Variation in Health Technology Assessment of new medicines: processes and outcomes

Iga Lipska

ISBN: 978-94-6182-831-6
Cover design: Andrzej Wozniak
Cover photo: Watchar/Shutterstock
Layout and printing: Off Page, www.offpage.nl

Variation in Health Technology Assessment of new medicines: processes and outcomes

Variatie in Health Technology Assessment van nieuwe geneesmiddelen: processen en uitkomsten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus,
prof.dr. G.J. van der Zwaan,

ingevolge het besluit van het college
voor promoties in het openbaar te verdedigen
op woensdag 11 oktober 2017 des middags te 2.30 uur

door

Iga Lipska
geboren op 30 juli 1972
te Biskupiec, Polen

Promotor:
Prof.dr. H.G.M.Leufkens

Copromotoren:
Dr. A.M. Hövels
Dr. N. McAuslane

CONTENTS

chapter 1

INTRODUCTION

INTRODUCTION

Because of globally rising healthcare costs, health technology assessment (HTA) has become an increasingly important policy tool to ensure the most rational use of limited resources (1-2), particularly in reimbursement decision making in Europe (3-4).

Access to new drugs

In general, drug reimbursement can be described as a policy system that defines which drugs are paid for by public funds within public healthcare systems (5). It is mostly determined by jurisdiction-specific policies but may also be controlled by pharmaceutical company policies regarding drug availability in particular markets.

A marketing authorisation (MA) issued by the European Medicines Agency (EMA) is a necessary but no longer sufficient condition for the availability of new drugs for European patients in need. Thus the HTA requirement for new drugs to represent good value for money is sometimes described as the fourth hurdle to medicines' availability, in addition to the medicine's quality, efficacy and safety, which are considered by regulatory agencies (6-7).

Timelines between regulatory approvals by EMA and HTA recommendations influence patients' access to new drugs and thus may be perceived as an access gap. Therefore in this thesis we investigate the timelines from regulatory approval to HTA recommendations in the context of jurisdiction-specific HTA processes. Closer collaboration between EMA and HTA bodies could result in better alignment of mutually acceptable HTA and regulatory evidence requirements both before and after regulatory approval, potentially decreasing timelines and providing earlier access to new medicines.

The analysis included in this thesis fits into broader academic research conducted at the interface of pharmacoepidemiology and policy analysis by Utrecht-World Health Organization Collaborating Centre for Pharmaceutical Policy and Analysis, at the Utrecht University in the Netherlands. Previous research through the Centre investigated pricing and reimbursement mechanisms (8), access to medicines (9), access to medicines with the focus on low- and middle-income countries (10), regulatory decision-making processes (11) and facilitated regulatory pathways (12).

The sustainability of healthcare systems

Total (public and private) healthcare expenditure in the European Union (EU) is around EUR 1 300 billion annually (13). Out of this amount, about 220 billion EUR is spent on pharmaceuticals (14). Organisation for Economic Cooperation and Development (OECD) countries' pharmaceutical spending reached approximately USD 800 billion in 2013, which constituted around 20% of total healthcare expenditure when pharmaceutical consumption in hospitals is added (15). Taking the financial implications of pharmaceutical spending into consideration, the reimbursement of new drugs, including those that target both small and huge populations, poses

challenges for healthcare systems and threatens their sustainability. Costs also raise ethical dilemmas with regard to new treatment options which, while they may be far more effective or may provide treatment for previously incurable diseases, are at the same time extremely expensive, as in the well-known examples of are the new pharmaceuticals in the treatment of hepatitis C (16) or melanoma (17).

Limited resources and value for money approach

As global healthcare resources continue to be particularly limited, financially sustainable healthcare systems are the focus of decision makers at both the European and national levels (1). The key issue for HTA is the determination of how to achieve the best health outcomes possible through evidence-based decision making, thereby maximising the value of available resources (18). However, if HTA is so important and plays such a prominent role in evidence- based decision making in healthcare why does it remain controversial and even more importantly, why are there such substantial differences in HTA recommendations across jurisdictions? One of the potential explanations may be that HTA is seen as a tool that restricts patients' access to new technologies, including in many cases extremely important but expensive drugs. Moreover, as an additional process after MA approval, HTA may be seen as the cause of delays for early patient access.

In this thesis, variation in the HTA of new medicines is examined with a particular focus on HTA processes and outcomes and on the comparison of the HTA of oncology and non-oncology drugs.

What is HTA?

HTA's origin lies in discussions around the perceived uncontrolled diffusion of expensive medical equipment in the 1970s, when the need for evaluation of the consequences of new technology for decision making became evident.

The definition for HTA developed by Health Technology Assessment international (HTAi) in collaboration with International Network of Agencies for Health Technology Assessment (INAHTA) is "the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods." (19). The term "health technology assessment" started being widely used in 1990s and replaced the previous term "medical technology assessment" (20).

Several other definitions of HTA are in use, including that from the European Federation of Pharmaceutical Industries and Associations (EFPIA), which states that "HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology, in

a systematic, transparent, unbiased and robust manner" (21). Importantly, all definitions emphasise the multidisciplinary character of HTA and most of them indicate also its relation to decision-making processes in healthcare.

Historically, HTA agencies have focused on producing comprehensive HTA reports to inform a wide range of decisions ranging from investment decisions for innovators, to clinical practice decisions for healthcare professionals, to resource allocation decisions for Ministry of Health officials. In this thesis we focus on HTA that informs resource allocation decisions, particularly with regard to the listing, coverage and reimbursement of new medicines.

HTA plays an important role in the implementation of a value-based paradigm in healthcare systems. It indicates technologies that add value in comparison with already available technologies and provide the best use of available and always limited resources. HTA also has an important role in evidence-based decision making processes in healthcare.

There has been an increasing trend in several jurisdictions to adapt the broad knowledge and wide scope of traditional HTA to a "fit for purpose" approach that applies to the needs of individual healthcare systems; for example, to inform resource allocation decisions on new drugs only. In this thesis, Poland has been studied as an example of this approach to HTA. In fact, the majority of European countries have implemented this approach to some extent; for example, by commissioning full HTA reports only if needed or by only evaluating required submissions on new drugs .

What technologies does HTA cover?

Health technology is defined by INAHTA as "any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. This includes pharmaceuticals, devices, procedures and organizational system used in healthcare" (22). Based on this definition, HTA covers all interventions including drugs, non-drug technologies, public health programmes and medical devices. Whilst devices seem to constitute a future trend in the field of HTA, they currently are not widely evaluated (23) and considerable methodological issues for their HTA evaluation have been raised in previous research (24). The focus of this thesis is on new medicines.

Evidence-based criteria to spend public money

The annual expenditure for drugs from public sources may constitute no more than 17% of available reimbursement resources in Poland, based on the "Reimbursement Law" of 2011 (25). Evidence-based criteria were partially embedded in a legal framework in Poland in 2009 and fully implemented in 2012 when the Reimbursement Law came into force. The Polish experience and the adoption of such a pragmatic model can be also considered by other countries with limited resources.

How can we compare various HTA outcomes across jurisdictions and what are determinants of these variations?

Previous research indicates substantial differences in HTA outcomes across jurisdictions (26) giving rise to questions regarding what these differences are and why this variation in HTA outcomes exists across jurisdictions. In this thesis we investigate differences in HTA outcomes in particular with regard to oncology and non-oncology drugs across EU jurisdictions and in Poland.

To enable international comparison of HTA outcomes a widely accepted classification of HTA recommendations is needed. Therefore we developed a trichotomous classification of HTA recommendations, *positive*, *positive with restrictions* and *negative*, based on jurisdiction-specific process maps (presented and discussed in chapter 2). The jurisdiction-specific HTA systems were analysed and the recommendations were translated to correspond with the three recommendation classifications. The agencies that offer the value-added extent advice (France, Germany and the Netherlands) were the most challenging to classify in the trichotomous system, as a drug's position on the value-added scale eventually affects its pricing level more than its listing. Prior research employed dichotomous classification of HTA recommendations (27) which can be considered useful or pragmatic and which we used to investigate the impact of effect magnitude of overall survival and progression-free survival on HTA recommendations for new anticancer drugs (chapter 6). This approach, however, provides substantial simplifications to HTA processes, which are by nature more complex.

