existing data, while in parallel working towards improving the level of information collected. A requirement for hospitals (and/or wholesalers) to report data on use of cancer medicines that allows to

calculate grams consumed and DDDs is the first step in that direction. If made publicly available, this information can be benchmarked against use in other countries. Comparison of utilisation of cancer medicines can help identifying outliers in terms of very high or very low use in comparison to the average use per capita in the other countries, or different geographical areas within one country, and spur investigation into what drives these differences. If these differences are not driven by medical need, then it is important to verify whether clinical practice is in line with current best available evidence and clinical guidelines. Such exercise can therefore help identifying gaps in access to medicines or shortcomings in responsible use of medicines.

2) *Prices represent a barrier to access to medicines and efforts to address their impact are needed at national and international levels*

High prices can hinder access to medicines. Several developments at international and global level have the potential to affect prices of new cancer medicines. The UN High-Level Panel on Innovation and Access to Health Technologies recommended increased use of TRIPS flexibilities, including compulsory licensing and higher requirements to grant patents, to tackle high prices (United Nations Secretary-General's high-level panel on access to medicines 2016). Strategic procurement and collaboration is one of the focus areas of the work of the WHO Regional Office for Europe in the area of medicines (Ferrario, Kanavos, et al. 2016b) and the Maltese EU Presidency (Espín et al. 2016). More recently, the WHO has launched a consultation on fair pricing (WHO 2017).

Strategic procurement has an important role to play in increasing access to medicines and preventing shortages. Efficient procurement of medicines means more than just obtaining the lowest price. It is about creating a healthy market where quality products are available at affordable prices on a sustainable basis at the right time (UNICEF 2016). In this context, a strategic approach to procurement is vital. Strategic procurement encompasses all activities aimed at improving the efficiency of procurement. These include, for example, activities to minimize low-value repetitive purchases, to increase the benefit of economies of scale and to reduce the transaction and transport costs (WHO 2000). In pharmaceutical procurement there are additional instruments which can be leveraged to improve efficiency. Examples include switching from branded medicines to non-branded generics or biosimilar products once the patent on the branded medicine expires, reducing the number of different medicines procured in a particular therapeutic area through the implementation of clinical guidelines and

formularies, and creating a competitive market where this would otherwise not exist, due to active patents, through analogue competition among others.

To the extent that the resources freed through increased efficiency are reinvested to into the health care system, strategic procurement can contribute to improve access to medicines. Examples from Norway and Denmark showed substantial savings being achieved by substituting the reference biologic product of infliximab for its biosimilars. In Norway, these savings were used to expand access to TNF-alpha medicines to a wider patient group.

In cases where a new product is coming to the market and there are no competitors yet, negotiation and, where possible, therapeutic tendering provides possible ways forward. Therapeutic tendering is based on therapeutic substitutability between molecules with assumed equivalent therapeutic effect (Johnston et al. 2011). Medicines considered to be substitutable may be from the same therapeutic class or from another class with assumed therapeutic equivalence (Johnston et al. 2011). In London, therapeutic tendering has been implemented with success in the procurement of HIV medicines. Denmark also implements therapeutic tendering. The latter relies on the availability of clinical guidelines to guide choice of medicines considered as therapeutic equivalent and to manage patients with the medicines procured. Results from the London HIV procurement group achieved savings of at least GBP 10.5 million (recurring full year savings) between 2011 and 2014, equivalent to about 5.2% reduced expenditure on anti-retroviral medicines procurement in London (i-base 2014).

Where these measures are not enough to ensure access to cost-effective medicines, additional interventions may be required. There is particular concern about limited use of TRIPS flexibilities to tackle issues of evergreening and unaffordable prices which preclude access to patients in Europe. Evergreening describes the process whereby the life of a patent on a particular molecule or the effective period of market exclusivity is extended through e.g. secondary patents, for minor variations or indications of the same compound, or other marketing strategies. The primary patent for treatment of chronic myeloid leukaemia with imatinib has expired in Cyprus and one month of treatment with generic imatinib costs EUR 117.6 (personal communication with procurement staff at the Ministry of Health of Cyprus). The existence of a secondary patent for the treatment of gastrointestinal stromal tumors (GIST) with imatinib means that treating patients with the same medicine, strength and

formulation, but a different diagnosis, GIST, costs EUR 2 168.4 (personal communication with procurement staff at the Ministry of Health of Cyprus). Unaffordable prices have led to countries at all income levels, to limit access to direct acting antiretrovirals for Hepatitis C to the most severe cases despite the high effectiveness of these medicines and their decreased side effects in comparison to standard treatment with interferons. This has led to strong reactions from medical professionals and civil society calling for payers and Governments to take action to increase access (Cattaneo and Maciocco 2016, Silverman 2016a).

While it is crucial to work towards a fairer pricing model, to generate efficiencies through strategic procurement and to take advantage of existing policy space to secure affordable prices, a certain level of investment in health systems is needed. Countries spending well below the average per capita spending on health are unlikely to achieve the same level of access. Estonia for example spent 6.3% of its gross domestic product on health in 2015 (OCED average 9%), which is equivalent to USD 1824 per capita at purchasing power parity (OCED average USD 3814 per capita at purchasing power parity) (OECD 2016a). At these levels of spending, it is difficult to achieve comparable access to other European countries which have decided to make a greater investment in health.

3) The need for a more comprehensive approach to entry of new medicines

Current efforts to improve access to cancer medicines in Europe have focused on price control, value assessment to guide prioritisation and coverage decisions, and more recently, on international collaboration. In contrast, the way medicines are financed and how this impacts on access has been given much less attention. While value assessment has been central in discussions around access to high cost medicines, more efforts are needed to implement models of managed introduction of new medicines. These should start with horizon scanning (pre-launch), use this information together with health technology assessment (peri-launch) to negotiate competitive prices for medicines which bring added clinical value to current standards of care and are affordable, and continue post-marketing activities including ensuring quality use of medicines and sustainable supply (WHO 2015a). Elements of this continuum are implemented in a number of countries, however, few perform well along the continuum. Examples from Australia (horizon scanning to plan the negotiation of directly acting antiretroviral medicines for the treatment of Hepatitis C), Denmark and Norway (fast uptake of the biosimilar infliximab for the treatment of rheumatoid arthritis post patent expiry of the reference product) have shown the importance of preparing the system

for entry of new medicines, to ensure their affordability and use. In addition, international collaborative initiatives (e.g. the Nordic pharmaceutical forum and the Beneluxa group) have started working together on various elements of this continuum (e.g. horizon scanning, HTA, and negotiation) with an aim of sharing experiences and leveraging on combined market power.

4) *An evaluation of the contribution of managed entry agreements in improving access is needed*

Managed entry and risk-sharing agreements are arrangements between manufacturers and payers aiming to address issues of high prices, uncertainty around effectiveness and uptake, and/or appropriate use of new medicines. Pure financial agreements include various forms of confidential discounts and rebates and dose capping schemes. Health-outcome based agreements may be performance-based, with refund for under-performance, or coverage with evidence development schemes whereby the new medicine is conditionally reimbursed for a certain period of time until sufficient evidence is available to make a final coverage decision. Registries are also used in this context to monitor appropriate use of medicines and to support the implementation of coverage with evidence development schemes.

Financial agreements have increasingly become price discrimination tools to offer confidential discounts off-list prices without touching reference prices. They are the preferred type of agreement in a number of countries as they offer a clear return, price reduction, and are generally simpler to implement than performance-based agreements. Their impact is largely unknown due to the confidentiality surrounding discounts and rebates and difficulties in accessing patient level data for agreements which cap the number of doses paid by the payer. Price-volume agreements in France have generated a net clawback between Euro 236 million in 2009 and Euro 386 million in 2014 (Comité économique des produits de santé 2015). By lowering the net price, financial agreements improve the cost-effectiveness of a medicine. In countries where cost-effectiveness is the main decision-making criterion for reimbursement, financial agreements can help bringing the incremental cost-effectiveness ratio (ICER) within the willingness to pay of a country.

At the time a reimbursement decision needs to be made, most of the evidence available is on efficacy and safety from randomised clinical trials. Little evidence is available therefore available on the effectiveness of the medicine in real life which is what decision-makers

ideally would want. To address issues of uncertainty, coverage with evidence development schemes have been introduced in some countries. As part of these schemes, a new medicine is initially funded for a certain time after which its reimbursement is re-evaluated using real-life data. Health-outcome based agreements are more demanding to implement as they require registries to collect information on the performance of the medicine in real-life and, for coverage with evidence development, additional data such as quality of life may be collected to complement RCT data in the context of cost-effectiveness analysis. The limited evidence on their implementation is mixed. Sweden seems to have been successful (i.e. data requests by TLV were satisfied by the manufacturer) in the implementation of coverage with evidence due to the simple nature of the additional data collection request (e.g. how the medicine is used in real-life) and availability of patient registries to support their implementation. The latter has also been the success factor in Italy (Montilla et al. 2015). Initial experience with these schemes has encountered a number of challenges in the Netherlands in terms of data collection and reversing decisions once a medicine has been introduced in clinical practice (Chapter 7). This is likely to be due to the more demanding nature of the additional data to be collected (efficacy and quality of life) and the need to set up registries. A limited number of performance-based agreements has been implemented in France. The manufacturer of glitazones for example claimed that they were equally effective as other dipeptidyl peptidase 4 (DPP-4) inhibitors but the claim was no attained in real-life and the price was decreased (Garrison et al. 2013). In contrast, the manufacturer's claim that risperidone would lead to better patient compliance and less hospitalisations was realised and the conditionally granted initial price was maintained (Garrison et al. 2013).

Uncertainty around effectiveness, safety, and uptake of a new medicine in real-life (i.e. outside the controlled conditions of clinical trials) will always be present at the time a reimbursement decision needs to be made. Learning from the experience of coverage with evidence development schemes will allow on one hand to improve the way these schemes are implemented. On the other hand, an evaluation of these schemes is likely to provide useful lessons learned for the implementation of EMA adaptive pathways to licensing in the European Union. Through adaptive pathways, selected medicines addressing high unmet medical need will be first authorised for a small patient population, based earlier data than usually required e.g. phase 2 clinical trials data, for which there is sufficient evidence of a positive benefit-risk balance. As new evidence on use of the medicine in real-life is being collected to supplement clinical trials data, the eligible patient population may be widened

through progressive licensing adaptations in process of evidence collection and re-evaluation of the benefit-risk balance (EMA 2016a). Such process will require some flexible forms of early reimbursement to support the introduction of new medicines earlier in the evidence generation process towards marketing authorisation. Lessons learned from real-work evidence collection through coverage with evidence development can thus provide lessons for the implementation of adaptive pathways and at the same time provide a flexible instrument of early reimbursement as more evidence on benefit-risk is generated.

Managed entry agreements, whether discount based or performance-based, contribute to a lack of transparency in pricing. Financial agreements generally grant an ex-ante discount on the list price or limit the number of doses paid by the payer irrespective of treatment length. Performance-based agreements are based on ex-post-refund or free additional stock but both effectively change the average price paid per dose used. With very limited information on the conditions offered to other countries, it is difficult for policy-makers to judge whether they could have been offered a better deal. Manufacturers on their side are left the discretion of offering the best deals to which country they prefer, probably countries with large markets, and not necessarily the countries which would most need a discount to provide access to their patients. Countries with more limited resources are also likely not to have the existing infrastructure in place to collect data (e.g. patient registries) and the negotiation skills to secure more competitive deals. As such there is a threat that MEAs could favour countries with larger markets and with existing resources data collection systems and good negotiation skills.

When deciding whether to engage in managed entry agreements, decision-makers should consider what their objective is (e.g. reduce uncertainty, reduce budget impact, improve cost-effectiveness). This will inform the choice of which managed entry agreement/s may be more suitable to meet the objective. Further, they should consider the requirements to implement different types of agreements, particularly those involving additional data collection, and whether existing data collection and reimbursement systems, would support their smooth implementation. If data collection systems are patchy and/or paper based, *ex ante* confidential discounts on the list price are likely to be the easiest scheme to implement.

5) Access to medicines as a means towards better health outcomes for all patients

Access to cancer medicines is a means towards better health outcomes for cancer patients. From a health system perspective, medicines, vaccines and health technologies are only one input towards better health outcomes. Other inputs include human resources, health services, including timely access to diagnosis, treatment (surgery, radiotherapy and chemotherapy) and palliative care, and financing. All these efforts need to be monitored by an efficient health information system, which allows to assess the impact of interventions to improve access, quality of care and financial protection against catastrophic expenditure or impoverishment as a result of seeking care. This can only be achieved through strong national and international governance and resilient policies. Through their action, these inputs and processes can influence coverage of interventions, including access to diagnosis and treatment, and the prevalence of risk factors, which, in turn, will impact health outcomes, equity and system responsiveness. If medicines have to contribute to better health outcomes for all patients, efforts to increase access to medicines should adopt a health system perspective when assessing existing barriers to access. This was highlighted in Chapter 6, where, despite similar levels of use of trastuzumab per new breast cancer case in Scotland and Estonia, access is likely to be worse in Estonia due to evidence suggesting possible under-diagnosis of breast cancer.

9.4 Limitations of this research

This thesis has several limitations. Specific limitations to each paper are discussed in Chapters 4-8. Here, I will summarise the main limitations of the overall thesis.

9.4.1 Data

The data used in this thesis were constrained by information available in the public domain or obtainable upon request from competent authorities.

9.4.1.1 Dependent variable: Utilisation

The majority of the 31 cancer medicines analysed in Chapter 5 were approved for the treatment of different cancer indications which are associated with different incidence levels. No data on utilisation of cancer medicines by indication were available which would have allowed me to adjust utilisation by incidence of different types of cancer in Chapter 5. Instead that adjustment was limited to population size in different countries. On the other hand, adjusting for the number of new cancer cases was possible in Chapter 6 given HER-2

targeted therapies are mainly used for breast cancer. Data on medicines use in hospitals were only available from April 2007 which means that I had to limit the observation time for Scotland from April 2007 to December 2014 in Chapter 4. The data used in this study are dispensing data, the quantity administered to patients may have been lower. Considering the high cost of new cancer medicines and the severity of cancer, it is unlikely that wastage (difference between dispensing and utilisation) will have significantly affected the results.

9.4.1.2 Independent variables

Limitations also apply to the independent variables. For example, data on medicines prices in Scotland represent list prices from the British National Formulary and as such does not include any confidential discounts which may apply. This has most likely led to an overestimation of prices paid in Scotland. That said, list prices are still the starting point for negotiation and the presence of special pricing arrangements at national level is captured by the MEA variable in Chapter 5. Prices in the other countries were calculated by dividing expenditure data by volume. In Sweden, the candidate was informed by the competent authority that this may actually represent the real price paid by providers. In Estonia, further discounts may apply at point of purchase. In Belgium, depending on whether hospitals report gross or net expenditure, some of discounts may have been included. It would have been interesting to include as a variable in the model the incremental cost-effectiveness ratio estimated for different indications in each country. This was not possible due to lack of data at indication level but also lack of cost-utility estimates for all the medicines in each country.

9.4.2 Methods of analysis

Cancer is a vast therapeutic area including many different types of tumours with different pathogenesis, affecting different parts of the body and treated in different ways. Of the three Chapters analysing use of cancer medicines (Chapter 4-6), only Chapter 6 could take into account factors specific to access to HER-2 targeted therapies for breast cancer like diagnosis of HER-2 overexpression and explore issues of use beyond progression. Chapters 4 and 5, which used quantitative methods to study time to entry and its determinants and determinants of differences in utilisation of different cancer medicines, had to rely on testing a limited number of determinants of entry and use.

Interviews were often difficult to arrange, particularly when the interviewees were busy oncologists. In Chapter 6, I conducted up to two interviews per country with medical

oncologists from different geographical areas (usually the capital and another major cancer centre). However, this is still a limited number of interviewers to fully represent the clinical perspective of treating breast cancer in the countries studied. Including oncologists from other areas, for example more remote areas of the country, may have provided a different perspective. Furthermore, all interviewees apart from one were senior oncologists (e.g. head of Department or Unit). Interviewing more junior oncologists may have provided a different picture though the one included in the study did not provide a different picture from the senior counterpart interviewed in the same country. Chapter 8 relies mainly on the literature, complemented by personal contacts with procurement bodies either on the telephone, email or in person, to review the impact of different procurement strategies on price, volume, expenditure, supply security and responsible use of medicines. Results published in the literature are likely to be affected by publication bias and over-represent positive results. Further, procurement staff may not see publication in peer-reviewed journals or translation of their annual reports into English as a priority, which prevented inclusion of relevant experiences in the literature review. Moreover, there may be a disincentive to publish too much information on how positive outcomes (e.g. competitive prices) were achieved (some countries may want to keep successful strategies of negotiating with industry for themselves) or negative outcomes as they would signal bad performance of those in charge of procurement. Speaking with more procurement bodies to learn about their efforts in obtaining better procurement outcomes for cancer medicines would have probably highlighted several good practices and challenges in the area. However, because the interviewees would have been procurement staff, the limitations just mentioned would still apply. In practice, time constraints and difficulties in arranging interviews with busy procurement staff prevented more primary data collection.