A previous comparative analysis of the systems of UK and France in rewarding added value for oncology drugs indicates that while the two agency approaches produce similar assessments of added value, they consider different attributes such as costs, timeliness, transparency and political acceptability (28).

Previous research also indicates that differences in HTA recommendations pose challenges for the pharmaceutical industry (27), in particular for research and development plans. A wide range of criteria underpin HTA recommendations in European jurisdictions, covering clinical efficacy and effectiveness, safety, cost-effectiveness, budget impact and social and ethical considerations (29). Differences in HTA outcomes can be explained by variations in healthcare systems and thus HTA processes in selected jurisdictions (chapter 2). Other factors also play a role; for example, information required by HTA agencies, interpretation of clinical and economic evidence, rigour of assessment and appraisal process and the use of appropriate comparators (26).

Can we benchmark (reliably compare) HTA agencies?

Benchmarking is a common tool used to measure performance and we therefore discuss whether this is a tool that may be applicable to HTA environment. We indicate that benchmarking should be based on agreement on common milestones in HTA

processes and on in-depth understanding of jurisdiction-specific processes provided through mapping.

There is a common understanding and general acceptance that HTA agencies should adhere to certain key principles, including independence, transparency, inclusiveness, scientific basis, timeliness, consistency, and legal framework (29). On the other hand, there is almost full agreement that differences in HTA processes and methodologies exist for clinical and economic assessments and national HTA procedures (30). To enable full comparative metrics for HTA agencies and their outcomes data from the public domain as well as detailed data provided by HTA agencies are required.

Countries with limited resources in healthcare such as Poland may benefit from such international benchmarking. Comparative metrics from other jurisdiction may support planning more timely effective HTA processes that optimise financial and human resources.

Differences in cancer care across EU jurisdictions

Cancer care indicators differ in Europe (31) and globally (32-33). The costs spent on cancer care is relatively stable (6%) but there has been an increase in cancer drugs and a decrease in inpatient care or a shift to outpatient care (34) Recent research indicates that age-adjusted cancer mortality rate in Europe is predicted to decline by 8.2% in men and 3.6% in women between 2012-2017 with the exception of pancreatic cancer in both sexes and lung cancer in women (35). However researchers also conclude that because of population aging, the total number of cancer death will not decline. This creates another challenge for the sustainability of healthcare systems, in particular with regard to the costs of new cancer drugs and provides space for HTA to play a role in determining value for money. Thus a focus of this thesis is on new oncology versus non-oncology medicines (Part A chapter 2 and Part C chapter 8) and how HTA agencies value the clinical benefits of oncology medicines (Part B chapters 5 and 6).

The issue of opportunity costs should be considered carefully. This means that money spent on a particular technology is not spent on other technologies; for example, money spent on expensive new cancer drugs with effectiveness is not spent for palliative care, neonatology, intensive care or any other areas in and beyond healthcare.

Due to the better understanding of the pathophysiology and pathomechanisms of cancers over the recent decades, cancer has become in many cases a chronic disease. Thus it requires reasonable approach from decision makers on how to spend public money on expensive albeit effective life-prolonging treatments. Anticancer treatments can cure patients, improve survival or improve quality of life. Although a research gap exists in quality of life research and much needs to be done to objectively consider quality of life (QoL) criteria in the decision-making process (36).

Exploring and understanding variations in HTA processes and outcomes is important for the future to ensure the sustainability of healthcare systems and to enable the evolution and improvement of the efficiencies of evidence-based decision-making processes across various jurisdictions. This could enable better health policy and the research and development of new drugs as well as improved alignment between regulatory and HTA processes and evidence requirements. In-depth understanding of the variations in HTA processes may also result in a a reduction of the so-called access gap between regulatory approval and HTA recommendation and expedite patients' access to new drugs, which is currently delayed and threatened in some jurisdictions (37). This research may also be utilized when considering European HTA collaboration, particularly the joint production of EU assessments within EUnetHTA Joint Action (JA) 3, which were piloted within EUnetHTA JA 2 with barriers and success factors identified in previous research (38). Moreover, understanding variations in HTA processes and outcomes may be also used to support the establishment of new HTA agencies and thus the design of the most efficient de novo HTA processes.

Methods and data sources

In this thesis, jurisdictional comparisons are made in HTA outcomes, timelines and processes. We collected the data on HTA outcomes for new active substances approved by EMA from the public domain, namely, agencies' websites. Based on this publicly available data we also calculate the time from EMA approval to HTA recommendation in the jurisdictions. In addition, we explored the impact of standard versus conditional regulatory pathways on HTA recommendations for new oncology drugs based on publicly available information (chapter 4). Since different outcomes of the recommendations may have different results in patient access we have tried to simplify the recommendations toward a dichotomous (chapter 4) or a trichotomous classification system (chapter 2). Information from the public domain; however, only gives information on the outcomes and the timelines, not on possible obstacles or facilitators during, for example, the deliberation process.

Therefore in order to develop a benchmarking method to use with HTA agencies, we used a survey to gather data directly from HTA agencies. Using these data, a generic HTA process was developed by identifying the common stages of the submission, assessment and appraisal of a new drug in an HTA agency recommendation process. We mapped jurisdiction-specific processes against agreed generic processes, along with the detailed characteristics of each agency. We also investigated the median timelines from assessment, via the appraisal phase up to the final HTA recommendation, based on the data provided by agencies included in this analysis.

This research also focusses on Poland and how the Polish experience can be used by other countries with limited resources (chapter 7 and 8). Based on publicly available information, we analysed the evolution of the HTA system and processes in Poland over the last decade as well as current developments. Timing and timing gaps from

regulatory approval through AOTMiT recommendation were calculated. AOTMiT recommendations were classified as *positive*, *positive with restrictions* and *negative* and defined reasons for restrictions as well as for negative recommendations as *clinical*, *economic*, *both clinical and economic*, and *organisational*. Results for oncology and non-oncology products were differentiated.

Objectives

The overall objective of this thesis is to investigate the variations in HTA processes and outcomes across jurisdictions, with a focus on oncology versus non-oncology medicines and on a country with limited resources (Poland).

Specifically we aimed to address the question of how HTA bodies differ in their approach to oncology versus non-oncology drugs and we also explored timelines from regulatory approval to HTA recommendations in the context of jurisdiction-specific HTA processes (chapter 2). In order to identify the variations in HTA processes and outcomes we identify and quantitate the common stages of the submission, assessment and appraisal of a new drug in an HTA agency recommendation process and the type of information required to enable comparative analysis and we also provide benchmarking data that can be used to enable increased clarity regarding the differences and similarities across HTA agencies (chapter 3). We also studied the extent to which the value of endpoints for cancer medicines differs among European decision makers and to study how HTA agencies determine the clinical relevance of new anticancer medicines based on overall survival (OS) and progression-free survival (PFS) (chapters 5 and 6). We also investigate the impact of conditional and standard marketing authorisation on HTA recommendations for oncology drugs (chapter 4).

With regards to Poland as a country of limited resources, we sought to illustrate and provide a better understanding of the role of HTA processes in decision making for drug reimbursement in Poland and how this approach could be considered by other countries of limited resources. We also specifically compare Polish HTA outcomes, determinants of outcomes and timelines of decision making for new oncology drugs with non-oncology drugs.

Outline of the thesis

Part A focuses on the international perspective on HTA, Part B explores HTA recommendations for new oncology medicines and Part C focuses on Poland as the example of one country with the successful implementation of a pragmatic HTA model whose experience can be utilised by other countries with limited resources. Finally the discussion section details the main findings and puts them in the context of existing research. Chapters 2-8 are based on publications in peer-reviewed scientific journals that have been either published, accepted or submitted and as such can be read independently.