The analysis on governance factors and possible links with the way countries implement MEAs in Chapter 7 was only of explorative nature due to the limited sample size. Nevertheless, it did enable to identify important differences and similarities in the way MEAs are implemented across the four study countries. These include similarities in the countries' objectives for implementing MEAs and at the same time differences in the ways countries employ MEAs. This analysis did not include MEAs implemented in only one or a few regions due to the lack of data on most of these agreements. This is likely to have affected only England where there is evidence of some schemes being offered at sub-national level for medicines which had not yet received a recommendation for use by NICE. No such evidence

was available for the other countries. That said, all MEAs negotiated at national level were included in the analysis.

9.4.3 Interpretation

In Chapter 4, analysis of time from EU-wide marketing authorisation to first use gives an indication of the time interval between licensing and first use of a medicine in a particular country. However, at the time of first use the medicine may not yet be available to all eligible patients according to the licensed treatment indication. This can be the case for medicines which have not yet obtained a positive reimbursement decision and which continue to be temporarily funded through temporary access programmes financed by the manufacturer or the public health system (e.g. temporary authorisation for use in France) (Degrassat-Théas et al. 2013). Further, first use does not provide information about the overall level of use and possible inequalities in access to medicines within a country. It is therefore important to analyse also actual utilisation levels and subnational disparities in access.

The studies on the impact of different procurement methods on prices, volume, supply security and responsible use of medicines reviewed in Chapter 8 have used a variety of methods. Due to the diversity in the methods used to evaluate the impact of different procurement methods, the way the same procurement method (e.g. tendering) is implemented in different countries, and other reforms which may have been ongoing in the pharmaceutical sector affecting procurement outcomes, caution is needed when aggregating conclusions from different studies. Further, some of the studies reviewed were conducted by those in charge of procurement and therefore, potentially biased towards showcasing mainly positive results.

9.5 Recommendations and future research

In my thesis, I identified a number of issues with existing data on use of cancer medicines which limits research on access to cancer medicines and its determinants. Studies on determinants of access to cancer medicines need to take a broader perspective and include factors affecting access to health services such as diagnosis, clinical practice, and health financing. A number of interventions and initiatives are implemented to improve access to cancer medicines, however, their evaluation and sharing of experiences with other countries is limited. These limitations represent a missed opportunity to generate evidence and share experiences which are useful for policy and practice.

First of all, basic indicators of access to cancer medicines (e.g. grams of active ingredient per 1000 capita) should be routinely collected and published across Europe. These should be used to identify disparities, question what may drive them and monitor the impact of interventions to improve access. As data on medicines utilisation per indication and treatment intention become more widely available, more refined indicators can also be reported and compared across Europe (e.g. use per patient, diagnosis, and treatment intention). Available data on cancer medicines utilisation have a number of challenges including limitations to public access, lack of standardisation in the way it is collected and reported and the need to clean the data before they can be used for analysis. To be fit for use, data need to be more easily accessible in a user-friendly format which supports analysis of utilisation across and within countries

While this thesis confirmed the importance of reimbursement to ensure access, it also highlighted that other factors like financial arrangements have been given less attention despite their important role enabling access to patients. More analyses of access to cancer medicines looking beyond reimbursement are needed to improve access and health outcomes. Future studies may want to focus on analyses of individual cancers (e.g. breast cancer, melanoma) and compare how the condition is treated in different countries including surgery, radiotherapy, chemotherapy, targeted therapies and immunotherapies. This would allow to highlight differences in the overall treatment of the condition rather than just focusing on new cancer medicines.

Finally, evaluation of existing efforts and initiatives to improve access to cancer medicines is needed. More evidence on the performance of country's experiences with strategic procurement and managed entry agreements is needed to inform policy and practice. Price is a key determinant of access and the latter is influenced by procurement. More evidence is needed on the impact of different procurement methods on price, volume, supply security and appropriate use of medicines. A number of initiatives, often pursued in a collaborative manner between different countries, to manage entry of new medicines have been implemented or are being introduced (e.g. adaptive pathways, horizon scanning, health technology assessment). Their evaluation and sharing of experience with other countries is important for mutual learning and identification of successful initiatives.

Appendices

Appendix 1: Key indicators and health system information on the study countries

	Belgium	Estonia	Scotland	Sweden
Gross domestic product (GDP) , in US$ PPP	40,023		37,041 (UK)	43,254
Total health care spending as % of GDP	11%	6%	9% (UK)	12%
Health care spending per capita, US$ PPP	4,392	1,668	3,277 (UK)	5,219
Spending on medicines (both, outpatient and inpatient) per capita, Euro	410 (2013)	N/A	314 (2013)	401 (2013)
Main source of health system financing	Social security contributions and subsidies from the federal government	Social health insurance contributions in the form of an earmarked social payroll tax	Taxation	Taxation
Population (million)	11,203	1,315	5,327 (2013)	9,644

Notes: purchasing power parity (PPP)

Sources: WHO Global Health Expenditure Database (http://apps.who.int/nha/database, accessed on 15 November 2016), data from Chapter 5, (Steel and Cylus 2012, Anell, Glenngård, and Merkur 2012, Lai et al. 2013, Gerkens and Merkur 2010)

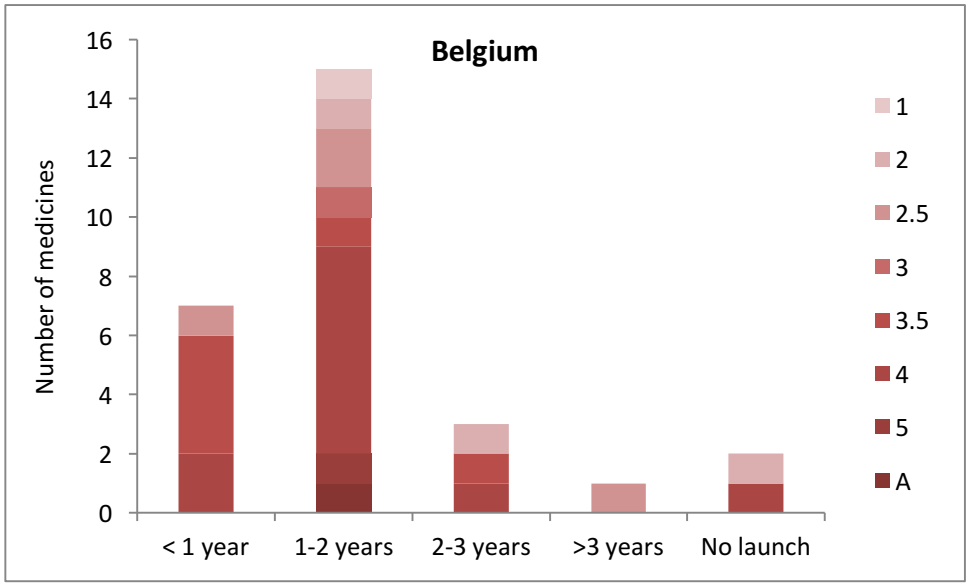
Appendix 2: List of medicines analysed in Chapter 4

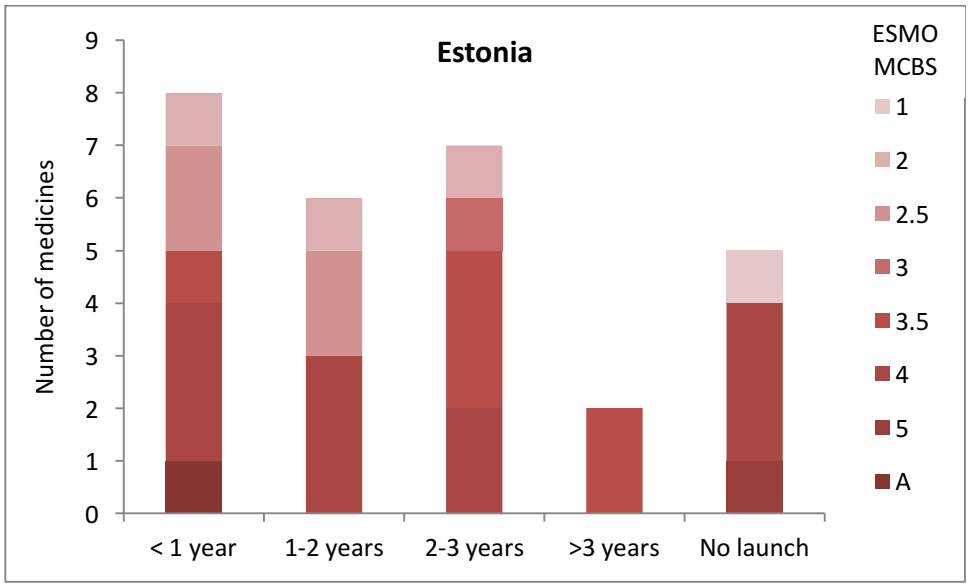
Medicine Name	Active Substance	ATC-5	Marketing Authorisation Holder	Authorisation date
Afinitor	everolimus	L01XE10	Novartis Europharm Limited	03/08/2009
Alimta	pemetrexed	L01BA04	Eli Lilly Nederland B.V.	20/09/2004
Ameluz	5-aminolevulinic acid hydrochloride	L01XD04	Biofrontera Bioscience GmbH	14/12/2011
Avastin	bevacizumab	L01XC07	Roche Registration Limited	12/01/2005
Caprelsa	vandetanib	L01XE12	AstraZeneca AB	17/02/2012
Erbitux	cetuximab	L01XC06	Merck KGaA	29/06/2004
Erivedge	vismodegib	L01XX43	Roche Registration Ltd	12/07/2013
Faslodex	fulvestrant	L02BA03	AstraZeneca UK Ltd	10/03/2004
Firmagon	degarelix	L02BX02	Ferring Pharmaceuticals A/S	17/02/2009
Foscan	temoporfin	L01XD05	biolitec pharma Itd.	24/10/2001
Giotrif	afatinib	L01XE13	Boehringer Ingelheim International GmbH	25/09/2013
Glivec	imatinib	L01XE01	Novartis Europharm Ltd	07/11/2001
Halaven	eribulin	L01XX41	Eisai Europe Ltd.	17/03/2011
Herceptin	trastuzumab	L01XC03	Roche Registration Limited	28/08/2000
Inlyta	axitinib	L01XE17	Pfizer Ltd	03/09/2012
Iressa	gefitinib	L01XE02	AstraZeneca AB	24/06/2009
Jakavi	ruxolitinib (as phosphate)	L01XE18	Novartis Europharm Ltd	23/08/2012
Javlor	vinflunine	L01CA05	Pierre Fabre Médicament	21/09/2009
Jevtana	cabazitaxel	L01CD04	sanofi-aventis groupe	17/03/2011
Kadcyla	trastuzumab emtansine	L01XC14	Roche Registration Ltd	15/11/2013
Lysodren	mitotane	L01XX23	Laboratoire HRA Pharma	28/04/2004
Mekinist	trametinib	L01XE25	Novartis Europharm Limited	30/06/2014
Panretin	alitretinoin	L01XX22	Eisai Ltd	11/10/2000
Perjeta	pertuzumab	L01XC13	Roche Registration Limited	04/03/2013
Pixuvri	pixantrone dimaleate	L01DB11	CTI Life Sciences Limited	10/05/2012
Removab	catumaxomab	L01XC09	Neovii Biotech GmbH	20/04/2009
Stivarga	regorafenib	L01XE21	Bayer Pharma AG	26/08/2013
Sutent	sunitinib	L01XE04	Pfizer Limited	19/07/2006

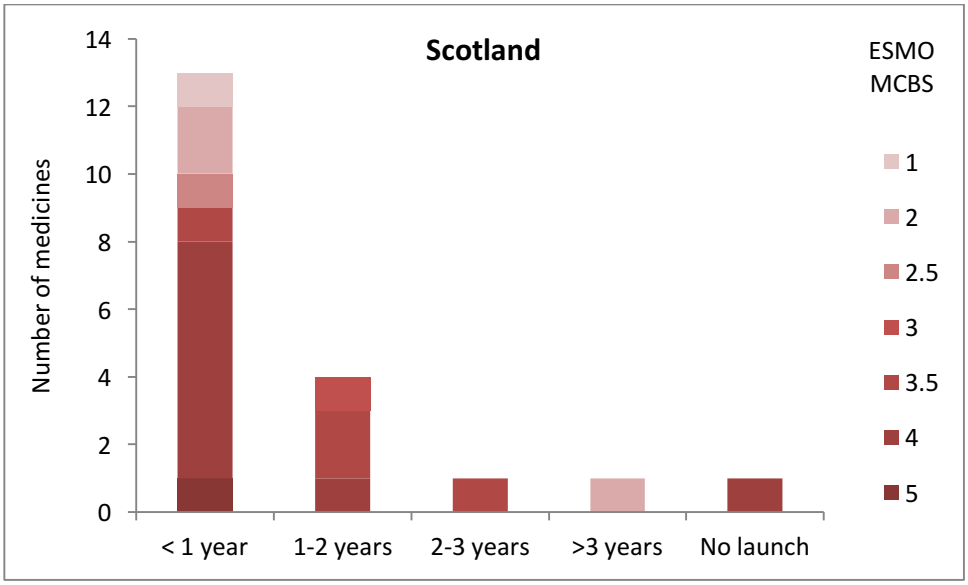
Medicine Name	Active Substance	ATC-5	Marketing Authorisation Holder	Authorisation date
Afinitor	everolimus	L01XE10	Novartis Europharm Limited	03/08/2009
Tafinlar	dabrafenib	L01XE23	Novartis Europharm Limited	26/08/2013
Tarceva	erlotinib	L01XE03	Roche Registration Limited	19/09/2005
Targretin	bexarotene	L01XX25	Eisai Ltd	29/03/2001
Teysuno	tegafur / gimeracil / oteracil	L01BC53	Nordic Group BV	14/03/2011
Trisenox	arsenic trioxide	L01XX27	Teva B.V.	05/03/2002
Tyverb	lapatinib	L01XE07	Novartis Europharm Limited	10/06/2008
Vargatef	nintedanib	L01XE31	Boehringer Ingelheim International GmbH	21/11/2014
Vectibix	panitumumab	L01XC08	Amgen Europe B.V.	03/12/2007
Velcade	bortezomib	L01XX32	Janssen-Cilag International NV	26/04/2004
Votrient	pazopanib	L01XE11	Novartis Europharm Limited	14/06/2010
Xalkori	crizotinib	L01XE16	Pfizer Ltd	23/10/2012
Xeloda	capecitabine	L01BC06	Roche Registration Limited	02/02/2001
Xtandi	enzalutamide	L02BB04	Astellas Pharma Europe B.V.	21/06/2013
Yervoy	ipilimumab	L01XC11	Bristol-Myers Squibb Pharma EEIG	13/07/2011
Zaltrap	aflibercept	L01XX44	Sanofi-Aventis Groupe	01/02/2013
Zelboraf	vemurafenib	L01XE15	Roche Registration Ltd	17/02/2012
Zydelig	idelalisib	L01XX47	Gilead Sciences International Ltd	18/09/2014
Zytiga	abiraterone acetate	L02BX03	Janssen-Cilag International N.V.	05/09/2011

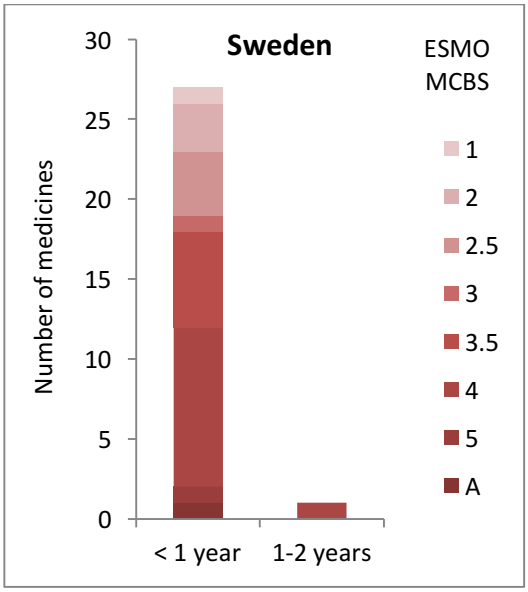
Notes: Extracted from EMA website on 20 July 2015

Appendix 3: Time to launch and distribution of launches and non-launches by ESMO-MCBS rating






Scotland
Number of medicines
14
12
10
8
6
4
2
0
< 1 year
1-2 years
2-3 years
>3 years
No launch
ESMO MCBS
1
2
2.5
3
3.5
4
5


Sweden
Number of medicines
30
25
20
15
10
5
0
< 1 year
1-2 years
ESMO MCBS
1
2
2.5
3
3.5
4
5
A

Appendix 4: Individual country models, Probability of launch T_3-T_0, Chapter 4

Model 1: Belgium	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.37***	0.12	-3.10	0.00	-0.60	-0.14
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	0.63	0.57	1.10	0.27	-0.49	1.75
Local manufacturer headquarter or sales representative (Estonia), baseline (no local headquarter/representative)						
-Local headquarter/representative	2.72	1.45	1.87	0.06	-0.13	5.57
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	-1.43	1.34	-1.06	0.29	-4.06	1.20
-L01C Plant alkaloids and other natural products	-2.21	1.16	-1.91	0.06	-4.48	0.06
-L01D Cytotoxic antibiotics and related substances						
-L02B Hormone antagonists and related agents	-0.11	1.04	-0.11	0.92	-2.16	1.93
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.01*	0.003	2.30	0.02	0.001	0.01
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	0.002	0.001	1.41	0.16	-0.001	0.005
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.56	0.91	0.61	0.54	-1.22	2.33
-Priority review only	-0.24	0.62	-0.38	0.70	-1.45	0.98
-Combination	0.17	0.51	0.33	0.74	-0.84	1.18
Year of marketing authorisation	0.01	0.08	0.13	0.90	-0.15	0.17
Time since EU-wide approval (quarters)	0.66***	0.15	4.52	0.00	0.38	0.95
Time since EU-wide approval (quarters), squared	-0.02***	0.01	-3.22	0.00	-0.03	-0.01
Constant	-5.33	1.27	-4.21	0.00	-7.81	-2.85
Log likelihood = -92.560633						
LR test of rho = 0: chibar2(01) = 0.00 Probability >= chibar2 = 1.000						

Number of observations = 395 Number of groups = 43

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 1: Estonia	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.28***	0.06	-4.84	0.00	-0.39	-0.16
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	-0.35	0.75	-0.47	0.64	-1.81	1.11
Local sales representative, baseline (no local representative)						
-Local representative	3.33***	0.92	3.63	0.00	1.53	5.14
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	0.49	0.94	0.52	0.61	-1.36	2.34
-L01C Plant alkaloids and other natural products	2.83*	1.03	2.74	0.01	0.80	4.85
-L01D Cytotoxic antibiotics and related substances						
-L02B Hormone antagonists and related agents	3.02*	1.07	2.83	0.01	0.93	5.12
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.00	0.00	0.75	0.46	0.00	0.01
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	0.02*	0.01	2.80	0.01	0.01	0.03
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.12	1.25	0.10	0.92	-2.33	2.57
-Priority review only	-1.11	0.89	-1.25	0.21	-2.84	0.63
-Combination	1.04	0.74	1.42	0.16	-0.40	2.49
Year of marketing authorisation	-0.29***	0.08	-3.76	0.00	-0.44	-0.14
Time since EU-wide approval (quarters)	0.58***	0.14	4.27	0.00	0.32	0.85
Time since EU-wide approval	-0.01*	0.00	-2.82	0.01	-0.02	0.00

(quarters), squared						
Constant	-4.87	1.52	-3.20	0.00	-7.85	-1.88
Log likelihood = -69.404113 LR test of rho=0: chibar2(01) = 0.00 Prob >= chibar2 = 1.000 Number of obs = 622 Number of groups = 45						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 1: Scotland	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.18*	0.08	-2.20	0.03	-0.34	-0.02
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	-0.08	0.90	-0.09	0.93	-1.85	1.68
Local manufacturer headquarter, baseline (no local headquarter)						
-Local headquarter	-0.36	0.73	-0.49	0.62	-1.78	1.07
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	-2.16	1.25	-1.72	0.09	-4.62	0.30
-L01C Plant alkaloids and other natural products	-5.86***	1.68	-3.49	0.00	-9.15	-2.57
-L01D Cytotoxic antibiotics and related substances	-2.87	1.51	-1.90	0.06	-5.84	0.10
-L02B Hormone antagonists and related agents	-1.67	0.86	-1.94	0.05	-3.35	0.02
Expected price in the therapeutic class (ATC-3), lagged one quarter	-0.02***	0.00	-3.18	0.00	-0.03	-0.01
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	-0.001	0.001	-1.01	0.31	0.003	0.001
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.40	1.09	0.37	0.71	-1.73	2.53
-Priority review only	2.94*	1.23	2.39	0.02	0.53	5.36

-Combination	2.66*	0.96	2.77	0.01	0.78	4.54
Year of marketing authorisation	0.10	0.16	0.64	0.52	-0.22	0.43
Time since EU-wide approval (quarters)	0.96***	0.22	4.42	0.00	0.53	1.38
Time since EU-wide approval (quarters), squared	-0.03*	0.01	-2.52	0.01	-0.05	-0.01
Constant	-5.03*	2.18	-2.30	0.02	-9.31	-0.75
Log likelihood = -52.749765 LR test of rho=0: chibar2(01) = 1.8e-05 Probability >= chibar2 = 0.498 Number of observations = 173 Number of groups = 31						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 1: Sweden	Coefficient	Standard error	z	P>z	[95% Conf.	Interval]
T1-T0, quarters	-0.09***	0.02	-3.72	0.00	-0.14	-0.04
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	0.93	0.63	1.47	0.14	-0.31	2.17
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	1.57	0.89	1.76	0.08	-0.17	3.31
-L01C Plant alkaloids and other natural products	1.95	1.10	1.77	0.08	-0.22	4.11
-L01D Cytotoxic antibiotics and related substances	2.31	1.47	1.58	0.12	-0.56	5.19
-L02B Hormone antagonists and related agents	1.09	0.85	1.29	0.20	-0.57	2.75
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.01*	0.00	2.41	0.02	0.00	0.01
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	0.00	0.00	-0.26	0.79	0.00	0.00
FDA expedited approval programme (EAP, baseline: no EAP)						

-Fast track only	1.39	0.87	1.60	0.11	-0.31	3.10
-Priority review only	3.03***	0.81	3.75	0.00	1.45	4.61
-Combination	2.82***	0.74	3.81	0.00	1.37	4.27
Year of marketing authorisation	-0.13	0.07	-1.71	0.09	-0.27	0.02
Time since EU-wide approval (quarters)	2.93***	0.59	4.95	0.00	1.77	4.09
Time since EU-wide approval (quarters), squared	-0.31***	0.08	-3.94	0.00	-0.46	-0.16
Constant	-6.37	1.44	-4.42	0.00	-9.20	-3.54
Log likelihood = -54.453156 LR test of rho=0: chibar2(01) = 8.9e-06 Probability >= chibar2 = 0.499 Number of observations = 279 Number of groups = 46						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 2: Belgium	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.44***	0.13	-3.41	0.00	-0.70	-0.19
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	0.73	0.59	1.22	0.22	-0.44	1.89
Local manufacturer headquarter, baseline (no local headquarter)						
-Local headquarter/representative	2.90	1.59	1.82	0.07	-0.23	6.03
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	-2.25	1.50	-1.50	0.13	-5.18	0.68
-L01C Plant alkaloids and other natural products	-2.03	1.16	-1.75	0.08	-4.31	0.24
-L01D Cytotoxic antibiotics and related substances						
-L02B Hormone antagonists and related agents	-0.51	1.16	-0.44	0.66	-2.78	1.76
Expected price in the	0.01*	0.003	2.67	0.01	0.002	0.01

therapeutic class (ATC-3), lagged one quarter						
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	0.000003	0.000001	1.81	0.07	-0.0000002	0.00001
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.83	0.95	0.88	0.38	-1.02	2.69
-Priority review only	-0.09	0.64	-0.13	0.89	-1.35	1.18
-Combination	0.29	0.57	0.50	0.61	-0.83	1.41
Year of marketing authorisation	-0.01	0.08	-0.08	0.94	-0.17	0.16
Time since EU-wide approval (quarters)	0.76***	0.16	4.68	0.00	0.44	1.07
Time since EU-wide approval (quarters), squared	-0.02***	0.01	-3.41	0.00	-0.03	-0.01
Prescrire rating	-0.18	0.20	-0.87	0.39	-0.58	0.22
Constant	-4.88	1.73	-2.81	0.01	-8.28	-1.48
Log likelihood = -86.799008 LR test of rho=0: chibar2(01) = 2.2e-05 Probability >= chibar Number of observations = 387 Number of groups = 40						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 2: Estonia	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.27	0.06	-4.76	0	-0.38	-0.16
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	-0.37	0.75	-0.49	0.62	-1.83	1.10
Local sales representative, baseline (no local representative)						

-Local representative	3.18	0.93	3.40	0	1.35	5.01
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	0.48	0.94	0.51	0.61	-1.35	2.31
-L01C Plant alkaloids and other natural products	2.91	1.08	2.70	0.01	0.80	5.02
-L01D Cytotoxic antibiotics and related substances						
-L02B Hormone antagonists and related agents	2.71	1.16	2.34	0.02	0.44	4.98
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.002	0.003	0.71	0.48	-0.004	0.01
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	0.00002	0.00001	2.68	0.01	0.000005	0.00003
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.09	1.24	0.08	0.94	-2.34	2.53
-Priority review only	-1.13	0.88	-1.29	0.20	-2.85	0.59
-Combination	1.03	0.74	1.40	0.16	-0.41	2.48
Year of marketing authorisation	-0.26	0.09	-2.97	0.003	-0.44	-0.09
Time since EU-wide approval (quarters)	0.58	0.14	4.15	0	0.31	0.86
Time since EU-wide approval (quarters), squared	-0.01	0.00	-2.78	0.01	-0.02	0.00
Prescrire rating	-0.12	0.23	-0.51	0.61	-0.58	0.34
Constant	-4.32	1.72	-2.51	0.01	-7.69	-0.95
Log likelihood = -69.05327 LR test of rho=0: chibar2(01) = 0.00 Probability >= chibar2 = 1.000 Number of observations = 602 Number of groups = 42						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 2: Scotland	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.15	0.09	-1.68	0.09	-0.32	0.02
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	-0.80	0.99	-0.81	0.42	-2.73	1.13
Local manufacturer headquarter, baseline (no local headquarter)						
-Local headquarter	-0.56	0.84	-0.66	0.51	-2.21	1.10
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	-3.05	1.68	-1.82	0.07	-6.33	0.24
-L01C Plant alkaloids and other natural products	-7.59***	2.04	-3.72	0.00	-11.59	-3.59
-L01D Cytotoxic antibiotics and related substances	-3.49	1.91	-1.83	0.07	-7.23	0.25
-L02B Hormone antagonists and related agents	-2.46	1.32	-1.86	0.06	-5.05	0.14
Expected price in the therapeutic class (ATC-3), lagged one quarter	-0.02***	0.01	-3.45	0.00	-0.04	-0.01
Expected volume at therapeutic class (ATC-3) in thousands DDDs, lagged one quarter	-0.000003	0.000001	-1.86	0.06	-0.00001	0.0000001
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	0.27	1.43	0.19	0.85	-2.53	3.07
-Priority review only	3.45*	1.48	2.32	0.02	0.54	6.36
-Combination	2.90*	1.29	2.26	0.02	0.38	5.42
Year of marketing authorisation	0.11	0.19	0.62	0.54	-0.25	0.48

Time since EU-wide approval (quarters)	1.08***	0.25	4.30	0.00	0.59	1.57
Time since EU-wide approval (quarters), squared	-0.03*	0.01	-2.50	0.01	-0.06	-0.01
Prescrire rating	0.31	0.25	1.21	0.23	-0.19	0.81
Constant	-6.25	2.74	-2.28	0.02	-11.63	-0.88
Log likelihood = -46.860869 LR test of rho=0: chibar2(01) = 0.00 Probability >= chibar2 = 1.000 Number of observations = 160 Number of groups = 28						

*p < 0.05, ** p < 0.01, *** p < 0.001

Model 2: Sweden	Coefficient	Standard error	z	P>z	[95% Confidence Interval]	
T1-T0, quarters	-0.09***	0.03	-3.30	0.00	-0.14	-0.04
Conditional marketing authorisation (CMA, baseline: no CMA)						
-Medicine approved with CMA	0.94	0.68	1.38	0.17	-0.39	2.28
Therapeutic group (baseline: other antineoplastic agents L01X)						
-L01B Antimetabolites	1.18	0.96	1.23	0.22	-0.71	3.07
-L01C Plant alkaloids and other natural products	2.07	1.16	1.78	0.08	-0.21	4.35
-L01D Cytotoxic antibiotics and related substances	1.90	1.57	1.21	0.23	-1.19	4.99
-L02B Hormone antagonists and related agents	0.68	0.95	0.71	0.48	-1.19	2.55
Expected price in the therapeutic class (ATC-3), lagged one quarter	0.01*	0.003	2.39	0.02	0.001	0.01
Expected volume at therapeutic class (ATC-3)	-0.0000002	0.000001	-0.36	0.72	-0.000001	0.000001

in thousands DDDs, lagged one quarter						
FDA expedited approval programme (EAP, baseline: no EAP)						
-Fast track only	3.32	1.25	2.65	0.01	0.86	5.77
-Priority review only	3.10***	0.88	3.53	0.00	1.38	4.82
-Combination	2.81***	0.85	3.32	0.00	1.15	4.47
Year of marketing authorisation	-0.07	0.09	-0.83	0.41	-0.25	0.10
Time since EU-wide approval (quarters)	3.30***	0.66	4.97	0.00	2.00	4.60
Time since EU-wide approval (quarters), squared	-0.35***	0.09	-4.11	0.00	-0.52	-0.18
Prescrire rating	-0.16	0.23	-0.68	0.50	-0.61	0.29
Constant	-6.55	1.86	-3.53	0.00	-10.19	-2.91

*p < 0.05, ** p < 0.01, *** p < 0.001

Appendix 5: List of medicines analysed in Chapter 5

Medicine Name	Active Substance	ATC code	Marketing Authorisation Holder	Authorisation date
Alimta	pemetrexed	L01BA04	Eli Lilly Nederland B.V.	20/09/2004
Xeloda	capecitabine	L01BC06	Roche Registration Ltd.	02/02/2001
Teysuno	tegafur / gimeracil / oteracil	L01BC53	Nordic Group BV	14/03/2011
Javlor	vinflunine	L01CA05	Pierre Fabre Médicament	21/09/2009
Jevtana	cabazitaxel	L01CD04	sanofi-aventis groupe	17/03/2011
Herceptin	trastuzumab	L01XC03	Roche Registration Ltd.	28/08/2000
Erbitux	cetuximab	L01XC06	Merck KGaA	29/06/2004
Avastin	bevacizumab	L01XC07	Roche Registration Limited	12/01/2005
Vectibix	panitumumab	L01XC08	Amgen Europe B.V.	03/12/2007
Removab	catumaxomab	L01XC09	Neovii Biotech GmbH	20/04/2009
Yervoy	ipilimumab	L01XC11	Bristol-Myers Squibb Pharma EEIG	13/07/2011
Foscan	temoporfin	L01XD05	biolitec pharma ltd.	24/10/2001
Glivec	imatinib	L01XE01	Novartis Europharm Ltd	07/11/2001
Iressa	gefitinib	L01XE02	AstraZeneca AB	24/06/2009
Tarceva	erlotinib	L01XE03	Roche Registration Ltd.	19/09/2005
Sutent	sunitinib	L01XE04	Pfizer Limited	19/07/2006
Tyverb	lapatinib	L01XE07	Glaxo Group Limited	10/06/2008
Afinitor	everolimus	L01XE10	Novartis Europharm Ltd.	03/08/2009
Votrient	pazopanib	L01XE11	Glaxo Group Ltd.	14/06/2010
Caprelsa	vandetanib	L01XE12	AstraZeneca AB	17/02/2012
Zelboraf	vemurafenib	L01XE15	Roche Registration Ltd.	17/02/2012
Xalkori	crizotinib	L01XE16	Pfizer Ltd.	23/10/2012
Inlyta	axitinib	L01XE17	Pfizer Ltd.	03/09/2012
Lysodren	mitotane	L01XX23	Laboratoire HRA Pharma	28/04/2004
Targretin	bexarotene	L01XX25	Eisai Ltd.	29/03/2001
Trisenox	arsenic trioxide	L01XX27	Teva Pharma B.V.	05/03/2002
Velcade	bortezomib	L01XX32	Janssen-Cilag International NV	26/04/2004

Medicine Name	Active Substance	ATC code	Marketing Authorisation Holder	Authorisation date
Alimta	pemetrexed	L01BA04	Eli Lilly Nederland B.V.	20/09/2004
Halaven	eribulin	L01XX41	Eisai Europe Ltd.	17/03/2011
Faslodex	fulvestrant	L02BA03	AstraZeneca UK Ltd.	10/03/2004
Firmagon	degarelix	L02BX02	Ferring Pharmaceuticals A/S	17/02/2009
Zytiga	abiraterone acetate	L02BX03	Janssen-Cilag International N.V.	05/09/2011

Notes: Extracted from EMA website on 26 February 2015

Appendix 6: Estimated age-standardised rates (European standard) of cancer incidence by sex, cancer site and country, 2012

	Oesophagus (C15)		Stomach (C16)		Colon (C18)		Rectum (C20)		Liver (C22)	
	M	F	M	F	M	F	M	F	M	F
Sweden	4.8	1.6	6.7	4.2	29.2	24.4	19.1	12.6	6.3	2.8
Scotland	24.9	10.2	15.6	6.7	23.9	16.4	10.5	5.9	11.7	6.6
Belgium	10.8	3.1	13.3	5.5	42.5	29.8	21.3	11.5	8.7	3.0

	Pancreas (C25)		Larynx (C32)		Bronchus and lung (C34)		Melanoma (C43)		Breast (C50)	Cervix (C53)
	M	F	M	F	M	F	M	F	F	F
Sweden	8.6	7.5	2.0	0.6	28.8	27.1	25.4	25.8	113.2	9.4
Scotland	17.5	13.7	3.5	0.8	100.3	76.8	5.3	2.7	168.9	4.1
Belgium	11.7	8.6	7.4	1.3	82.5	31.5	17.2	21.4	147.2	10.6

Data sources: Belgium (http://www.kankerregister.org/), Scotland (http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/), Sweden (http://www-dep.iarc.fr/NORDCAN/)

Appendix 7: General semi-structured questionnaire for interviews with oncologists, Chapter 6

Diagnosis

1. Do you have national estimates of the percentage of patients with primary breast cancer overexpressing HER-2?
2. Who is tested for HER-2 among breast cancer patients?
   2.1. Is this fully implemented in practice?
   2.2. If yes, since when is this the case?
   2.3. Which diagnostic method is used?