HTA recommendations with the focus on new oncology versus non-oncology drugs across European jurisdictions are investigated in chapter 2. In this chapter the timelines between regulatory approvals by EMA and HTA recommendations, defined as an access gap, are explored in detail and compared based on publicly available information. In chapter 3 the development of methodology for benchmarking HTA agencies is presented with challenges and opportunities and the common milestones of HTA review processes and the type of information required to enable comparative analysis are described. Timelines for HTA processes presented here are based on detailed information provided by HTA agencies and in many cases not available in the public domain. Chapter 4 investigated the impact of EMA conditional versus standard regulatory pathways for new oncology drugs on HTA recommendation across EU jurisdictions. In chapter 5, the focus remained on new oncology drugs as we investigated the extent to which the value of the endpoints OS, PFS, QoL and safety differ among European decision makers in relative effectiveness assessment and in chapter 6 we investigated the impact of effect magnitude of OS and PFS on HTA recommendations. The focus of chapter 7 and 8 is on Poland as the example of country with limited resources in which HTA was successfully implemented in the decision-making processes, especially for new drugs, while noting that there is still room for improvement. Polish HTA recommendations for new oncology and non-oncology drugs are explored in particular in the context of the changing HTA environment, the reasons for restrictions and negative HTA recommendations are analysed and timelines, including the access gap and HTA review time are investigated and discussed as they considerably impact patients' access to new drugs.

REFERENCES

1. Kristensen FB. Growing importance of HTA. WMJ. 2016:23.
2. Oortwijn W, Mathijssen J, Banta D. The role of health technology assessment on pharmaceutical reimbursement in selected middle-income countries. Health Policy. 2010;95(2-3):174-84.
3. Kristensen FB, Nielsen C, Chase B, Lampe K, Lee-Robin SH, Makela M. Health technology assessment and health policy-making in Europe. Current status, challenges and potential. European Observatory of Health Systems and Policies 2008.
4. Cleemput I, Franken M, Koopmanschap M, le Polain M. European drug reimbursement systems' legitimacy: five-country comparison and policy tool. Int J Technol Assess Health Care. 2012;28(4):358-66.
5. Pujolras LM, Cairns J. Why do some countries approve a cancer drug and others don't? Journal of Cancer Policy. 2015;4:21-5.
6. Rawlins MD. Crossing the fourth hurdle. Br J Clin Pharmacol. 2012;73(6):855-60.
7. Hutton J, McGrath C, Frybourg JM, Tremblay M, Bramley-Harker E, Henshall C. Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies (fourth hurdle systems). Int J Technol Assess Health Care. 2006;22(1):10-8.
8. Leopold C, Vogler S, Habl C, Mantel-Teeuwisse AK, Espin J. Personalised medicine as a challenge for public pricing and reimbursement authorities - A survey among 27 European countries on the example of trastuzumab. Health Policy. 2013;113(3):313-22.
9. Stephens P, Ross-Degnan D, Wagner AK. Does access to medicines differ by gender? Evidence from 15 low and middle income countries. Health Policy. 2013;110(1):60-6.
10. Cameron A, Mantel-Teeuwisse AK, Leufkens HG, Laing RO. Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved? Value Health. 2012;15(5):664-73.
11. Tafuri G, Leufkens HG, Laing R, Trotta F. Therapeutic indications in oncology: emerging features and regulatory dynamics. Eur J Cancer. 2010;46(3):471-5.
12. Liberti L, Stolk P, McAuslane N, Somauroo A, Breckenridge AM, Leufkens H. Adaptive licensing and facilitated regulatory pathways: A survey of stakeholder perceptions. Clin Pharmacol Ther. 2015.
13. Eurostat. Found at http://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_expenditure_statistics (accessed 28th June 2017)
14. OECD/EU (2016), Health at a Glance: Europe 2016: State of Health in the EU Cycle, OECD Publishing, Paris.http://dx.doi.org/10.1787/9789264265592-en.
15. OECD (2015), Health at a Glance 2015: OECD Indicators, OECD Publishing, Paris. http://dx.doi.org/10.1787/health_glance-2015-en
16. Facing ethical dilemmas for a health system's sustainability; 3rd plenary session of HTAi conference June 2017 http://www.htai2017.org/ (accessed 28th June 2017)
17. Watson I, Dominguez PP, Donegan E, Charles Z, Robertson J, Adam EJ. NICE guidance on pembrolizumab for advanced melanoma. The Lancet Oncology. 2016;17(1):21-2.
18. Gray JAM. Evidence-based Healthcare: Churchill Livingstone; 1997.
19. HTA Glossary Net. Found at http://htaglossary.net/health+technology+assessment+%28HTA%29 (accessed 17th June 2017)
20. Banta D. What is technology assessment? Int J Technol Assess Health Care. 2009;25(Supplement 1):7-9.
21. http://efpia.eu/relative-efficacy-assessment (accessed 12th May 2017)
22. Tracey K. In: Topfer LA, Chan L. on behalf of the International Network of Agencies for Health Technology Assessment. Health Technology Assessment (HTA) Glossary. First ed. Stokholm: INAHTA Secretariat; 2006.

23. Fuchs S, Olberg B, Panteli D, Perleth M, Busse R. HTA of medical devices: Challenges and ideas for the future from a European perspective. Health Policy. 2017;121(3):215-29.
24. Drummond M, Griffin A, Tarricone R. Economic evaluation for devices and drugs–same or different? Value Health. 2009;12.
25. Internetowy System Aktów Prawnych [Polish online legal database]. The Reimbursement Law on the reimbursement of medicinal products, special purpose dietary supplements and medical devices. Available at http://isap.sejm.gov.pl/DetailsServlet?id=WDU20111220696 (accessed 28th June 2017)
26. Kanavos P. The impact of heath technology assessment: an international comparison. EuroObserver. 2010.
27. Context Matters. Global Variability in HTA Decisions Poses Challenges for Innovative Biopharmaceutical Research and Development. 2014. http://phrma-docs.phrma.org/sites/default/files/pdf/context-matters-global.pdf (accessed 30th June 2017)
28. Drummond M, de Pouvourville G, Jones E, Haig J, Saba G, Cawston H. A comparative analysis of two contrasting European approaches for rewarding the value added by drugs for cancer: England versus France. Pharmacoeconomics. 2014;32(5):509-20.
29. Drummond M. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care . 2008;24:3:244-58.
30. European Commission; DG SANCO. Strengthening of the EU cooperation on Health Technology Assessment (HTA). 2016. https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/20161020_frep_en.pdf (accessed 30th June 2017)
31. Wilking N. Comparator report on patient access to cancer drugs in Europe. 2009.
32. Jonsson B, Wilking N. A global comparison regarding patient access to cancer drugs. Ann Oncol. 2007;18 Suppl 3:iii1-iii77.
33. Ades F, Zardavas D, Senterre C, de Azambuja E, Eniu A, Popescu R, et al. Hurdles and delays in access to anti-cancer drugs in Europe. Ecancermedicalscience. 2014;8:482.
34. Jonsson B, Hofmarcher T, Lindgren P, Wilking N. The cost and burden of cancer in the European Union 1995-2014. Eur J Cancer. 2016;66:162-70.
35. Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, et al. European cancer mortality predictions for the year 2017, with focus on lung cancer. Ann Oncol. 2017.
36. Kleijnen S, Leonardo Alves T, Meijboom K, Lipska I, De Boer A, Leufkens HG, et al. The impact of quality-of-life data in relative effectiveness assessments of new anti-cancer drugs in European countries. Qual Life Res. 2017.
37. Wilsdon; T, Fiz; E, Haderi; A, EFPIA rbCRAfPa. A comparative analysis of the role and impact of Health Technology Assessment: 2013 Final report CRA Project No. D19197-00. 2014.
38. Kleijnen S, Toenders W, de Groot F, Huic M, George E, Wieseler B, et al. European collaboration on relative effectiveness assessments: What is needed to be successful? Health Policy. 2015(0).

part A

INTERNATIONAL PERSPECTIVE ON HTA

chapter 2

HEALTH TECHNOLOGY ASSESSMENT RECOMMENDATIONS AND THE ACCESS GAP FOR NEW ONCOLOGY AND NON-ONCOLOGY DRUGS ACROSS EUROPEAN JURISDICTIONS

Iga Lipska
Neil McAuslane
Hubert G.M. Leufkens
Anke M. Hövels

Prepared for submission

ABSTRACT

Background

Health Technology Assessment (HTA) has become an important policy instrument that informs decisions on the reimbursement of new oncology and non-oncology drugs. However HTA agencies vary considerably in HTA outcomes and timelines across European jurisdictions. Timelines between regulatory approvals by European Medicines Agency (EMA) and HTA recommendations influence patients' access to new drugs and thus is perceived as an access gap.