Referral and waiting times

3. Where are the majority of breast cancer cases detected or sent for referral (e.g. primary care, national screening programme, self-referral)?
4. Do patients need to visit their family doctor to be referred to an oncologist?
5. Is there evidence on waiting times for oncology and are there targets? If yes, to what extent are they met?

Clinical guidelines

6. Which guidelines are followed in the country for the treatment of breast cancer (national, international, institutional)?
7. Do these include also criteria to start/stop treatment (e.g. side effects, response) for trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine?

Clinical practice

8. Within the field of breast cancer treatment, does clinical practice closely match clinical guidance? If not, in which aspects does it differ?

Financing

9. How are inpatient medicines financed?
10. Are there additional mechanisms for funding expensive medicines (e.g. special funds)?
11. Are there any limits imposed on the number of patients that can be treated with HER-2 targeted therapies?
12. Can you prescribe medicines which do not have a positive reimbursement decision or for which a decision is still pending?
13. How do you work within a finite budget, i.e. how do you set priorities? E.g. age, stage, fitness of the patient, presence of co-morbidities, fixed cap on patients treated with certain expensive medicines, prior authorization, etc.

References

14 juillet 1994. Loi sur l'assurance obligatoire soins de santé et indemnités.

2016. "Prescrire." accessed 19 February 2016. http://www.prescrire.org.

[No authors listed]. 2010. "Growing threat from counterfeit medicines." *Bull World Health Organ.* 88 (4):247-8.

Abrantes-Metz, R, C Adams, and A Metz. 2004. Pharmaceutical Development Phases: A Duration Analysis

http://www.ftc.gov/be/workpapers/wp274.pdf In *Working paper no. 274*. Washington, DC: US Federal Trade Commission: Bureau of Economics.

Access to Medicine Foundation. 2015. The 2016 Access to Medicine Index Methodology. Haarlem.

Access to Medicine Foundation. 2016. "What is the Index?", accessed 7 September 2016. http://www.accesstomedicineindex.org/what-index.

Adamski, J., B. Godman, G. Ofierska-Sujkowska, B. Osinska, H. Herholz, K. Wendykowska, O. Laius, S. Jan, C. Sermet, C. Zara, M. Kalaba, R. Gustafsson, K. Garuoliene, A. Haycox, S. Garattini, and L. L. Gustafsson. 2010. "Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers." *BMC Health Serv Res.* 10. doi: 153

10.1186/1472-6963-10-153.

Agence Intermutualiste. 2014. Programme de Dépistage du Cancer du Sein. Comparaison du troisième tour (2007-2008) et du quatrième tour (2009-2010). In *Rapport numéro 8 de l'Agence Intermutualiste*. Brussels.

Aggarwal, A, O Ginsburg, and T Fojo. 2014. "Cancer Economics, policies and politics: What informs the debate? Lessons from the EU, Canada and US." *J Cancer Policy* 2 (1):1-11.

Allison, PD. 2010. "Survival Analysis." In *The Reviewer's Guide to Quantitative Methods in the Social Sciences*, edited by GR Hancok and RO Mueller. New York: Taylor and Francis.

Alpert, A, M Duggan, and JK Hellerstein. 2013. "Perverse reverse price competition: Average wholesale prices and Medicaid pharmaceutical spending." *J Public Econ* 108:44-62.

Amaral, SMS, and CR Blatt. 2011. "Municipal consortia for medicine procurement: impact on the stock-out and budget." *Rev Saúde Pública* 45 (3).

Amgros. 2016a. The past year 2015. Copenhagen.

Amgros. 2016b. The past year: 2015 In *Annual report*. Copenhagen.

Anell, A, AH Glenngård, and S Merkur. 2012. *Sweden: Health system review*. Vol. 14, *Health Systems in Transition*.

Anis, AH, DP Guh, and J Woolcott. 2003. "Lowering generic drug prices: less regulation equals more competition." *Med Care.* 41 (1):135-41.

APME. 2016. "Website of the Association of Pharmaceutical Manufacturers in Estonia." accessed 15 March 2016. http://rtl.ee/en/members/.

Arickx, F. 2016. Belgium, Netherlands, Luxembourg and Austria (Beneluxa): A Collaboration Initiative for the reimbursement of medicines. In *Presentation, WHO Consultation on Strategic Procurement, Copenhagen 23 September 2016*.

Arnberg, K. 2014. "The ability of CED to address uncertainties and improve performance in drug use." LSE Summit on risk sharing and managed entry agreements, London, United Kingdom, 14 February 2014.

Baburin, A, T Aareleid, P Padrik, V Valvere, and K Innos. 2014. "Time trends in population-based breast cancer survival in Estonia: Analysis by age and stage." *Acta Oncol.* 53 (2):226-34.

Baburin, A, T Aareleid, M Rahu, L Reedik, and K Innos. 2016. "Recent changes in breast cancer incidence and mortality in Estonia: Transition to the west." *Acta Oncol.* 55 (6):728–33.

Bach, PB, RM Conti, RJ Muller, GC Schnorr, and LB Saltz. 2016. "Overspending driven by oversized single dose vials of cancer drugs." *BMJ* 352::i788.

Bach, PB, and SD Pearson. 2015. "Payer and Policy Maker Steps to Support Value-Based Pricing for Drugs." *JAMA* 314 (23):2503-4.

Baldi, S, and D Vannoni. 2015. "The Impact of Centralization on Pharmaceutical Procurement Prices: The Role of Institutional Quality and Corruption." *Regional Studies* DOI:10.1080/00343404.2015.1101517.

Baldo, P, and P De Paoli. 2014. "Pharmacovigilance in oncology: evaluation of current practice and future perspectives." *J Eval Clin Pract.* 20 (5):559-69.

Balduzzi, S, S Mantarro, V Guarneri, L Tagliabue, V Pistotti, L Moja, and R D'Amico. 2014. "Trastuzumab-containing regimens for metastatic breast cancer." *Cochrane Database of Systematic Reviews* (6).

Barros, P. P. 2011. "The simple economics of risk-sharing agreements between the NHS and the pharmaceutical industry." *Health Econ.* 20 (4):461-470. doi: 10.1002/hec.1603.

Bartels, D. 2016. "Centralizing procurement of medicines to save costs for Denmark." *Eurohealth Observer* 22 (2).

Bartsch, R, C Wenzel, G Altorjai, U Pluschnig, M Rudas, RM Mader, M Gnant, CC Zielinski, and GG Steger. 2007. "Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer." *J Clin Oncol.* 25 (5):3853-8.

Basch, E. 2016. "Toward a Patient-Centered Value Framework in Oncology." *JAMA* 315 (19):2073-4.

BBC. 2016. Scots nurse to get cancer drug after funding u-turn.

Belgian Cancer Registry. 2015. Cancer burden in Belgium 2004-2013. In *Trends, incidence, survival, prevalence, mortality, projections*. Brussels.

Belgian Health Care Knowledge Centre (KCE). 2014. Informed choice on breast cancer screening: Messages to support informed decisions. In *KCE Report 2016*. Brussels.

Benjamin, L, V Buthion, G Vidal-Trécan, and P Briot. 2014. "Impact of the health care payment system on patient access to oral anticancer drugs: an illustration from the French and United States contexts." *BMC Health Serv Res.* 14 (274).

Bergman, MA , D Granlund, and N Rudholm. 2015. Squeezing the last drop out of your suppliers: an empirical study of market-based purchasing policies for generic pharmaceuticals.

Bertoldi, AD, AJ Barros, A Wagner, D Ross-Degnan, and PC Hallal. 2008. "A descriptive review of the methodologies used in household surveys on medicine utilization." *BMC Health Serv Res.* 8 (222).

Bigdeli, M, B Jacobs, G Tomson, R Laing, A Ghaffar, B Dujardin, and W Van Damme. 2013. "Access to medicines from a health system perspective." *Health Policy Plan.* 28 (7):692-704.

Bigdeli, M, S Zafar, H Assad, and A Ghaffar. 2013. "Health system barriers to access and use of magnesium sulfate for women with severe pre-eclampsia and eclampsia in Pakistan: evidence for policy and practice." *PLoS One* 8 (3):e59158.

Blankart, CR, and T Stargardt. 2016. "Preferred supplier contracts in post-patent prescription drug markets." *Health Care Manag Sci* Feb 22. [Epub ahead of print].

Blau, J, C Hoestlandt, A D Clark, L Baxter, AG Felix Garcia, B Mounaud, and L Mosina. 2015. "Strengthening national decision-making on immunization by building capacity for economic evaluation: Implementing ProVac in Europe." *Vaccine* 33 (Suppl 1):A34-9.

Blehar, MC, G Spong, C Grady, SF Goldkind, L Sahin, and JA Clayon. 2013. "Enrolling Pregnant Women: Issues in Clinical Research." *Womens Health Issues* 23 (1):e39-e45.

Blommestein, HM, MG Franken, SG Verelst, M van Agthoven, PC Huijgens, and CA Uyl-de Groot. 2014. "Access to expensive cancer drugs in Dutch daily practice: should we be concerned?" *Neth J Med.* 72 (4):235-41.

Blumenthal, D. 2016. "Value-Based Drug Pricing: Watch Out for Side Effects." *To the Point*.

Bochenek, T, B Godman, A Bucsics, E De Weerdt, J Fürst, E Gailite, TA Hotvedt, I Huys, A Inotai, R Joppi, A Malaj, K Margus, V Marković-Peković, S Simoens, J Slaby, L Sović Brkičić, EU Gürpınar, P Vella Bonanno, EJ Warminska, and A Pilc. 2016. "Systemic Solutions, Legislative And Organizational Frameworks Aimed To Prevent Or Mitigate Drug Shortages In European Countries." *Value Health.* 19 (7):A445.

Bocquet, F, P Paubel, I Fusier, AL Cordonnier, C Le Pen, and M Sinègre. 2014. "Biosimilar granulocyte colony-stimulating factor uptakes in the EU-5 markets: a descriptive analysis." *Appl Health Econ Health Policy* 12 (3):315-26.

Bonair, A, and J Persson. 1996. "Innovation and diffusion of health care technologies." In *Assessment of health care technologies*, edited by Kankaanpaa J Szczepura A, 17–28. Chichester: Wiley.

Burstein, HJ. 2005. "The distinctive nature of HER2-positive breast cancers." *N Engl J Med.* 353 (16):1652-4.

Canada's Premiers. 2016a. "The pan-Canadian Pharmaceutical Alliance." accessed 22 October 2016. http://www.pmprovincesterritoires.ca/en/initiatives/358-pan-canadian-pharmaceutical-alliance.

Canada's Premiers. 2016b. "Pan-Canadian Pharmaceutical Alliance: Active Negotiations." accessed 30 September 2016. http://www.pmprovincesterritoires.ca/phocadownload/pcpa/2016/pcpa_active_negotiations_sept30_2016.pdf.

Canada's Premiers. 2016c. "Pan-Canadian Pharmaceutical Alliance: Completed Negotiations." accessed 30 September 2016. http://www.pmprovincesterritoires.ca/phocadownload/pcpa/2016/pcpa_completed_negotiations_sept30_2016.pdf.

Cancer Research Technology. 2016. "Clinical development." accessed 16 September 2016. http://www.cancertechnology.co.uk/clinical-development.

Cancer Research UK. 2016. "Research opportunities for cancers with substantial unmet need." accessed 28 September 2016. http://www.cancerresearchuk.org/funding-for-researchers/research-opportunities-for-cancers-with-substantial-unmet-need.

Cancerfonden. 2015. Cancerfondsrapporten. Stockholm.

Carbonneil, C., F. Quentin, S. H. Lee-Robin, and Asse European Network Hlth Technol. 2009. "A common policy framework for evidence generation on promising health technologies." *Int J Technol Assess Health Care.* 25:56-67. doi: 10.1017/s0266462309990699.

Carletto, A. 2016. "Value-based reimbursement through the AIFA registries. Differential reimbursement for drugs with multiple indications through outcome-based agreements." The LSE Summit, Rethinking regulation and value assessment of medical technologies: challenges and opportunities, London, 8-9 March 2016.

Carlson, J. J., S. D. Sullivan, L. P. Garrison, P. J. Neumann, and D. L. Veenstra. 2010. "Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between health care payers and manufacturers." *Health Policy* 96 (3):179-190. doi: 10.1016/j.healthpol.2010.02.005.

Carradinha, H. 2009. "Tendering short-term pricing policies and the impact on patients, governments and the sustainability of the generic medicines industry." *J Generic Med.* 6 (4):351-361.

Carter, AJ, B Delarosa, and H Hur. 2015. "An analysis of discrepancies between United Kingdom cancer research funding and societal burden and a comparison to previous and United States values." *Health Res Policy Syst.* 13 (62).

Carter, AJR, and CN Nguyen. 2012. "A comparison of cancer burden and research spending reveals discrepancies in the distribution of research funding." *BMC Public Health* 12 (526).

Casado, B, S Ruiz, K Genenz, and F Schmidt. 2009. Nuevas tendencias en la evaluación y financiación de medicamentos en Europa: Estrategias de Riesgo Compartido. In *Simon Kucher & Partners Strategy & Marketing Consultants*, edited by Presentation in Malaga 19.07.2009.

Castellblanch, R. 2003. "Challenging pharmaceutical industry political power in Maine and Vermont." *J Health Polit Policy Law.* 28 (1):109-32.

Cattaneo, A, and G Maciocco. 2016. "Compulsory licensing for direct-acting antivirals drugs for Hepatitis C. Response to: A pill too hard to swallow: how the NHS is limiting access to high priced drugs." *BMJ* 354:i4117.

Caudron, JM, N Ford, M Henkens, C Macé, R Kiddle-Monroe, and J Pinel. 2008. "Substandard medicines in resource-poor settings: a problem that can no longer be ignored." *Trop Med Int Health.* 13 (8):1062-72.

CBIP. 2016. "Centre Belge d'Information Pharmacothérapeutique." Last Modified Last accessed 2 May 2016. http://www.cbip.be/.

Center for Pharmaceutical Management. 2003. Defining and Measuring Access to Essential Drugs, Vaccines, and Health Commodities: Report of the WHO-MSH Consultative Meeting, Ferney-Voltaire, France, December 11–13, 2000. Arlington, VA: Management Sciences for Health.

Chamberlain, C, SM Collin, P Stephens, J Donovan, A Bahl, and W Hollingworth. 2014. "Does the cancer drugs fund lead to faster uptake of cost-effective drugs? A time-trend analysis comparing England and Wales." *Br J Cancer.* 111 (9):1693-702.

Chandra, A, J Shafrin, and R Dhawan. 2016. "Utility of Cancer Value Frameworks for Patients, Payers, and Physicians." *JAMA* 315 (19):2069-70.

Chaudhury, RR, R Parameswar, U Gupta, S Sharma, U Tekur, and JS Bapna. 2005. "Quality medicines for the poor: experience of the Delhi programme on rational use of drugs." *Health Policy Plan.* 20 (2):124-36.

Chauhan, D, and A Mason. 2008. "Factors affecting the uptake of new medicines in secondary care – a literature review." *J Clin Pharm Ther.* 33 (4):339–348.

Chaumont, C, S Bautista-Arredondo, JJ Calva, RI Bahena-González, GH Sánchez-Juárez, A González de Araujo-Muriel, C Magis-Rodríguez, and M Hernández-Ávila. 2015. "Antiretroviral purchasing and prescription practices in Mexico: constraints, challenges and opportunities." *Salud Publica Mex.* 57 (Suppl 2):s171-82.

Cheema, PK, S Gauvra, M Migus, B Godman, L Yeung, and ME Trudeau. 2012. "International variability in the reimbursement of cancer drugs by publically funded drug programs." *Curr Oncol.* 19 (3):e165–e176.

Cherny, N, R Sullivan, J Torode, M Saar, and A Eniu. 2016. "ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe." *Ann Oncol.* 27 (8):1423-43.

Cherny, NI, R Sullivan, U Dafni, JM Kerst, A Sobrero, C Zielinski, EG de Vries, and MJ Piccart. 2015. "A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)." *Ann Oncol.* 26 (8):1547-73.

Chirac, P, and E Torreele. 2006. "Global framework on essential health R&D." *Lancet* 367 (9522):1560-1.