Objective

This study aims to address the question how HTA bodies differ in their approach to oncology versus non-oncology drugs. It also explores timelines from regulatory approval to HTA recommendations in the context of jurisdiction-specific HTA processes.

Methods

We developed a trichotomous classification of HTA recommendations based on jurisdiction-specific process maps to compare HTA outcomes across different European jurisdictions. We collected the data on HTA outcomes for new active substances approved by EMA between 2007 and 2013 from the public domain, namely, agencies' websites. Six European jurisdictions: England, France, Germany, Netherlands, Poland and Scotland were included in our study. Based on publicly available data we also calculated the time from EMA approval to HTA recommendation in the jurisdictions.

Results

Overall, 470 HTA reports were included in our study. Almost 40% (n=180) of all HTA recommendations were negative while over 60% were positive (28,3%, n=133) and positive with restrictions (33,4%, n=157) across all six jurisdictions included in our study. About half of HTA recommendations for this time period in Scotland, Germany and France were negative (52%, 50%, 49% respectively). The proportion of negative HTA recommendations for new oncology drugs rose to 79% in Scotland while it decreases to 26% in Germany and 38% in France. Median timing from MA approval by EMA to HTA recommendation was 211 days for all drugs across all jurisdictions and it was 220 and 197 days for oncology and non-oncology drugs respectively. The lowest median time from MA approval to HTA recommendation was 135 days for Germany (117 days for oncology drugs) and the highest median time from MA approval to HTA recommendation was 572 days for Poland (616 days for oncology drugs).

Conclusions

HTA agencies differ in their approach to oncology and non-oncology drugs, with Germany issuing more positive recommendations for oncology drugs and England issuing more positive recommendations for non-oncology drugs. ZIN in the Netherlands was the only studied agency with recommendations that were consistent across oncology and non-oncology drugs. Timelines vary considerably across jurisdictions, which can be a barrier for joint EU assessments. Both HTA outcomes and timelines can only be interpreted with in-depth understanding of jurisdiction-specific HTA processes.

INTRODUCTION

Health technology assessment (HTA) has become an important policy instrument for the introduction of new drugs, including specific circumstances for the introduction of oncology drugs (1). A marketing authorisation (MA) issued by the European Medicines Agency (EMA) is a necessary but no longer sufficient condition for the availability of new drugs for European patients in need. Thus the HTA requirement for new drugs to represent good value for money is sometimes described as the fourth hurdle to medicines' availability, in addition to the medicine's quality, efficacy and safety, which are considered by regulatory agencies (2) (3).

Substantial differences exist in healthcare systems and HTA processes across European jurisdictions (4), impacting HTA outcomes and timelines for oncology and non-oncology drugs. A wide range of criteria underpin HTA recommendations in European jurisdictions, covering clinical efficacy and effectiveness, safety, cost-effectiveness, budget impact and social and ethical considerations (5).

Previous research investigated the influence of regulatory pathways; that is, conditional versus standard approval by EMA, on HTA recommendations for new oncology drugs and concluded little to no differences in HTA recommendations between these two groups however considerable differences in HTA recommendations between the individual HTA bodies were observed which was rather explained by institutional differences in national legal requirements, HTA criteria used and systems of weighing benefits and risks in particular with regards to high unmet medical need and uncertainty in case of less than complete data package (6). This research also suggested that to some extent, HTA bodies operate independently from the MA approval status of new drugs.

In some healthcare systems, a negative HTA recommendation for a new drug may or may not affect its availability to patients, but a premium price for these drugs will not be paid. In most healthcare systems the final decision for access is made by the Minister of Health and many healthcare systems provide alternative ways for access to particular treatments irrespective of HTA recommendations, in particular for oncology drugs (7) .

The features of European healthcare systems have to be considered when comparing HTA recommendations across jurisdictions and must also be taken into account at both strategic and operational levels when considering European HTA collaboration, particularly the joint production of EU assessments. The variation in HTA outcomes across European jurisdictions requires in-depth investigation, especially in the light of the strengthening of EU cooperation in HTA and the envisaged joint EU assessments. These assessments are part of the goals of the European Network for HTA Joint Action 3 (EUnetHTA JA3) until 2020 and will most probably proceed beyond this project timeframe (8).

Strategic discussion of European HTA cooperation has already been initiated by the European Commission, in particular with regard to the scope, joint HTA work and

impact of the EU cooperation on the national decision-making processes (9). EUnetHTA JA2 activities include pilots for the joint assessments of new drugs (10) and there are plans within EUnetHTA JA 3 to perform joint assessments and even more importantly to use them in real decision-making processes at a national level (11). However, previous research indicates there are substantial differences between European jurisdictions in both HTA processes and outcomes for new drugs (12). Critical success factors as well as potential barriers for joint EU assessments have been identified (11). Success factors listed by Kleijnen and colleagues included continuous cooperation of competent partners and the quality and timely availability of the assessments whilst potential barriers were mainly methodological issues, resource limitations and challenges regarding implementation in the national processes (13). Before EU cooperation in joint HTA production can be initiated on a larger scale, an in-depth understanding HTA processes and outcomes within healthcare systems is needed.

OBJECTIVE

This study aims to address the question how HTA bodies differ in their approach to oncology versus non-oncology drugs. It also explores timelines from regulatory approval to HTA recommendations in the context of jurisdiction-specific HTA processes.

METHODS

Research design

We analysed new active substances (NASs) approved for use by EMA in the years 2007–2013 and their evaluation by HTA institutions in six European jurisdictions. We retrieved the list of relevant NASs from the EMA website together with basic approval elements; that is, the exact date of approval and the approved indication(s). Subsequently, we collected HTA outcomes and the date of HTA recommendation for these NASs from the websites of the relevant HTA agencies. We only collected data from publicly available sources.

Selection of HTA jurisdictions and HTA reports

We included HTA agencies that conduct formal assessments of medicines to inform pricing and reimbursement decisions and for that produce publicly available HTA reports. Hence, the following six jurisdictions and their HTA agencies were included:

- England (EN) – National Institute for Health and Care Excellence (NICE);
- France (FR) – Haute Autorité de Santé (HAS);
- Germany (GER) – Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) ;
- Netherlands (NL) – Zorginstituut Nederland (ZIN);

» Poland (PL) – Agencji Oceny Technologii Medycznych i Taryfikacji (AOTMiT), and
» Scotland (SCO) – Scottish Medicines Consortium (SMC).