Chorzelski, S, B Grosch, H Rentmeister, S Völler, B Landré, J Pfitzner, C Wechselmann, R Busse, S Edwards, and C Henschke. 2015. Breaking through the Wall: Enhancing Research and Development of Antibiotics in Science and Industry. In *Global Union for Antibiotics Research and Development (GUARD) Initiative Commissioned by the German Federal Ministry of Health*. Berlin: Boston Consulting Group, ÖPP Deutschland AG, Technische Universität Berlin.

Clement, FM, A Harris, JJ Li, K Young, KM Lee, and BJ Manns. 2009. "Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada." *JAMA. 2009 Oct 7;302(13):1437-43* 302 (13):1437–1443.

Cockburn, I, JO Lanjouw, and M Schankerman. 2014. Patents, Price Controls, and Access to New Drugs: How Policy Affects Global Market Entry. In *CEP Discussion Paper No 1298*.

Cohen, J., L Faden, S Predaris, and B Young. 2007. "Patient access to pharmaceuticals: an international comparison." *Eur J Health Econ.* 8 (3):253-266.

Colpaert, C, and R Salgado. 2007. "Belgian guidelines for HER2/neu testing in breast cancer." *BJMO* 1 (1):22-29.

Comité économique des produits de santé. 2015. Rapport d'activité 2014/15. Paris: Ministère des affaires sociales et de la santé.

Costa-Font, J, A McGuire, and N Varol. 2015. "Regulation effects on the adoption of new medicines." *Empirical Economics* 49:1101–1121.

Côté, A, and B Keating. 2012. "What is wrong with orphan drug policies?" *Value Health* 15 (8):1185-91.

Council of the European Union. 2016a. "Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States." accessed 28 September 2016. http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/.

Council of the European Union. 2016b. Shortages of human medicines in the European Union. Brussels.

Crawford, M, V Sauerzapf, R Haynes, D Forman, and AP Jones. 2012. "Social and geographical factors affecting access to treatment of colorectal cancer: a cancer registry study." *BMJ Open* 2 (2):e000410.

Crawford, SM, V Sauerzapf, R Haynes, H Zhao, D Forman, and AP Jones. 2009. "Social and geographical factors affecting access to treatment of lung cancer." *Br J Cancer.* 101 (6):897-901.

CVZ. 2012a. Pay-for-Performance Overeenkomst omalizumab (Xolair) voor de behandeling van ernstige astma.

CVZ. 2012b. "Voorwaardelijk toegelaten geneesmiddelen [List of MEAs implemented in the Netherlands]." Last Modified 1 October 2012, accessed 23 April 2013. http://www.cvz.nl/hetcvz/actualiteit/121005-voorwaardelijk-toegelaten-geneesmiddelen.html.

D'Sa, MM , DS Hill, and TP Stratton. 1994. "Diffusion of innovation I: Formulary acceptance rates of new drugs in teaching and non-teaching British Columbia hospitals--a hospital pharmacy perspective." *Can J Hosp Pharm* 47 (6):254-60.

D'Sa, MM, DS Hill, and TP Stratton. 1995. "Diffusion of innovation II: Formulary acceptance rates of new drugs in teaching and non-teaching British Columbia hospitals--a drug development perspective." *Can J Hosp Pharm* 48 (1):7-15.

Dafny, LS, CJ Ody, and MA Schmitt. 2016. "Undermining Value-Based Purchasing - Lessons from the Pharmaceutical Industry." *N Engl J Med.* 375 (21):2013-2015.

Daniel, MG, TM Pawlik, AN Fader, NF Esnaola, and MA Makary. 2016. "The Orphan Drug Act: Restoring the Mission to Rare Diseases." *Am J Clin Oncol.* 39 (2):210-3.

Danzon, P, A Towse, and J Mestre-Ferrandiz. 2015. "Value-based differential pricing: efficient prices for drugs in a global context." *Health Econ.* 24 (3):294-301.

Danzon, PM , and AJ Epstein. 2012. "Effects of regulation on drug launch and pricing in interdependent markets." *Adv Health Econ Health Serv Res* 23:35-71.

Danzon, PM , YR Wang, and L Wang. 2005. "The impact of price regulation on the launch delay of new drugs--evidence from twenty-five major markets in the 1990s." *Health Econ.* 14 (3):269-92.

Danzon, PM, and LW Chao. 2000. "Cross-national price differences for pharmaceuticals: how large, and why?" *J Health Econ.* 19 (2):159-95.

Danzon, PM, and MF Furukawa. 2003. "Prices and availability of pharmaceuticals: evidence from nine countries." *Health Aff (Millwood)* Suppl Web Exclusives:W3-521-36.

Danzon, PM, and MF Furukawa. 2006. "Prices and availability of biopharmaceuticals: an international comparison." *Health Aff (Millwood)* 25 (5):1353-62.

Danzon, PM, and MF Furukawa. 2008. "International prices and availability of pharmaceuticals in 2005." *Health Aff (Millwood)* 27 (1):221-33.

Darrow, JJ , and AS Kesselheim. 2014. "Drug development and FDA approval, 1938-2013." *N Engl J Med* 370 (26):e39.

De Lott, LB, JF Burke, KA Kerber, LE Skolarus, and BC Callaghan. 2016. "Medicare Part D payments for neurologist-prescribed drugs." *Neurology* 86 (16):1491-8.

de Souza, JA, and TY Seiwert. 2014. "A value framework in head and neck cancer care." *Am Soc Clin Oncol Educ Book*:e304-9.

Degrassat-Théas, A, M Bensadon, C Rieu, M Angalakuditi, C Le Pen, and P Paubel. 2012. "Hospital reimbursement price cap for cancer drugs: the French experience in controlling hospital drug expenditures." *Pharmacoeconomics* 30 (7):565-73.

Degrassat-Théas, A, P Paubel, O Parent de Curzon, C Le Pen, and M Sinègre. 2013. "Temporary authorization for use: does the French patient access programme for unlicensed medicines impact market access after formal licensing?" *Pharmacoeconomics* 31 (4):335-43.

Department of Health. 2008. The Pharmaceutical Price Regulation Scheme 2009. London.

Derbyshire, M. 2015. "Patent expiry dates for best-selling biologicals." *GaBI Journal* 4 (4):178-9.

Devlin, G. 2010. "Women and elderly: subgroups under-represented in clinical trials." *Curr Opin Cardiol.* 25 (4):335-9.

DiMasi, JA , L Feldman, A Seckler, and A Wilson. 2010. "Trends in risks associated with new drug development: success rates for investigational drugs." *Clin. Pharmacol. Ther.* 87 (3):272–7.

DIMDI. 2016. Anatomisch-therapeutisch-chemische Klassifikation mit Tagesdosen. In *Amtliche Fassung des ATC-Index mit DDD-Angaben für Deutschland in Jahre 2016*. Berlin: Deutschen Institut für Medizinische Dokumentation und Information.

Dranitsaris, G, WK Evans, D Milliken, and B Zanke. 2005. "The impact of practice guidelines and funding policies on the use of new drugs in advanced non-small cell lung cancer." *J Eval Clin Pract.* 11 (4):350-6.

Drugs for Neglected Diseases initiative (DNDi). 2016. "Website of Drugs for Neglected Diseases initiative." accessed 15 September 2016. http://www.dndi.org/.

Drummond, M, and A Towse. 2014. "Orphan drugs policies: a suitable case for treatment." *Eur J Health Econ.* 15 (4):335-40.

Dupree, R, and P Pasman. 2013. Pakketbeheer specialistische geneesmiddelen. College voor zorgverzekeringen.

Dutch National Health Care Institute. 2014. "Website of the Dutch National Health Care Institute." http://www.zorginstituutnederland.nl/.

Dylst, P, A Vulto, and S Simoens. 2011. "Tendering for outpatient prescription pharmaceuticals: What can be learned from current practices in Europe?" *Health Policy* 101:146-152.

EAHP. 2014. Medicines shortages in European hospitals. In *Results of the largest pan-European survey on medicines supply shortages in the hospital sector, its prevalence, nature and impacts for patient care*. Brussels: European Association of Hospital Pharmacists.

ECDC. 2016. "European Surveillance of Antimicrobial Consumption Network (ESAC-Net)." European Centre for Disease Prevention and Control, accessed 1 November 2016. http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-consumption/ESAC-Net/Pages/ESAC-Net.aspx.

EFPIA. 2014. Improving patient access to innovative medicines: The framework in which differentiated pricing may offer a solution. Brussels: European Federation of Pharmaceutical Industries and Associations.

EFPIA. 2015. Patients W.A.I.T. Indicator 2015 Report. Brussels: European Federation of Pharmaceutical Industries.

Eichler, HG , K Oye, LG Baird, E Abadie, J Brown, CL Drum, J Ferguson, S Garner, P Honig, M Hukkelhoven, JCW Lim, R Lim, MM Lumpkin, G Neil, B O'Rourke, E Pezalla, D Shoda, V Seyfert-Margolis, EV Sigal, J Sobotka, D Tan, TF Unger, and G Hirsch. 2012. "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval." *Clin Pharmacol Ther.* 91 (3):426-437.

Eichler, HG, F Pignatti, B Flamion, H Leufkens, and A. Breckenridge. 2008. "Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma." *Nat Rev Drug Discov.* 7:818-826.

Elek, P, A Harsányi, T Zelei, K Csetneki, and Z Kaló. 2017. "Policy objective of generic medicines from the investment perspective: The case of clopidogrel." *Health Policy* [Epub on 7 March 2017 ahead of print].

Ellis, LM, DS Bernstein, EE Voest, JD Berlin, D Sargent, P Cortazar, E Garrett-Mayer, RS Herbst, RC Lilenbaum, C Sima, AP Venook, M Gonen, RL Schilsky, NJ Meropol, and LE Schnipper. 2014. "American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes." *J Clin Oncol.* 32 (12):1277-80.

EMA. 2004. Herceptin: EPAR Scientific Discussion London: European Medicines Agency.

EMA. 2015. "Website of the European Medicines Agency." accessed 29.07.2015. http://www.ema.europa.eu.

EMA. 2016a. "Adaptive pathways: key learnings and next steps." accessed 3 December 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/08/news_detail_002586.jsp&mid=WC0b01ac058004d5c1.

EMA. 2016b. Final report on the adaptive pathways pilot London: European Medicines Agency.

EMA. 2016c. "Orphan designation." European Medicines Agency, accessed 15 September 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp.

EMA. 2016d. "Website of the European Medicines Agency." European Medicines Agency, accessed 8 November 2016. http://www.ema.europa.eu/.

ESMO. 2015. "ESMO Magnitude of Clinical Benefit Scale." European Society for Medical Oncology, accessed 18.04.2015. http://www.esmo.org/Policy/Magnitude-of-Clinical-Benefit-Scale.

Espín, J, J Rovira, A Calleja, N Azzopardi-Muscat, E Richardson, W Palm, and D Panteli. 2016. How can voluntary cross-border collaboration in public procurement improve access to health technologies in Europe? . In *Policy brief 21*. Copenhagen: European Observatory on Health Systems and Policies.

Esti Haigekassa. 2015. [Disease prevention programs in the 2014 annual results]. Tallinn: Estonian Health Insurance Fund.

Esti Haigekassa. 2016a. Estonian Health Insurance Fund. In *Yearbook 2015*. Tallinn.

Esti Haigekassa. 2016b. "Website of the Estonian Health Insurance Fund." accessed Last accessed on 15 July 2016. https://www.haigekassa.ee/en.

European Biopharmaceutical Enterprises. 2015. "What pricing and reimbursement policies to use for off-patent biologicals? – Results from the EBE 2014 biological medicines policy survey." *GaBI Journal* 4 (1):17-24.

European Cancer Observatory (EUCAN). 2016. "EUCAN website ", accessed 20 July 2016. http://eco.iarc.fr/eucan/.

European Commission. 2014. Medical countermeasures that could be procured in common under the joint procurement agreement. Luxembourg.

European Commission, Health and consumers Directorate-General. 2012. General report on experience acquired as a result of the application of the paediatric regulation. Brussels.

European Parliament, and European Council. 2004. "Regulation (EC) No 726/2004 of the European Parliament and of the council of 31 March 2004." *Official Journal of the European Union* L 136/1.

FDA. 2016a. Novel drugs 2015. U.S. Food and Drug Administration, Center of Drug Evaluation and Research.

FDA. 2016b. "Website of the U.S. Food & Drug Administration." U.S. Department of Health and Human Services, accessed 8 November 2016. http://www.fda.gov/.

Ferguson, JSJ, M Summerhayes, S Masters, S Schey, and IE Smith. 2000. "New treatments for advanced cancer: an approach to prioritization." *Br J Cancer.* 83 (10):1268–73.

Ferlay, J , E Steliarova-Foucher, J Lortet-Tieulent, S Rosso, JW Coebergh, H Comber, D Forman, and F Bray. 2013. "Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012 " *Eur J Cancer* 49 (6):1374-403.

Ferrario, A, and P Kanavos. 2013. Managed entry agreements for pharmaceuticals: the European experience. Brussels, Belgium: EMiNet.

Ferrario, A, and P Kanavos. 2014. "Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden." *Soc Sci Med.* 124:39-47.

Ferrario, A, P Kanavos, T Humbert, K Iwamoto, and H Bak-Pedersen. 2016a. Challenges and opportunities in improving access to medicines through efficient public procurement in the WHO European Region Copenhagen: World Health Organization Regional Office for Europe.

Ferrario, A, P Kanavos, T Humbert, K Iwamoto, and H Bak-Pedersen. 2016b. Challenges and opportunities in improving access to medicines through efficient public procurement in WHO European region Copenhagen: World Health Organization Regional Office for Europe.

Ferrario, A, M Reinap, H Bak-Petersen, and P Kanavos. 2016. Availability of medicines in Estonia: an analysis of existing barriers and options to address them. Copenhagen: World Health Organization.

Foreman, C, B Gazzard, M Johnson, P Sharott, and S Collins. 2012. "Maintaining cost-effective access to antiretroviral drug therapy through a collaborative approach to

drug procurement, consensus treatment guidelines and regular audit: the experience of London HIV commissioners and providers." *Sex Transm Infect.* 88 (2):112-5.

Foy, R, J So, E Rous, and JH Scarffe. 1999. "Perspectives of commissioners and cancer specialists in prioritising new cancer drugs: impact of the evidence threshold." *BMJ* 318 (7181):456-9.

Frost, LJ, and MR Reich. 2008. *Access: how do good health technologies get to poor people in poor countries?* Cambridge, Massachusetts: Harvard Center for Population and Development Studies.

GaBi. 2016. Celltrion submits trastuzumab biosimilar application to EMA.

Gandjour, A. 2009. "Pharmaceutical Risk-Sharing Agreements." *Pharmacoeconomics* 27 (5):431-432.

Garattini, L, K van de Vooren, and A Curto. 2015. "Cost-effectiveness of trastuzumab in metastatic breast cancer: mainly a matter of price in the EU?" *Health Policy* 119 (2):212-6.

Garrison, LP Jr , A Towse, A Briggs, G de Pouvourville, J Grueger, PE Mohr, JL Severens, P Siviero, and M Sleeper. 2013. "Performance-based risk-sharing arrangements-good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force." *Value Health* 16 (5):703-19.

Gerkens, S , and S Merkur. 2010. *Belgium: Health system review*. Vol. 12, *Health Systems in Transition*.

German Ministry of Health. 2016. "Rabattverträge." Bundesministerium für Gesundheit, accessed 23 October 2016. https://www.bundesgesundheitsministerium.de/service/begriffe-von-a-z/r/rabattvertraege.html.

Gotham, D, KH Onarheim, and MJ Barber. 2016. "How the MDGs gave up on measuring access to medicines." *Lancet Glob Health* 4 (5):e296-7.

GRADE working group. 2016. "Website of the GRADE working group." accessed 10 November 2016. http://gradeworkinggroup.org/.

Gray, A, and HR Jr. Manasse. 2012. "Shortages of medicines: a complex global challenge." *Bull World Health Organ.* 90 (3):158-158A.

Groot, MT, PC Huijgens, and CA Uyl-de Groot. 2006. "Introduction of expensive pharmaceuticals in haematooncology in the Netherlands and throughout Europe." *EJHP* 12 (6):30-36.

Gustafsson, LL, B Wettermark, B Godman, E Andersén-Karlsson, U Bergman, J Hasselström, LO Hensjö, P Hjemdahl, I Jägre, M Julander, B Ringertz, D Schmidt, S Sjöberg, F Sjöqvist, CO Stiller, E Törnqvist, R Tryselius, S Vitols, C von Bahr, and Regional Drug Expert Consortium. 2011. "The 'wise list'- a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm." *Basic Clin Pharmacol Toxicol.* 108 (4):224-33.

HAI. 2016. "Survey reports." Health Action International, accessed 7 September 2016. http://haiweb.org/medicineprices/surveys.php.

Harris, RP, TJ Wilt, A Qaseem, and High Value Care Task Force of the American College of Physicians. 2015. "A value framework for cancer screening: advice for high-value care from the American College of Physicians." *Ann Intern Med.* 162 (10):712-7.

Hay, M, DW Thomas, JL Craighead, C Economides, and J Rosenthal. 2014. "Clinical development success rates for investigational drugs." *Nat Biotechnol.* 32 (1):40-51.