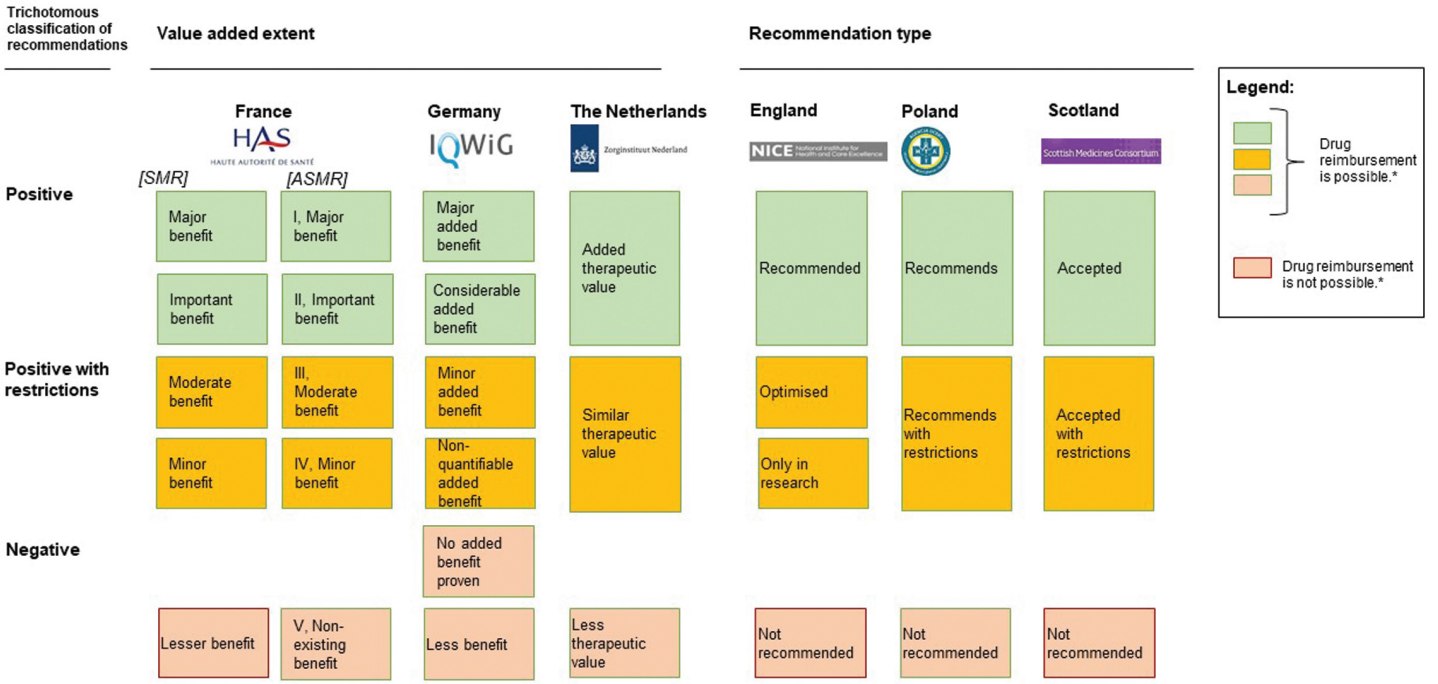
NASs approved by EMA between 1 January 2007 and 31 December 2013 served as the basis for the analysis. We excluded pharmaceuticals no longer authorised for use by the EMA and those used for diagnostic or surgical purposes. We included drugs for which four or more HTA reports from different jurisdictions were available before the 27 March 2015 (data collection cut-off date). In order to allow consistent comparison, we included only the first HTA reports produced in the chosen jurisdictions.

Trichotomous classification of HTA recommendations

To enable the comparison of HTA recommendations across jurisdictions a trichotomous (positive/ positive with restrictions/ negative) classification of HTA recommendations was developed. The jurisdiction-specific HTA systems were analysed and the recommendations were translated to correspond with the *positive*, *positive with restrictions* or *negative* categories (Figure 1). A distinction was made between jurisdictions that advise on the value-added extent of a medicine (FR,GER,NL) and those that issue a clear-cut recommendation type (EN, PL, SCO). The agencies that offer the value-added extent advice were challenging to classify in the trichotomous system, as a drug's position on the value-added scale eventually affects its pricing level more than its listing (FR, GER, NL). The assumption was made that NASs with a benefit score: *important, major* (FR), *considerable, major* (GER) or *added therapeutic value* (NL) were classified as having received positive recommendations. Whereas those with *moderate, minor* (FR), *non-quantifiable, minor* (GER) and *similar therapeutic value* (NL) were classified as having received positive recommendations with restrictions. Lastly, the categories *lesser, non-existing* (FR), *less, no added benefit* (GER) and less therapeutic value (NL) were grouped as negative recommendations. The trichotomous classification of HTA recommendations was based on detailed mapping of HTA processes in all jurisdictions included in our research (Supplementary Material 1).

Data collection

Two researchers collected the data from the HTA reports between January and March 2015. The data were collected in a dedicated Excel database designed to collect key details about NASs, regulatory approval by EMA, HTA recommendation outcomes and the dates of regulatory approval and HTA recommendation. In order to compare the recommendations' outcomes and timelines across jurisdictions, specific features of each individual HTA system had to be recognised and translated to our research (Figure 1; Supplementary Material 1). Except for NICE, the exact dates of HTA recommendations were extracted directly from individual agency websites. Because only the month and year of guidance is provided on the NICE website, we assumed that a date for each guidance of the fifteenth of the respective month.



* HTA agencies provide recommendations/advice on the medicines that can be reimbursed by the healthcare system. A relevant decision-making-body (eg. Ministry of Health) makes the final reimbursement decision.
Sources: G-BA, ZIN, HAS, NICE, SMC, AOTMiT websites

Figure 1. Trichotomous classification of HTA recommendations for drugs issued by HTA agencies in six EU jurisdictions.

Data analysis

Descriptive statistics were used to present the percentage of *positive, positive with restrictions* and *negative* HTA recommendations in line with the trichotomous classification for each jurisdiction. The timeline statistics were based on two data points; that is, the MA approval and HTA recommendation date for each NAS. Calendar days were used to calculate timelines. We calculated the differences between the date of MA approval and date of HTA recommendation per drug for each jurisdiction. The maximum and minimum times were identified together with the median value per jurisdiction. We analysed the whole sample of drugs and two subsamples; oncology and non-oncology drugs.

RESULTS

We retrieved the list of 175 NASs approved by EMA between 2007 and 2013, of which 14 were excluded (9 withdrawn from marketing authorisation and 5 considered out of the scope of HTA agencies). In the next step, we only included drugs for which 4 or more HTA reports were available from the EU jurisdictions included in our study (before 27 March 2015). In order to allow consistent comparison, we included only the first HTA reports produced in the chosen jurisdictions. Thus, our cohort for these analyses included 98 NASs resulting in 470 HTA reports in 6 EU jurisdictions. The selection process of NASs included in our study is described in Figure 2.

Almost 40% (n=37) of the 98 NASs analysed were oncology drugs, which accounted for 180 HTA reports. Non-oncology drugs constituted 62% (n=61) of the group, which accounted for 290 HTA reports in the 6 analysed jurisdictions.

The French HAS assessed all 98 NASs, The Netherlands and Scotland assessed 93 and 95 respectively, NICE assessed 56 and IQWiG assessed 50 drugs. For the Polish AOTMiT, 78 (approximately 80%) drug reports were available online before the cut-off date. Overall, almost 40% (n=180) of all HTA recommendations were negative while over 60% were positive (28%, n=133) and positive with restrictions (33%, n=157) across all 6 jurisdictions included in our study.

HTA recommendations outcomes for oncology and non-oncology drugs

Jurisdictions included in our study differ in their approach to oncology and non-oncology drugs (Figure 3). The Scottish SMC is quite restrictive, with 52% of their 95 assessments resulting in negative recommendations. When it comes to oncology drugs this figure rises up to 79%. Only 9% of oncology drugs assessed by SMC receive a positive recommendation, compared with 28% for non-oncology drugs.

NICE and AOTMiT are also more restrictive in assessing oncology compared with non-oncology drugs. NICE issued negative recommendations for 7% and positive