Health & Consumer Protection Directorate-General. 2006. European guidelines for quality assurance in breast cancer screening and diagnosis. edited by M. Broeders N. Perry, C. de Wolf, S. Törnberg, R. Holland, L. von Karsa. Luxembourg.

Hedeker, D , and RD Gibbons. 2006. *Longitudinal Data Analysis*. Hoboken, New Jersey: John Wiley & Sons, Inc.

Hickson, SS , B Skinner, N Bosnic, A Smith, Y Zhang, and B Millson. 2015. "A Comparison of Time to Launch and Reimbursement for New Medicines across Developed Countries." *Value Health* 18 (7):A335.

Hills, G, J Bradley, T Murphy, J Rickard, K Sanghani, A Shields, and S Cheesman. 2010. Bortezomib vial sharing is cost-saving in comparison to the Velcade Response Scheme (VRS). Universtity College London Hospitals, NHS Trust: unpublished poster.

Hinsch, M, M Kaddar, and S Schmitt. 2014. "Enhancing medicine price transparency through price information mechanisms." *Global Health.* 10 (34).

Hogerzeil, HV. 2006. "Essential medicines and human rights: what can they learn from each other?" *Bull World Health Organ.* 84 (5):371-5.

Hughes, DA, and RE Ferner. 2010. "New drugs for old: disinvestment and NICE." *BMJ* 340:c572.

i-base. 2014. London Therapeutic Tender Implementation: Guidance for Clinical Use. In *Presentation*.

IBM. 2014. Pan Canadian Drugs Negotiations Report.

IMI. 2016. "GetReal: Incorporating real-life clinical data into drug development." Innovative Medicines Initiative, accessed 6 November 2016. https://www.imi.europa.eu/content/getreal.

INAMI-RIZIV. 2015. "Website of the Belgian Institute of National Health Insurance and Disability." accessed Last accessed 20 July 2016. http://www.inami.fgov.be/.

INAMI-RIZIV. 2016a. "Fonds Spécial de Solidarité." Institut national d'assurance maladie-invalidité, accessed Last accessed 12 December 2016. http://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/fonds-solidarite/Pages/default.aspx.

INAMI-RIZIV. 2016b. "Liste des spécialités pharmaceutiques remboursables : les catégories de remboursement." Institut national d'assurance maladie-invalidité, accessed 4 November 2016. http://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/medicament-produits-sante/remboursement/specialites/Pages/liste-specialites-pharmaceutiques-remboursables-categories-remboursement.aspx#.WBxaN_ntlHw.

Institute for Clinical and Economic Review. 2016. "How we do our work." accessed 13 September 2016. https://icer-review.org/methodology/icers-methods/.

ISD. 2016a. Cancer Waiting Times in NHS Scotland: April to June 2016 National Services Scotland.

ISD. 2016b. "Website of the Information Services Division (ISD) Scotland." accessed 15 July 2016. http://www.isdscotland.org/.

Iyengar, S, L Hedman, G Forte, and S Hill. 2016. "Medicine shortages: a commentary on causes and mitigation strategies." *BMC Med.* 14 (1).

Iyengar, S, K Tay-Teo, S Vogler, P Beyer, S Wiktor, K de Joncheere, and S Hill. 2016a. "Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis." *PLoS Med.* 13 (5):e1002032.

Iyengar, S, K Tay-Teo, S Vogler, P Beyer, S Wiktor, K de Joncheere, and S Hill. 2016b. "Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis." *PLoS Med* 13 (5).

Janusinfo. 2016. "[Recommendations of the NT Council]." accessed 1 August 2016. http://www.janusinfo.se/Nationellt-inforande-av-nya-lakemedel/Nationellt-inforande-av-nya-lakemedel/Rekommendationer1/.

Jaroslawski, S., and M. Toumi. 2011. "Market Access Agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts." *BMC Health Serv Res* 11 (1):259. doi: 10.1186/1472-6963-11-259.

Johnston, A, R Asmar, B Dahlöf, K Kate Hill, DA Jones, J Jordan, M Livingston, G MacGregor, M Sobanja, P Stafylas, E Agabiti Rosei, and J Zamorano. 2011. "Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe." *Br J Clin Pharmacol.* 72 (5):727–30.

Jönsson, B, T Hofmarcher, P Lindgren, and N Wilking. 2016. Comparator report on patient access to cancer medicines in Europe revisited. In *IHE report 2016:4*. Lund: The Swedish Institute for Health Economics.

Kalo, Z, L Annemans, and LP Garrison. 2013. "Differential pricing of new pharmaceuticals in lower income European countries." *Expert Rev. Pharmacoecon. Outcomes Res.* 13 (6):735–741.

Kanavos, P. 2012. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands and Germany. In *EmiNet*: London School of Economics and Political Science.

Kanavos, P, L Seeley, and S Vandoros. 2009. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium. In *EminNet*: London School of Economics and Political Science.

Kanavos, P, and S Vandoros. 2011. "Determinants of branded prescription medicine prices in OECD countries." *Health Econ Policy Law* 6:337–367.

Kaoru, I. 1976. *Guide to Quality Control. Asian Productivity Organization*: Asian Productivity Organization.

Kaplan, W, V Wirtz, AK Mantel-Teeuwisse, P Stolk, B Duthey, and R Laing. 2013. Priority medicines for Europe and the world 2013 update. Geneva: World Health Organization.

Karunamoorthi, K. 2014. "The counterfeit anti-malarial is a crime against humanity: a systematic review of the scientific evidence." *Malar J.* 13 (209).

Kastanioti, C, N Kontodimopoulos, D Stasinopoulos, N Kapetaneas, and N Polyzos. 2013. "Public procurement of health technologies in Greece in an era of economic crisis." *Health Policy* 109:7-13.

Kawalec, P, A Sagan, and A Pilc. 2016. "The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe." *Orphanet J Rare Dis.* 11 (1):122.

Kawalec, P, A Sagan, E Stawowczyk, I Kowalska-Bobko, and A Mokrzycka. 2016. "Implementation of the 2011 Reimbursement Act in Poland: Desired and undesired effects of the changes in reimbursement policy." *Health Policy* 120 (4):356-61.

Kelesidis, T, I Kelesidis, PI Rafailidis, and ME Falagas. 2007. "Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence." *J Antimicrob Chemother.* 60 (2):214-36.

Kelly, E, CY Lu, S Albertini, and A Vitry. 2015. "Longitudinal trends in utilization of endocrine therapies for breast cancer: an international comparison." *J Clin Pharm Ther.* 40 (1):76-82.

Kesselheim, AS , J Avorn, and A Sarpatwari. 2016. "The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform." *JAMA* 316 (8):858-71.

Kesselheim, AS, B Wang, JM Franklin, and JJ Darrow. 2015. "Trends in utilization of FDA expedited drug development and approval programs, 1987-2014: cohort study." *BMJ* 351.

Kessides, I, R Miniaci, C Scarpa, and P Valbones. 2009. Toward defining and measuring the affordability of public utility services. In *Policy Research Working Paper WPS4915*. Washington, DC: World Bank.

Kieny, MP. 2016. A comprehensive and fair solution to the price of medicines. *World Health Organization Media Centre*.

Kirkwood, BR, and JAC Sterne. 2003. *Medical statistics*. Oxford: Blackwell.

Klemp, M, KB Frønsdal, K Facey, and on behalf of the HTAi Policy Forum. 2011. "What principles should govern the use of managed entry agreements?" *Int J Technol Assess Health Care* 27 (1):77-83.

Kogan, JN, J Schuster, C Nikolajski, P Schake, T Carney, SC Morton, C Kang, and CF Reynolds. 2016. "Challenges encountered in the conduct of Optimal Health: A patient-centered comparative effectiveness study of interventions for adults with serious mental illness." *Clin Trials.* Sep 28. pii: 1740774516670895. [Epub ahead of print].

Kola, I , and J Landis. 2004. "Can the pharmaceutical industry reduce attrition rates?" *Nat. Rev. Drug Discov.* 3 (8):711–5.

Koppel, A, K Kahur, T Habicht, P Saar, J Habicht, and E van Ginneken. 2008. Estonia: Health system review. Health Systems in Transition.

Korchagina, D, F Tavella, C Rémuzat, A Kornfeld, and M Toumi. 2014. "Comparative Analysis of HTA Decisions, Price and Reimbursement Level of Orphan Drugs In France and Italy." *Value Health.* 17 (7):A539-40.

Kos, M, M Obradovic, and A Mrhar. 2008. "Accessibility to targeted oncology drugs in Slovenia and selected European countries." *Eur J Cancer* 44 (3):408-18.

Kweder, SL, and S Dill. 2013. "Drug shortages: the cycle of quantity and quality." *Clin Pharmacol Ther.* 93 (3):245-51.

Kwong, D, A Ferrario, J Adamski, A Inotai, and Z Kalo. 2014. "Managing the introduction of new and high-cost drugs in challenging times: the experience of Hungary and Poland." *EuroHealth* 20 (2):25-28.

Kyle, M. 2006. "The Role of Firm Characteristics in Pharmaceutical Product Launches." *Rand J Econ.* 37 (3):483–761.

Kyle, M. 2007. "Pharmaceutical Price Controls and Entry Strategies." *Rev Econ Stat.* 89 (1):88-99.

Kyle, M, and A McGahan. 2012. "Investments in pharmaceuticals before and after TRIPS." *Rev Econ Stat.* 94 (4):1157–1172.

Lai, T, T Habicht, K Kahur, M Reinap, R Kiivet, and E van Ginneken. 2013. *Estonia: health system review*. Vol. 15, *Health Systems in Transition*.

Läkemedelsverkets. 2016. "Website of the Swedish Medical Products Agency." accessed Last accessed 3 August 2016. https://lakemedelsverket.se/.

Lambrelli, D, and O O'Donnell. 2009. Why does the utilization of pharmaceuticals vary so much across Europe? Evidence from micro-data on older Europeans. In *HEDG Working Paper 09/06*: University of York.

Lancet Oncology. 2010. "Pancreatic cancer: a neglected killer?" *Lancet Oncol.* 11 (12):1107.

Lanjouw, JO. 2005. Patents, price controls and access to new drugs: How policy affects global market entry. In *NBER working paper series*. Cambridge, MA: National Bureau of Economic Research.

Launois, R , and O Ethgen. 2013. "[Risk-sharing agreements: choice of study design and assessment criteria]." *Ann Pharm Fr.* 71 (5):346-57.

Leopold, C, JD Chambers, and AK Wagner. 2016. "Thirty Years of Media Coverage on High Drug Prices in the United States--A Never-Ending Story or a Time for Change?" *Value Health* 19 (1):14-6.

Leopold, C, AK Mantel-Teeuwisse, L Seyfang, S Vogler, K de Joncheere, RO Laing, and H Leufkens. 2012. "Impact of external price referencing on medicine prices - a price comparison among 14 European countries." *South Med Rev.* 5 (2):34-41.

Leopold, C, AK Mantel-Teeuwisse, S Vogler, K de Joncheere, RO Laing, and HG Leufkens. 2013 "Is Europe still heading to a common price level for on-patent medicines? An exploratory study among 15 Western European countries." *Health Policy* 112 (3):209-16.

Leopold, C, AK Mantel-Teeuwisse, S Vogler, S Valkova, K de Joncheere, HG Leufkens, AK Wagner, D Ross-Degnan, and R Laing. 2014. "Effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries." *Bull World Health Organ.* 92 (9):630-640D.

Lexchin, J. 2014. "Postmarket safety in Canada: are significant therapeutic advances and biologics less safe than other drugs? A cohort study." *BMJ Open* 4 (2):e004289.

Lexchin, J. 2015. "Health Canada's use of its priority review process for new drugs: a cohort study." *BMJ Open* 5 (5):e006816.

Lexchin, J, and B Mintzes. 2008. "Medicine reimbursement recommendations in Canada, Australia, and Scotland." *Am J Manag Care.* 14 (9):581-8.

Lipska, I, J Hoekman, N McAuslane, HG Leufkens, and AM Hövels. 2015. "Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions?" *Clin Pharmacol Ther.* 98 (5):489-91.

Lobovs, A. 2016. Joint procurement of the Baltic states. In *Presentation, WHO Consultation on Strategic Procurement, Copenhagen 23 September 2016*.

Lublóy, Á. 2014. "Factors affecting the uptake of new medicines: a systematic literature review." *BMC Health Serv Res.* 14 (469).

Magrini, N, J Robertson, G Forte, B Cappello, LP Moja, K de Joncheere, and MP Kieny. 2015. "Tough decisions on essential medicines in 2015." *Bull World Health Organ.* 93 (4):283-4.

Management Sciences for Health. 2012. "Chapter 18: Managing procurement." In *MDS-3: Managing access to medicines and health technologies*. Arlington, VA: Management Sciences for Health.

Marmot, M, D Altman, D Cameron, J Dewar, S Thompson, and M Wilcox. 2013. "The benefits and harms of breast cancer screening: an independent review." *Br J Cancer.* 108:2205–40.

Mason, A, M Drummond, S Ramsey, J Campbell, and D Raisch. 2010. "Comparison of anticancer drug coverage decisions in the United States and United Kingdom: does the evidence support the rhetoric?" *J Clin Oncol.* 28 (20):3234-8.

Matrix insight. 2012. Study on the Availability of Medicinal Products for Human Use. In *Specific Request EAHC/2011/Health/14 for the Implementation of Framework Contract EAHC/2010/Health/01 Lot 1*.

McCabe, C. J., T. Stafinski, R. Edlin, D. Menon, and A. E. D. Summit Behalf Banff. 2010. "Access with Evidence Development Schemes A Framework for Description and Evaluation." *Pharmacoeconomics* 28 (2):143-152.

McClure, L. 2016. Joint procurement with England for recombinant factor VIII and IX. How aggregating volumes could lead to price reductions. In *Presentation, WHO Consultation on Strategic Procurement, Copenhagen 23 September 2016*.

McNamara, L, and S McNamara. 2014. "Testing the utility of the NHS's Systemic Anti-Cancer Therapy data set for multi-indication pricing." *Value Health* 17 (7):A659.

MDG Gap Task Force. 2008. Delivering on the Global Partnership for Achieving the Millennium Development Goals. In *Millennium Development Goal 8*. New York: United Nations.

MDG Gap Task Force. 2009. Strengthening the Global Partnership for Development in a Time of Crisis. In *Millennium Development Goal 8*. New York: United Nations.

MDG Gap Task Force. 2010. The Global Partnership for Development at a Critical Juncture. In *Millennium Development Goal 8*. New York: United Nations.

MDG Gap Task Force. 2011. The Global Partnership for Development: Time to Deliver. In *Millennium Development Goal 8*. New York: United Nations.

MDG Gap Task Force. 2012. The Global Partnership for Development: Making Rhetoric a Reality. In *Millennium Development Goal 8*. New York: United Nations.

MDG Gap Task Force. 2013. The Global Partnership for Development: The Challenge We Face. In *Millennium Development Goal 8*. New York: United Nations.

MDG Gap Task Force. 2014. The State of the Global Partnership for Development. In *Millennium Development Goal 8*. New York: United Nations.

MDG Gap Task Force. 2015. Taking Stock of the Global Partnership for Development. In *Millennium Development Goal 8*. New York: United Nations.

Medicines for Malaria Venture (MMV). 2016. "Website of Medicines for Malaria Venture." accessed 15 September 2016. http://www.mmv.org/.

Medicines Patent Pool. 2016. Five years of patent pooling for public health. In *Annual report 2015*. Geneva.

Mehta, AB, and E Low. 2007. "Access to expensive drugs in the NHS: myths and realities for cancer patients." *Int J Clin Pract* 61 (12):2126-9.

Memorial Sloan Kettering Cancer Center. 2016. "Drug Abacus Methods." http://www.drugabacus.org/drug-abacus/methods/.

Ménard, S, and on behalf of the Demetra Group. 2008. "Observational Demetra study: Survival of metastatic breast carcinoma patients after treatment with trastuzumab." *J Clin Oncol.* 26 (90150):1062-1062.

Mestre-Ferrandiz, J, A Towse, L Dellamano, and M Pistollato. 2015. Multi-indication pricing: pros, cons and applicability to the UK. In *Seminar briefing 18*. London: Office of Health Economics.

Milliken, D, J Venkatesh, R Yu, Z Su, M Thompson, and D Eurich. 2015. "Comparison of drug coverage in Canada before and after the establishment of the pan-Canadian Pharmaceutical Alliance." *BMJ Open.* 5 (9):e008100.

Milne, CP, and JB Bruss. 2008. "The economics of pediatric formulation development for off-patent drugs." *Clin Ther.* 30 (11):2133-45.

Moe, L. 2016. Nor-Switch: – Safe switch to biosimilar. *Dagens Medisin*.

Moja, LP, L Tagliabue, S Balduzzi, E Parmelli, V Pistotti, V Guarnieri, and R D'Amico. 2012. "Trastuzumab containing regimens for early breast cancer." *Cochrane Database of Systematic Reviews* (4).

Montilla, S, E Xoxi, P Russo, A Cicchetti, and L Pani. 2015. "Monitoring registries at Italian Medicines Agency: Fostering access, guaranteeing sustainability." *Int J Technol Assess Health Care.* 31 (4):210-3.

Moon, S, E Jambert, M Childs, and T von Schoen-Angerer. 2011. "A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries." *Global Health.* 7 (39).

Morel, CM, and E Mossialos. 2010. "Stoking the antibiotic pipeline." *BMJ* 349:c2115.

Morel, T, F Arickx, G Befrits, P Siviero, C van der Meijden, E Xoxi, and S Simoens. 2013. "Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries." *Orphanet J Rare Dis.* 24 (8):198.

Morgan, SG, PA Thomson, JR Daw, and MK Friesen. 2013a. "Inter-jurisdictional cooperation on pharmaceutical product listing agreements: views from Canadian provinces." *BMC Health Serv Res* 13 (34).

Morgan, Steven G, Paige A Thomson, Jamie R Daw, and Melissa K Friesen. 2013b. "Canadian policy makers' views on pharmaceutical reimbursement contracts involving confidential discounts from drug manufacturers." *Health Policy* 112 (3):248-254.

Mycka, J, R Dellamano, W Lobb, N Dalal, E Pereira, L Dellamano, and O Sagaydachnaya. 2014. "Regulatory Approval to Patient Access, An Evaluation of EU5 And Us National Timing Differences: An Update." *Value Health* 17 (7):A323.

National Board for Health and Welfare. 2014. National guidelines for breast, prostate, colon and rectal cancer in 2014. In *Support for governance and management*. Stockholm.

National Comprehensive Cancer Network. 2016. "NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with NCCN Evidence Blocks™." accessed 13 September 2016. https://www.nccn.org/evidenceblocks/.

Nederlandse Zorgautoriteit. BELEIDSREGEL BR/CU-2017: Dure Geneesmiddelen.

Nederlandse Zorgautoriteit. 2012. BELEIDSREGEL BR/CU-2068: Prestaties en tarieven medisch specialistische zorg. In *Artikel 12: Add-ons*.

Neumann, PJ, and JT Cohen. 2015. "Measuring the Value of Prescription Drugs." *N Engl J Med.* 373 (27):2595-7.

NHS. 2016. "NHS data model and dictionary for England." National Health Service, accessed 2 November 2016. http://www.datadictionary.nhs.uk/.

NHS England. 2014. Quarterly figures – including notifications and Individual Cancer Drug Fund Requests (ICDFRs). In *The Cancer Drugs Fund*.

NHS England. 2016a. "The Cancer Drugs Fund." accessed Last accessed 12 December 2016. http://www.england.nhs.uk/ourwork/pe/cdf/.

NHS England. 2016b. "Commissioning through evaluation." accessed 30 September 2016. https://www.england.nhs.uk/commissioning/spec-services/npc-crg/comm-eval/.

NHS Northern, Eastern and Western Devon Clinical Commissioning Group. 2013. "List of Patient Access Schemes (October 2013)." accessed 5 November 2013. http://www.newdevonccg.nhs.uk/who-we-are/medicines-and-treatments/patient-access-schemes/100335.

NICE. 2006. Final Appraisal Determination Bortezomib monotherapy for relapsed multiple myeloma National Institute for Health and Clinical Excellence.

NICE. 2007. Final Appraisal Determination Bortezomib monotherapy for relapsed multiple myeloma National Institute for Health and Care Excellence.

NICE. 2008. Ranibizumab and pegaptanib for age-related macular degeneration. National Institute for Health and Clinical Excellence.

NICE. 2009. Appraising life-extending, end of life treatments - Supplementary advice to the Appraisal Committees. In *Addendum to section 6.2.25 of the Guide to the Methods of Technology Appraisal* London.

NICE. 2012. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. In *NICE technology appraisal guidance 269*. London.

NICE. 2014a. NICE calls for a new approach to managing the entry of drugs into the NHS. In *Press release*: National Institute for Health and Care Excellence.

NICE. 2014b. "Website of the National Institute for Health and Clinical Excellence." http://www.nice.org.uk/.

NICE. 2016a. "List of technologies with approved Patient Access Schemes." accessed 16 November 2016. https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit/list-of-technologies-with-approved-patient-access-schemes.

NICE. 2016b. "Office for Market Access." National Institute for Health and Care Excellence, accessed 30 September 2016. https://www.nice.org.uk/about/what-we-do/office-for-market-access.

NICE. 2016c. "Website of the National Institute for Health and Care Excellence." accessed 9 November 2016. https://www.nice.org.uk/.

Nicod, E. 2016. "Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four European countries." *Eur J Health Econ.* 18 August 2016 [Epub ahead of print].

Nicod, E , and P Kanavos. 2012. "Commonalities and differences in HTA outcomes: a comparative analysis of five countries and implications for coverage decisions." *Health Policy* 108 (2-3):167-77.

Niezen, MGH , EA Stolk, A Steenhoek, and CA Uyl-De Groot. 2006. "Inequalities in Oncology Care: Economic Consequences of High Cost Drugs." *Eur J Cancer.* 42 (17):2887-2892.

Nolte, E , and J Corbett. 2014. International variation in drug usage. An exploratory analysis of the “causes” of variation. RAND Europe.

Nolte, E , J Newbould, and A Conklin. 2010. International variation in the usage of medicines. A review of the literature. Cambridge, UK: RAND Europe and London School of Hygiene and Tropical Medicine.

NSD NHS Scotland. 2016. "Risk Share ", accessed Last accessed 12 December 2016. http://www.nsd.scot.nhs.uk/services/riskshare/.

Nye Metoder. 2015. Nordic contact point for prioritization. Annual meeting May 19th 2016, Oslo.

O'Brien, EC, MA Greiner, Y Xian, GC Fonarow, DM Olson, LH Schwamm, DL Bhatt, EE Smith, L Maisch, D Hannah, B Lindholm, ED Peterson, MJ Pencina, and AF Hernandez. 2015. "Clinical Effectiveness of Statin Therapy After Ischemic Stroke: Primary Results From the Statin Therapeutic Area of the Patient-Centered Research Into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) Study." *Circulation* 132 (15):1404-13.

O'Sullivan, CC, I Bradbury, C Campbell, M Spielmann, EA Perez, H Joensuu, JP Costantino, S Delaloge, P Rastogi, D Zardavas, KV Ballman, E Holmes, E de Azambuja, M Piccart-Gebhart, JA Zujewski, and RD Gelber. 2015. "Efficacy of Adjuvant Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer and Tumors ≤ 2 cm: A Meta-Analysis of the Randomized Trastuzumab Trials." *J Clin Oncol.* 33 (24):2600-8.

O'Neill, P, and J Sussex. 2014. International Comparison of Medicines Usage: Quantitative Analysis. London, UK: Office of Health Economics and the Association of the British Pharmaceutical Industry.

OANDA website. 2016. "Historical rates." accessed 14 November 2016. https://www.oanda.com/solutions-for-business/historical-rates/main.html.

Ocana, A, E Amir, and IF Tannock. 2016. "Toward Value-Based Pricing to Boost Cancer Research and Innovation." *Cancer Res.* 76 (11):3127-9.

OECD. 2013. Cancer care: Assuring quality to improve survival. In *OECD Health Policy Series*. Paris.

OECD. 2014. Geographic Variations in Health Care: What DoWe Know and What Can Be Done to Improve Health System Performance?, OECD Health Policy Studies. Paris.

OECD. 2016a. OECD Health Statistics 2016. In *Frequently Requested Data*.

OECD. 2016b. Pharmaceutical consumption by DDDs In *OECD Health Statistics 2016. Definitions, Sources and Methods*. Paris.

Outterson, K, and AS Kesselheim. 2009. "How Medicare could get better prices on prescription drugs." *Health Aff (Millwood)* 28 (5):w832-41.

Paniz, VM, AG Fassa, MF Maia, MR Domingues, and AD Bertoldi. 2010. "Measuring access to medicines: a review of quantitative methods used in household surveys." *BMC Health Serv Res.* 10 (146).

Paris, V, and A Belloni. 2013. Value in Pharmaceutical Pricing. In *OECD Health Working Papers No. 63*.

Parkinson, B, C Sermet, F Clement, S Crausaz, B Godman, S Garner, M Choudhury, SA Pearson, R Viney, R Lopert, and AG Elshaug. 2015. "Disinvestment and Value-Based Purchasing Strategies for Pharmaceuticals: An International Review." *Pharmacoeconomics* 33 (9):905-24.

Patel, N, R Adatia, A Mellemgaard, R Jack, and H Møller. 2007. "Variation in the use of chemotherapy in lung cancer." *Br J Cancer.* 96 (5):886–890.

Penchansky, R, and JW Thomas. 1982. "The Concept of Access: Definition and Relationship to Consumer Satisfaction." *Medical Care* 19 (2):127-140.

Petrou, P. 2016. "Long-term effect of tendering on prices of branded pharmaceutical products." *Health Policy Technol.* 5 (1):40-46.

Petrou, P, and MA Talias. 2014. "Tendering for pharmaceuticals as a reimbursement tool in the Cyprus." *Health Policy Technol.* 3 (3):167-175.

Petrovsky, K. 2015. "The Joint EU Member States Procurement of Rare Disease Medicines Initiative." *The Source* Winter 2015:21-22.

Pichon-Riviere, A, OU Garay, F Augustovski, C Vallejos, L Huayanay, Mdel P Bueno, Rodriguez A, CJ de Andrade, JA Buendía, and M Drummond. 2015. "Implications of global pricing policies on access to innovative drugs: The case of trastuzumab in seven Latin American countries." *Int J Technol Assess Health Care.* 31 (1-2):2-11.

Pickin, M., C. L. Cooper, T. Chater, A. O'Hagan, K. R. Abrams, N. J. Cooper, M. Boggild, J. Palace, G. Ebers, J. B. Chilcott, P. Tappenden, and J. Nicholl. 2009. "The Multiple Sclerosis Risk Sharing Scheme Monitoring Study--early results and lessons for the future." *BMC Neurol* 9:1. doi: 10.1186/1471-2377-9-1.

PICORI. 2016. "Patient-Centered Outcomes Research Institute." accessed 10 November 2016. http://www.pcori.org/.

Pitts, PJ, HL Louet, Y Moride, and RM Conti. 2016. "21st century pharmacovigilance: efforts, roles, and responsibilities." *Lancet Oncol.* 17 (11):e486-e492.

Poulsen, TS, MLM Espersen, V Kofoed, T Dabetic, E Høgdall, and E Balslev. 2013. "Comparison of Fluorescence In Situ Hybridization and Chromogenic In Situ Hybridization for Low and High Throughput HER2 Genetic Testing." *Int J Breast Cancer.* Article ID 368731:1-5.

Rabe-Hesketh, S, and A Skrondal. 2012. *Multilevel and Longitudinal Modeling Using Stata*. Third Edition ed. Vol. Volume I, *Continuous Responses*. College Station, Texas: Stata Press.

Rägo, L, and B Santoso. 2008. "Chapter 6: Drug Regulation: History, Present and Future." In *Drug Benefits and Risks: International Textbook of Clinical Pharmacology*, edited by B. Santoso and I.R. Edwards C.J. van Boxtel. IOS Press and Uppsala Monitoring Centre.

Raventós, P, and S Zolezzi. 2015. "Electronic tendering of pharmaceuticals and medical devices in Chile." *J Bus Res.* 68 (12):2569–2578.

Regionala Cancercentrum I Samverkan. 2016. Årsrapport 2015 från Nationella Bröstcancerregistret. Stockholm.

Representatives of Bulgaria, Representatives of Croatia, Representatives of Estonia, Representatives of Hungary, Representatives of Latvia, Representatives of Macedonia, Representatives of Romania, Representatives of Serbia, Representatives of Slovak Republic, and Representatives of Slovenia. 2016. Declaration of Sofia on ensuring adequate access to pharmaceutical products at sustainable and affordable prices. Sofia.

Richards, M. 2010. Extent and causes of international variations in drug usage. In *A report for the Secretary of State for Health by Professor Sir Mike Richards CBE*.

Ridge, AL, LA Bero, and SR Hill. 2010. "Identifying barriers to the availability and use of Magnesium Sulphate Injection in resource poor countries: a case study in Zambia." *BMC Health Serv Res* 10 (340).

Ridley, DB. 2005. "Price Differentiation and Transparency in the Global Pharmaceutical Marketplace." *Pharmacoeconomics* 23 (7):651-8.

Ross, JS, and AS Kesselheim. 2013. "Prescription-drug coupons--no such thing as a free lunch." *N Engl J Med.* 369 (13):1188-9.

Royaume de Belgique. 21 décembre 2001. Arrêté royal fixant les procédures, délais et conditions en matière d'intervention de l'assurance obligatoire soins de santé et indemnités dans le coût des spécialités pharmaceutiques edited by Service Public Federal Securite Sociale Royaume de Belgique.

Russo, P., F. S. Mennini, P. D. Siviero, and G. Rasi. 2010. "Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers." *Ann Oncol.* 21 (10):2081-2087. doi: 10.1093/annonc/mdq097.

SACT. 2016. "Systemic anti-cancer therapy chemotherapy dataset." NHS, accessed 1 November 2016. http://www.chemodataset.nhs.uk/.

Schnipper, LE, and A Bastian. 2016. "New Frameworks to Assess Value of Cancer Care: Strengths and Limitations." *Oncologist.* 21:654–658.

Schnipper, LE, NE Davidson, DS Wollins, DW Blayney, AP Dicker, PA Ganz, JR Hoverman, R Langdon, GH Lyman, NJ Meropol, T Mulvey, L Newcomer, J Peppercorn, B Polite, D Raghavan, G Rossi, L Saltz, D Schrag, TJ Smith, PP Yu, CA Hudis, JM Vose, and RL Schilsky. 2016. "Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received." *J Clin Oncol.* 34 (24):2925-34.

Schnipper, LE, NE Davidson, DS Wollins, C Tyne, DW Blayney, D Blum, AP Dicker, PA Ganz, JR Hoverman, R Langdon, GH Lyman, NJ Meropol, T Mulvey, L Newcomer, J Peppercorn, B Polite, D Raghavan, G Rossi, L Saltz, D Schrag, TJ Smith, PP Yu, CA Hudis, RL Schilsky, and American Society of Clinical Oncology. 2015. "American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options." *J Clin Oncol.* 33 (23):2563-77.

Scotland Government. 2013. "Medicines Fund." accessed Last accessed 15 November 2014. http://www.scotland.gov.uk/news/releases/2013/01/medicines-fund14012013.

Scottish Intercollegiate Guidelines Network (SIGN). 2013. Treatment of primary breast cancer. A national clinical guideline. Edinburgh.

SFK. 2015. Facts and figures 2014 On pharmaceutical care in The Netherlands. The Hague: The Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen (SFK)).

Shenoy, P, and A Harugeri. 2015. "Elderly patients' participation in clinical trials." *Perspect Clin Res.* 6 (4):184–189.

Silverman, E. 2016a. Colorado is latest state to be sued for restricting access to hepatitis C drugs. *Statnews*.

Silverman, E. 2016b. Drug maker fined for shorting supplies of cancer drugs in order to raise prices. *Pharmalot*.

Silverman, E. 2016c. Q&A: Why the World Health Organization plans a fair pricing model for drugs. *Pharmalot*.

Sion, JL. 2016. EU Joint Procurement for Influenza vaccines success and challenges. In *WHO EURO workshop on strategic procurement of new medicines*. Presentation, Copenhagen 23 September 2016.

Siviero, P. 2014. Improving rational drug use through monitoring registries In *LSE Summit on risk-sharing and managed entry agreements*. Presentation, 14 February 2014, London, United Kingdom.

Slamon, DJ, GM Clark, SG Wong, WJ Levin, A Ullrich, and WL McGuire. 1987. "Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene." *Science* 235 (4785):177-82.

SMC. 2006. trastuzumab 150mg vial (Herceptin®) In *No. (278/06)*. Glasgow: Scottish Medicines Consortium.

SMC. 2014a. Re-submission pertuzumab 30mg/mL concentrate for solution for infusion (Perjeta®). In *SMC No. (897/13)*: Scottish Medicines Consortium.

SMC. 2014b. Trastuzumab emtansine, 100mg and 160mg, powder for concentrate for solution for infusion (Kadcyla ®). Scottish Medicines Consortium.

SMC. 2015. "SMC Advice for drugs accepted with a PAS." Scottish Medicines Consortium, accessed 12 March 2015. https://www.scottishmedicines.org.uk/Submission_Process/Submission_Guidance_and_Templates_for_Submission/Advice_for_PAS_submissions.

SMC. 2016a. "Scottish Medicines Consortium (SMC)." accessed 1 August 2016. https://www.scottishmedicines.org.uk/.

SMC. 2016b. Scottish Medicines Consortium Update Report 2016. Edinburgh: Healthcare Improvement Scotland

Socialstyrelsen. 2016. "Website of the National Board of Health and Welfare (Socialstyrelsen)." accessed 3 August 2016. http://www.socialstyrelsen.se/riktlinjer/nationellascreeningprogram/brostcancer-screeningmedmammog.