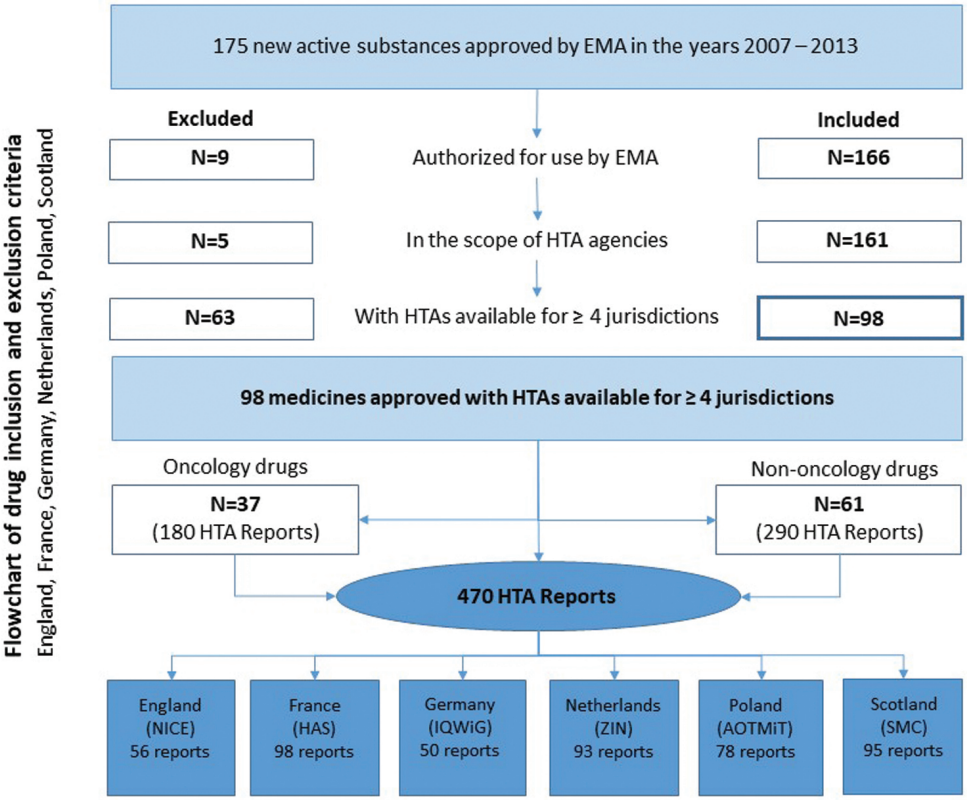
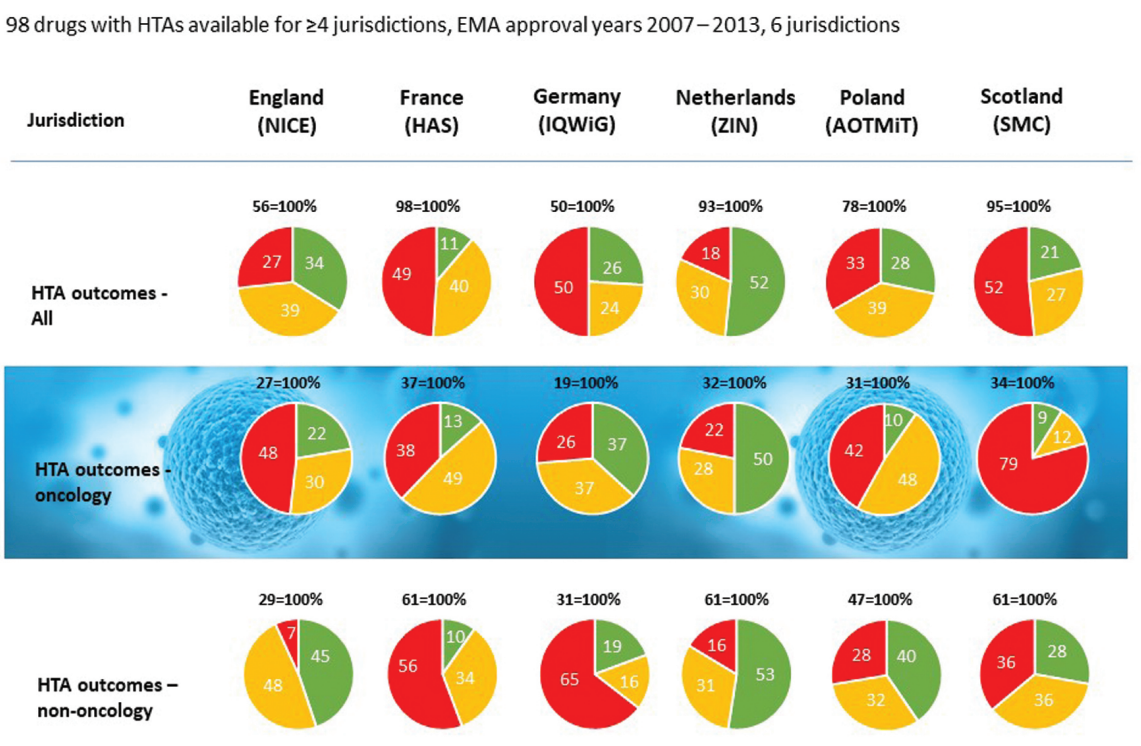


Figure 2. The selection process for NASs included and number of HTA reports per jurisdiction.

recommendations for 45% of 29 non-oncology drugs. AOTMiT issued 28% negative and 40% positive recommendations for non-oncology drugs. Whereas, for oncology drugs evaluated by NICE, 48% of 27 recommendations were negative, 22% were positive and 30% were restricted. Only 10% of 31 recommendations for oncology drugs were positive in Poland while 42% were negative and 48% were restricted.

These proportions were inverted for IQWiG and HAS, where more than half of non-oncology HTAs analysed resulted in a negative recommendation. On the other hand, 26% of recommendations that related to oncology drugs were negative in Germany and 38% in France. Overall, IQWiG and HAS issued negative decisions in approximately 50% of studied cases. However, the share of positive recommendations differed between the two jurisdictions; that is, 26% for IQWiG and only 11% for HAS. It is worth noting that while HAS analysed all 98 medicines, the analysis for IQWiG is based on 50 HTA reports.

ZIN assessed a total of 93 medicines. No substantial differences in the ZIN approach toward oncology vs. non-oncology drugs were observed. More than 50%



Germany and France: More positive recommendations for oncology than non-oncology therapies.

England: More negative recommendations for oncology than non-oncology drugs. This may be due to the fact that many oncology drugs were available through the Cancer Drug Fund.

Scotland: SMC's approach is restrictive for oncology drugs: 79% negative recommendations. Some oncology drugs may be made available to patients through „Individual Patient Treatment Requests".

Sources: EMA, NICE, HAS, IQWiG, ZIN, AOTMiT, SMC websites

Figure 3. HTA outcomes for all NASs, oncology and non-oncology drugs.

of analysed HTA outcomes in the Netherlands were positive and approximately 30% were restricted regardless of the oncology or non-oncology indication. A negative outcome could be observed for 22% of 32 recommendations that related to oncology drugs and 16% of 61 recommendations for non-oncology drugs.

Timelines from regulatory approval to HTA recommendation

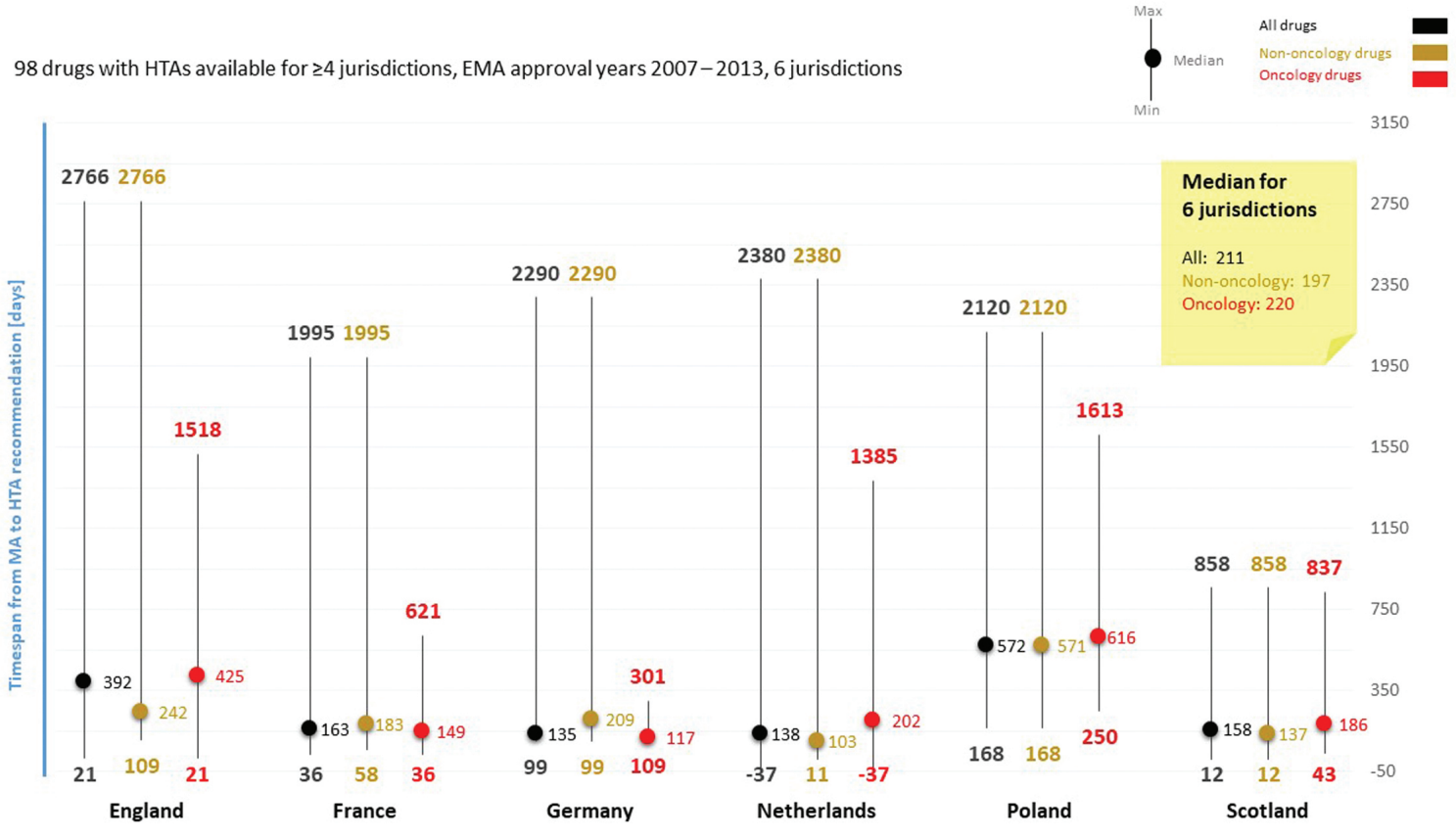
Median time from regulatory approval (MA approval by EMA) to HTA recommendation was 211 days for all drugs across all jurisdictions; 220 and 197 days for oncology and non-oncology drugs respectively (Figure 4). The timespan from regulatory approval to HTA recommendation varied from -37 days (afatinib for non-small cell lung cancer) by ZIN to 2766 days (the ultra-orphan drug eculizumab indicated for paroxysmal nocturnal haemoglobinuria) by NICE. IQWiG had the lowest median time from MA to HTA recommendation (135 days) across the six jurisdictions in question. In contrast, this data point was highest for Poland, at a median of 572 days.