Sorenson, C, D Drummond, A Torbica, G Callea, and C Mateus. 2014. "The role of hospital payments in the adoption of new medical technologies: an international survey of current practice." *Health Econ Policy Law.* 17:1-27.

Stafinski, T., C. McCabe, and D. Menon. 2010. "Funding the unfundable: Mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into health care systems." *Pharmacoeconomics* 28 (2):113-142.

StataCorp. 2013. Stata multilevel mixed-effects. In *Reference manual release 13*. College Station, Texas: StataCorp LP.

Steel, D, and J Cylus. 2012. *United Kingdom (Scotland): Health system review*. Vol. 14, *Health Systems in Transition*.

Stemmler, HJ, S Kahlert, W Siekiera, M Untch, B Heinrich, and V Heinemann. 2005. "Prolonged survival of patients receiving trastuzumab beyond disease progression for HER2 overexpressing metastatic breast cancer (MBC)." *Onkologie* 28 (11):582-6.

Stewart, BW, and CP Wild, eds. 2014. *World Cancer Report 2014*. Lyon: International Agency for Research on Cancer.

Stolk, P, HE Heemstra, HGM Leufkens, B Bloechl-Daum, and ER Heerdink. 2009. "No difference in between-country variability in use of newly approved orphan and non-orphan medicinal products - a pilot study." *Orphanet J Rare Dis.* 4 (27):1-7.

Sullivan, R, J Peppercorn, K Sikora, J Zalcberg, NJ Meropol, E Amir, D Khayat, P Boyle, P Autier, IF Tannock, T Fojo, J Siderov, S Williamson, S Camporesi, JG McVie, AD Purushotham, P Naredi, A Eggermont, MF Brennan, ML Steinberg, M De Ridder, SA McCloskey, D Verellen, T Roberts, G Storme, RJ Hicks, PJ Ell, BR Hirsch, DP Carbone, KA Schulman, P Catchpole, D Taylor, J Geissler, NG Brinker, D Meltzer, D Kerr, and M Aapro. 2011. "Delivering affordable cancer care in high-income countries." *Lancet Oncol.* 12 (10):933-80.

Sveriges Kommuner och Landsting. 2013. Ännu bättre cancervård. In *Insatser inom cancerstrategin 2010-2012*. Stockholm.

Sydsvenska Bröstcancergruppen. 2016. Sydsvenska bröstcancergruppens lathund för kirurgisk och onkologisk behandling av bröstcancer – regional anpassning av nationellt vårdprogram. In *taget vid styrelsemöte 3 March 2016, valid until 31 March 2017*.

Tan, YX, RJ Moles, and BB Chaar. 2016a. "Medicine shortages in Australia: causes, impact and management strategies in the community setting." *Int J Clin Pharm.* 38 (5):1133-41.

Tan, YX, RJ Moles, and BB Chaar. 2016b. "Medicine shortages in Australia: causes, impact and management strategies in the community setting." *Int J Clin Pharm* 38 (5):1133–1141.

Taylor, P. 2016. Biocon and Mylan claim lead as EMA starts review of Herceptin biosimilar. *FiercePharma*. Accessed 9 December 2016.

Thaker, NG, TN Ali, ME Porter, TW Feeley, RS Kaplan, and SJ Frank. 2016. "Communicating Value in Health Care Using Radar Charts: A Case Study of Prostate Cancer." *J Oncol Pract.* 12 (9):813-20.

Thaker, NG, TJ Pugh, U Mahmood, S Choi, TE Spinks, NE Martin, TT Sio, RJ Kudchadker, RS Kaplan, DA Kuban, DA Swanson, PF Orio, MJ Zelefsky, BW Cox, L Potters, TA Buchholz, TW Feeley, and SJ Frank. 2016. "Defining the value framework for prostate brachytherapy using patient-centered outcome metrics and time-driven activity-based costing." *Brachytherapy* 15 (3):274-82.

The Boston Consulting Group. 2015. The Advance Market Commitment Pilot for Pneumococcal Vaccines: Outcomes and Impact Evaluation. The Boston Consulting Group and GAVI The Vaccine Alliance.

The Cochrane Collaboration. 2011. "Chapter 5: Defining the review question and developing criteria for including studies." In *Cochrane Handbook for Systematic Reviews of Interventions*, edited by Sally Green and Julian PT Higgins Denise O'Connor.

The Council of the European Communities. 1988. "Council Directive of 21 December 1988." *Official Journal of the European Union* No L 40/8.

The Council of the European Union. 2016. "Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States." accessed 26 July 2016. http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/.

The European Parliament and the Council of the European Union. 2004. "DIRECTIVE 2004/27/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use." *Official Journal of the European Union* L 136/34.

The official United Nations site for the MDG indicators. 2012. "8.13 Proportion of population with access to affordable essential drugs on a sustainable basis." accessed 6 September 2016. http://mdgs.un.org/unsd/mi/wiki/8-13-Proportion-of-population-with-access-to-affordable-essential-drugs-on-a-sustainable-basis.ashx.

The Parliamentary Office of Science and Technology. 2015. Value Based Assessment of Drugs. In *POSTnote 487*. London: Houses of Parliament.

The Scottish Government. 2016. "Breast screening." http://www.gov.scot/Topics/Health/Services/Screening/Breast.

Theidel, U, and JM von der Schulenburg. 2016. "Benefit assessment in Germany: implications for price discounts." *Health Econ Rev.* 6 (1):33.

Thomas, DW , J Burns, J Audette, A Carroll, C Dow-Hygelund, and M Hay. 2016. Clinical Development Success Rates 2006-2015. Amplion, Biomedtracker and Biotechnology Innovation Organization.

TLV. 2006. Besult: Adartel 061023. Stockholm.

TLV. 2012. Besult: Adartel 121212. Stockholm.

TLV. 2013. "Types of reimbursement." Last Modified 27 June 2012, accessed 14 August 2013. http://www.tlv.se/in-english-old/medicines-new/pricing-and-reimbursement-of-medicines/types-of-reimbursement/.

TLV. 2016a. "Cost ceiling." accessed 18 February 2016. http://www.tlv.se/lakemedel/hogkostnadsskyddet/.

TLV. 2016b. "How does the high-cost threshold work?". The Dental and Pharmaceutical Benefits Agency, accessed 15 July 2016. http://www.tlv.se/In-English/medicines-new/the-swedish-high-cost-threshold/how-it-works/.

TLV. 2016c. "Website of the Swedish Dental and Pharmaceutical Benefits Agency (TLV)." accessed Last accessed 20 July 2016. http://www.tlv.se/.

Tordoff, JM, PT Norris, and DM Reith. 2005. "Managing prices for hospital pharmaceuticals: a successful strategy for New Zealand?" *Value Health.* 8 (3):201-8.

Towse, A., and L. P. Garrison. 2010. "Can't Get No Satisfaction? Will Pay for Performance Help? Toward an Economic Framework for Understanding Performance-Based Risk-Sharing Agreements for Innovative Medical Products." *Pharmacoeconomics* 28 (2):93-102.

Tran, DN, and LA Bero. 2015. "Barriers and facilitators to the quality use of essential medicines for maternal health in low-resource countries: An Ishikawa framework." *J Glob Health* 5 (1).

U.S. Food & Drug Administration. 2016a. "The Drug Development Process." accessed 15 September 2016. http://www.fda.gov/ForPatients/Approvals/Drugs/default.htm.

U.S. Food & Drug Administration. 2016b. "Novel Drug Approvals Reports 2015-2011." accessed 22 March 2016. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm.

UK Department of Health, and ABPI. 2008. The pharmaceutical price regulation scheme 2009.

UNICEF. 2016. Supply Annual Report 2015. Copenhagen: UNICEF Supply Division.

UNITAID. 2016. An economic perspective on delinking the cost of R&D from the price of medicines. Geneva: World Health Organization.

United Nations. 2008. The right to health. In *General Assembly*.

United Nations. 2016. "Sustainable development goal 3." accessed 15 November 2016. https://sustainabledevelopment.un.org/sdg3.

United Nations Secretary-General's high-level panel on access to medicines. 2016. Promoting innovation and access to health technologies. United Nations Development Programme.

US Food and Drug Administration. 2016a. "Accelerated Approvals." accessed 20 March 2016. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373430.htm.

US Food and Drug Administration. 2016b. "Breakthrough Therapy Approvals." accessed 20 March 2016. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373418.htm.

US Food and Drug Administration. 2016c. "Drugs@FDA: FDA Approved Drug Products." accessed 15 November 2016. http://www.accessdata.fda.gov/scripts/cder/daf/.

US Food and Drug Administration. 2016d. "Fast Track Approvals for Drugs, 1998-2006." accessed 21 March 2016. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm200716.htm.

US Food and Drug Administration. 2016e. "Priority NDA and BLA Approvals." accessed 21 March 2016. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm200712.htm.

Van Dyck, W, J De Grève, R Schots, A Awada, and T Geldof. 2016. The Future of Access to Innovative Medicines in Cancer Therapy: Towards Conditional Dialogue Fostering Affordable Therapeutic Innovation. In *Vlerick Policy Paper Series*. Brussels: Vlerick Business School.

Varol, N, J Costa-Font, and A McGuire. 2012. "Does adoption of pharmaceutical innovation respond to changes in the regulatory environment? ." *Appl Econ Perspect Policy.* 34 (3):531-553.

Versporten, A, G Bolokhovets, L Ghazaryan, V Abilova, G Pyshnik, T Spasojevic, I Korinteli, L Raka, B Kambaralieva, L Cizmovic, A Carp, V Radonjic, N Maqsudova, HD Celik, M Payerl-Pal, HB Pedersen, N Sautenkova, H Goossens, and WHO/Europe-ESAC Project Group. 2014. "Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe." *Lancet Infect Dis.* 14 (5):381-7.

Vitry, AI, NH Shin, and P Vitre. 2013. "Assessment of the therapeutic value of new medicines marketed in Australia." *J Pharm Policy Pract.* 13 (6):2.

Vitry, AI, LP Thai, and CY Lu. 2011. "Time and geographical variations in utilization of endocrine therapy for breast cancer in Australia." *Intern Med J.* 41 (2):162-6.

Vogler, S , N Zimmermann, C Habl, J Piessnegger, and A Bucsics. 2012. "Discounts and rebates granted to public payers for medicines in European countries." *South Med Rev* 5 (1):38–46.

Vogler, S, K Kilpatrick, and ZU Babar. 2015. "Analysis of Medicine Prices in New Zealand and 16 European Countries." *Value Health.* 18 (4):484-92.

Vogler, S, L Lepuschütz, P Schneider, and V Stühlinger. 2015. Study on enhanced cross-country coordination in the area of pharmaceutical product pricing. Luxembourg: European Union.

Vogler, S, A Vitry, and ZU Babar. 2016. "Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study." *Lancet Oncol.* 17 (1):39-47.

Vogler, S, N Zimmermann, and ZU Babar. 2016. "Price comparison of high-cost originator medicines in European countries." *Expert Rev Pharmacoecon Outcomes Res.* Sep 22. [Epub ahead of print].

Vogler, S, N Zimmermann, C Leopold, C Habl, and J Mazag. 2013. "Discounts and Rebates Granted for Medicines for Hospital Use in Five European Countries." *TOPHARMEJ* 5:1-10.

Von Minckwitz, G, A Du Bois, M Schmidt, N Maass, T Cufer, FE de Jongh, E Maartense, C Zielinski, M Kaufmann, W Bauer, KH Baumann, MR Clemens, R Duerr, C Uleer, M Andersson, RC Stein, V Nekljudova, and S Loibl. 2009. "Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study." *J Clin Oncol.* 12:1999-2006.

Vork, A, J Habicht, K Xu, and J Kutzin. 2010. Income-related inequality in health care financing and utilization in Estonia since 2000. Copenhagen: WHO Regional Office for Europe.

Waddell, T, A Kotsori, A Constantinidou, N Yousaf, S Ashley, M Parton, M Allen, N Starling, P Papadopoulos, M O'Brien, I Smith, and S Johnston. 2011. "Trastuzumab beyond progression in HER2-positive advanced breast cancer: the Royal Marsden experience." *Br J Cancer.* 104 (11):1675-9.

Wahlster, P , S Scahillb, CY Lu, and Z Babar. 2015. "Barriers to access and use of high cost medicines: A review." *Health Policy Technol.* 4 (3):191–214.

Westrich, K. 2016. Current Landscape: Value Assessment Frameworks. Washington, DC: National Pharmaceutical Council.

WHO. 2000. WHO Medicines Strategy: 2000-2003. In *WHO Policy Perspectives on Medicines*. Geneva: World Healh Organization.

WHO. 2002. Promoting rational use of medicines: core components. In *WHO Policy Perspectives on Medicines*. Geneva: World Health Organization.

WHO. 2003. Introduction to drug utilization research. Geneva, Switzerland: World Health Organization.

WHO. 2004. Equitable access to essential medicines: a framework for collective action. In *WHO Policy Perspectives on Medicines*. Geneva: World Health Organization.

WHO. 2011. WHO Expert Committee on specifications for pharmaceutical preparations. In *WHO Technical Report Series 961*. Geneva: World Health Organization.

WHO. 2015a. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Copenhagen: World Health Organization Regional Office for Europe.

WHO. 2015b. WHO procurement strategy. Geneva: World Health Organization.

WHO. 2016a. Addressing the global shortage of medicines and vaccines. Geneva: World Health Organization.

WHO. 2016b. "Essential medicines." World Health Organization, accessed 5 December 2016. http://www.who.int/topics/essential_medicines/en/.

WHO. 2016c. "Selection of essential medicines." World Health Organization, accessed 9 November 2016. http://www.who.int/selection_medicines/en/.

WHO. 2016d. "WHO World Health Survey." World Health Organization, accessed 6 December 2017. http://www.who.int/healthinfo/survey/en/.

WHO. 2017. Fair pricing forum: Informal advisory group meeting. Geneva: World Health Organization.

WHO, and HAI. 2008. Measuring medicine prices, availability, affordability and price components. Geneva: World Health Organization and Health Action International.

WHO Collaborating Centre for Drug Statistics Methodology, (WHO). 2016. "ATC/DDD Index ". http://www.whocc.no/atc_ddd_index/.

Wildiers, H, S Stordeur, J Vlayen, R Scholten, F van de Wetering, C Bourgain, B Carly, M-R Christiaens, V Cocquyt, E Lifrange, J-C Schobbens, M Van Goethem, G Villeirs, E Van Limbergen, and P Neven. 2013. Breast cancer in women: diagnosis, treatment and follow-up. In *Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE)*. Brussels: College of Oncology.

Wilkens, J, H Thulesius, I Schmidt, and C Carlsson. 2016. "The 2015 National Cancer Program in Sweden: Introducing standardized care pathways in a decentralized system." *Health Policy.* 120 (12):1378-1382.

Wilking, N, and B Jönsson. 2005. A pan-European comparison regarding patient access to cancer drugs. Stockholm: Karolinska Institutet.

Wilking, N, B Jönsson, and D Högberg. 2009. Comparator Report on Patient Access to Cancer Drugs in Europe. Stockholm: Karolinska Institutet.

Wilking, U, B Jönsson, N Wilking, and J Bergh. 2010. "Trastuzumab use in breast cancer patients in the six Health Care Regions in Sweden." *Acta Oncol.* 49 (6):844-50.

Williamson, S. 2009. A Report into the Uptake of Patient Access Schemes in the NHS. Cancer Network Pharmacist Forum.

Willis, M., U. Persson, Y. Zoellner, and B. Gradl. 2010. "Reducing uncertainty in value-based pricing using evidence development agreements: the case of continuous intraduodenal infusion of levodopa/carbidopa (Duodopa(R)) in Sweden." *Appl Health Econ Health Policy* 8 (6):377-86. doi: 10.2165/11531160-000000000-00000.

Wilson, A, and J Cohen. 2011. "Patient access to new cancer drugs in the United States and Australia." *Value Health.* 14 (6):944-5.

Wirtz, V, H Hogerzeil, A Gray, M Bigdeli, CP de Joncheere, MA Even, M Gyansa-Lutterodt, S Jing, VL Luiza, RM Mbindyo, Möller, H, C Moucheraud, B Pécoul, L Rägo, A Rashidian, D Ross-Degnan, PN Stephens, Y Teerawattananon, 't Hoen EF, AK Wagner, P Yadav, and MR Reich. 2016. "Essential medicines for universal health coverage." *Lancet* Published Online November 7, 2016.

Young, RC. 2015. "Value-Based Cancer Care." *N Engl J Med.* 373 (27):2593-5.

Zaric, G. S., and J. O'Brien B. 2005. "Analysis of a pharmaceutical risk sharing agreement based on the purchaser's total budget." *Health Econ* 14 (8):793-803. doi: 10.1002/hec.976.

Zaric, G. S., and B. Xie. 2009. "The Impact of Two Pharmaceutical Risk-Sharing Agreements on Pricing, Promotion, and Net Health Benefits." *Value Health.* 12 (5):838-845. doi: 10.1111/j.1524-4733.2009.00510.x.

Zorginstituut Nederland. 2015. GIPeilingen 2014. In *Ontwikkelingen genees- en hulpmiddelengebruik. Genees- en hulpmiddelen Informatie Project.*