The timing from MA to HTA recommendation by NICE ranged from 21 days (gefitinib for non-small-cell lung cancer) to 2766 days (eculizumab), with the median being 392 days. In France the timing ranged from 36 days (lapatinib for breast cancer) 1995 days (aliskiren, hypertension), with a median of 163 days. In Germany, the shortest recommendation time was for ivacaftor (cystic fibrosis), issued 99 days after the MA and the decision regarding sitagliptin (diabetes) was given 2290 days after the MA date. In the Netherlands, HTA decisions in some cases may be taken prior to the MA itself, as occurred for afatinib (for non-small cell lung cancer).

HTA timing after MA was the longest in the Netherlands for febuxostat (hyperuricaemia) at 2380 days; and the median timing for HTA recommendation in this jurisdiction was 138 days. AOTMiT issued HTA recommendations within a minimum of 168 days for roflumilast (chronic obstructive pulmonary disease) to a maximum of 2120 days for amfenac amide (pain and inflammation post-cataract removal). The time between MA and the Scottish SMC recommendation ranged from 12 days for elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate (anti-HIV treatment) to 858 days for pirfenidone (idiopathic pulmonary fibrosis); the median timing for HTA recommendation after MA in Scotland was 158 days.

As seen in Figure 4, there were observable differences in the timespan from regulatory approval to HTA recommendation between countries and also between groups of medicines analysed; that is, oncology versus non-oncology drugs. For oncology drugs, the minimum time delay from MA to NICE guidance ranged from 21 days to 1518 days. For non-oncology drugs, the timespan ranged between 109 days and 2766 days and the median time was 425 days for oncology drugs and 242 for non-oncology drugs.

In France, the timelines were also shorter for anti-cancer medicines, ranging from a minimum of 36 days to a maximum of 621 days and from 58 days to 1995 days for non-cancer medicines. Overall, the median time to recommendation was 163 days,



Sources: EMA, NICE, HAS, IQWiG, ZIN, AOTMiT, SMC, author's analysis

Figure 4. Timelines from regulatory approval to HTA recommendation per jurisdiction for all NASs, oncology and non-oncology drugs.

149 days for oncology drugs and 183 days for non-cancer medicines. In Germany, the minimum time delay for an oncology drug was 109 days and the maximum, 301 days, while for non-cancer drugs the range was 99 days to 2290 days. The median time for HTA recommendation for oncology drugs was the shortest of all 6 jurisdictions in Germany at 117 days while the median timing for the non-cancer medicines was 209 days and 135 days for all drugs. The Netherlands had the lowest median time for non-oncology drugs (103 days) and timing ranged from 11 days to 2380 days. ZIN was the only agency with a negative time line for an oncology drug, when the HTA recommendation for afatinib was made 37 days before the MA was granted. The maximum delay for an oncology drug in the Netherlands was 1385 days and the median was 202 days.

Poland had the highest median timing for HTA recommendations for all medicine groups by far; that is, 616 days for oncology drugs, 571 days for non-oncology drugs and 572 days for all drugs. The minimum timelines are also the highest in Poland out of all six jurisdictions at 250 days for oncology and 168 days for non-oncology drugs. Scotland is consistent when it comes to the time delays between different product groups. For oncology drugs the time interval from MA to HTA outcome ranged from 43 to 837 days (median, 186 days) and for non-oncology drugs from 12 days to 858 days (median,137 days). Overall the median timing between MA and HTA recommendation in Scotland was 158 days.

Varying timelines from regulatory approval to HTA recommendation over time (for subgroups of NASs approved by EMA in a given year)

Separately we analysed timelines from regulatory approval to HTA recommendation for NASs approved by EMA in a given year (from 2007 to 2013) in selected jurisdictions. The most approvals (n=19) were granted in 2007 and the fewest approvals (n=8) in 2008 and 2010. Each of the six jurisdictions in question exhibits a different median value from the approval to the HTA outcome in the above mentioned time period.

The median values have noticeably decreased for England, Poland and Germany. England began with a median timing between MA and HTA recommendation exceeding 2000 days for drugs approved by EMA in 2007, with a median of 882 days. This median decreased to 233 days for drugs approved by EMA in 2013. Poland reached a peak in the median delay of HTA recommendation of 931 days for drugs approved by EMA in 2009, which decreased to 360 days for drugs approved by EMA in 2013 (still the highest median time among all jurisdictions included in our study).

The Netherlands, France and Scotland were more consistent throughout the analysed years with no extreme deviations in the median value. For drugs analysed by the French HAS, the median time from MA to HTA outcome increased from 126 days for drugs approved by EMA in 2007 to 261 days for drugs approved by EMA 2013. The same applies for ZIN, where timing increased from 124 days for drugs approved by EMA in 2007 to 163 days for drugs approved by EMA in 2013. The Scottish

median values oscillated between approximately 100 and 200 median days for drugs approved by EMA in the years 2007 to 2013, with the lowest median value being 106 days for drugs approved by EMA in 2012 and the highest being 202 days for drugs approved by EMA in 2009. The outliers were AOTMiT and IQWIG, with the longest time to recommend the drugs approved by EMA in 2009 (almost 1,000 days and 1,400 days respectively); however, timelines for drugs approved by EMA in these jurisdictions decreased steadily in subsequent years reaching the shortest timeline for drugs approved by EMA in 2013 (360 days and 120 days in Poland and Germany respectively).

DISCUSSION

This study investigated the variation in HTA outcomes for new oncology and non-oncology drugs across six EU jurisdictions and timelines from regulatory approval by EMA to HTA recommendation (perceived as access gap) in the context of jurisdiction-specific HTA processes.

HTA recommendations vary substantially between jurisdictions

Our study provided evidence that adds to the understanding of the considerable variation in HTA outcomes for new oncology and non-oncology drugs across EU jurisdictions. HTA recommendations differ considerably across European jurisdictions. Overall, almost 40% of all HTA recommendations were negative, while over 60% were positive and positive with restrictions across all six jurisdictions included in our study. However when this is viewed at a jurisdiction level, about half of HTA recommendations in Scotland, Germany and France were negative. These differences can be explained by variations in healthcare systems and thus HTA processes in selected jurisdictions. Other factors also play a role; for example, information required by HTA agencies, interpretation of clinical and economic evidence, rigour of assessment and appraisal process and the use of appropriate comparators (4).

Based on the results, SMC would appear as the most restrictive, with more than half of HTA recommendations being negative and importantly, SMC assesses all new drugs that are granted an MA by EMA. The proportion of negative recommendations issued by HAS and IQWIG was extremely close to that by SMC. However, HAS and IQWIQ typically base their recommendations on the therapeutic value of new drugs and do not consider cost-effectiveness criteria. ZIN in the Netherlands belongs to the group of jurisdictions that base their recommendations mainly on the added value of new medicines. In the Netherlands, all innovative specialist drugs are reimbursed unless they are specifically not recommended by ZIN and the proportion of negative recommendations was the smallest of studied jurisdictions. In Germany the approval of orphan drugs results in simultaneous proof of added benefit for those drugs for IQWiG.

Importantly, in our study we investigated and compared initial HTA recommendations in jurisdictions included. Over time reassessments of new medicines can be undertaken by HTA bodies due to clinical reasons (new evidence being generated, changes in clinical practice), economic reasons (drug prices changes, cost-effectiveness criteria being implemented) or policy changes (eg. legal requirements for reassessments of indicated medicines, different health priorities).

Variation in HTA outcomes for oncology and non-oncology drugs

Our study shows particular contrasts in HTA assessments with regard to oncology versus non-oncology drugs. Based on our study results, ZIN in the Netherlands seems to be the only institution with consistent proportions of negative, restricted and positive recommendations for oncology and non-oncology drugs.

Recent SMC process changes that may result in more positive recommendations for anti-cancer drugs in the future were not considered during the timeframe of our study and more research on this issue would be required (14). During our study period, anticancer drugs were available for patients in the Netherlands via "individual patient treatment requests" and also via New Medicines Fund (7).Cost-effectiveness criteria seemed to have been the most prevalent reason for negative SMC recommendations, which is consistent with previous research (15) .

Reasons for negative recommendations for new oncology drugs have been investigated in our previous research (16) which concluded that both the clinical profile of a new drug; that is, its benefits, harms and its costs or cost-effectiveness together or separately were the primary reason for negative recommendations in jurisdictions such as England, Poland and Scotland, which use cost-effectiveness criteria. Nevertheless, our study results show a more negative approach to oncology drugs by these countries. Previous research indicated that clinical profile of a new drug can also be primary reason for negative recommendation in this group of jurisdictions (16). All of these jurisdictions; however, provide alternative ways of access to oncology drugs.

Other factors may play a role in HTA recommendations. Kleijnen and colleagues (16) investigated the impact of clinical trial end points on HTA recommendations for new anticancer drugs in the same European jurisdictions, revealing that the impact of overall survival was mainly positive or neutral, the impact of progression-free survival was also mainly positive (if included as it varied considerably across jurisdictions) and quality-of-life data had limited impact on less than half of recommendations; however, that impact was mainly neutral or positive.

Patient access to new cancer drugs through the Cancer Drugs Fund (CDF) in England as an alternative to HTA recommendation was relevant for our research. CDF provides alternative access to cancer drugs that had not been appraised by NICE or that had not been recommended for use due to clinical or/and cost-effectiveness criteria (17).Between 2010-2016 CDF spent 1.3 billion GBP (approximately 1,6 billion EUR), the equivalent of 1 year's total spent on all cancer drugs in the NHS (18). Recent

research has shown that making the new cancer drugs available for patients through the CDF without meeting clinical or/and cost-effectiveness criteria has not delivered value to society (18).

In Poland, individual patients' requests for cancer drugs were possible for several years until December 2011 but the impact of this access has not yet been explored. Scotland also provided some alternative ways of accessing new drugs via individual patient treatment requests and the New Medicines Fund (7). These special pathways available for oncology patients can explain the availability of anti-cancer drugs in clinical practice for patients in need in some jurisdictions despite the high proportion of negative HTA recommendations.

Timely assessments (access gap - timelines from regulatory approval to HTA recommendation)

The potential delay, or access gap, from the time when the regulator has approved a medicine to the time when it is available is important from a patient's perspective, particularly in cases of unmet medical need and as such, can affect treatment efficacy and effectiveness. Time is an indicator that can be measured easily and objectively, assuming the availability of the data in the public domain, and thus allows the comparison across different jurisdictions. However, timelines should be considered carefully only in relation to decision outcome and with in-depth understanding of each jurisdiction specific HTA system (Suppl. Mat. 1). The design of HTA processes can have an impact on the time necessary to develop recommendations in individual jurisdictions. Longer timelines might be expected for example, in jurisdictions where draft HTA recommendations such as NICE guidance are available for public consultation and various group of stakeholders including patients and clinicians participate actively at different stages of the whole process.

Considerable variation in timelines between jurisdictions can be explained by basic differences in HTA systems and reimbursement of new drugs. For example, in Germany a new drug is reimbursed by default at the time of regulatory approval by EMA until an IQWIG recommendation is made that may change it, while in Poland a new drug is reimbursed only when it is recommended by AOTMiT and in the Netherlands, as previously mentioned, all innovative specialist drugs are reimbursed unless they are specifically not recommended by ZIN. There the reimbursement process starts with a submission of a notification from the sponsor to ZIN. If the expected budget impact for the medicine is above EUR 2.5 million based on pharmacoeconomic data provided by the sponsor, then the full HTA process is performed If not, the date of notification was considered as ZIN's positive recommendation date).

Timelines calculated in our study represent timelines from regulatory approval to HTA recommendation, which also covers the time gap between MA approval and pharmaceutical company submission to the HTA agency. The latter depends mostly on

business-driven decisions made independently by a particular company, considering a wide range of factors including international reference pricing systems applied in particular jurisdictions. Therefore, potential delays maybe built in by companies not submitting in a timely manner.

Our timelines also cover company time during HTA, which could include time dedicated, for example, to interactions between HTA agencies and companies requiring additional evidence or time dedicated to clarifications on the submission. In previous research comparing five international regulatory agencies' approval time, so-called company (or sponsor) time was excluded (19). As our study is based on publicly available data, the exclusion of company time was not possible, which is one of our study limitations. This issue needs further investigation; however, the unavailability of HTA submission date in the public domain could be perceived as a lack of transparency.

It is worth noting that marketing authorisation holder (MAH) activities can significantly impact timelines. However, in our study it was not feasible to extract company time from the timeline based on publicly available information. Therefore, whilst HTA agencies may be frequently held accountable for delaying patients' access to innovative new drugs, reasons for this delay may include pharmaceutical company strategy to delay access in particular markets, based on international reference pricing. Previous research indicated that although the new drug sofosbuvir, was approved for the treatment of hepatitis C in Europe, the MAH had not yet submitted the application for reimbursement for sofosbuvir in five Eastern European countries (20). From that perspective it should be considered that in the group of jurisdictions included in our study, Poland, with the longest median timelines between regulatory approval and HTA recommendation is the only country that represents Central Eastern Europe and as such may potentially not be a priority for pharmaceutical industry submission due to international reference pricing. Further investigation of the detailed timelines, notably the exclusion of pharmaceutical company time can provide explanation.

Poland has by far the highest median times for all medicine groups, which means that patients do not have timely access to new available treatments. Our finding indicates substantially longer timelines between regulatory approval and HTA recommendations in Poland (78 HTAs for NASs) than previous research, which was based only on several case studies for which median timing was approximately 320 days (minimum, 311 days, maximum, 413 days) (21). However, our findings, which show that Poland had the longest timelines for HTA recommendation, are consistent with other research in which the time from EMA MA to the achievement of a considerable sales level for cancer drugs was measured and compared with other EU countries and Switzerland (22).

Careful consideration needs to be given when the minimum timespans from regulatory approval to HTA recommendation are far below the HTA agency target

timelines, which could suggest that applications were submitted to the agency prior to the MA official approval date; that is, likely during the time between Committee for Human Medicinal Products (CHMP) positive opinion and the European Commission decision date (usually approximately 60 days). This may potentially become commonplace way to r narrow the time gap between EMA approval and HTA recommendation which HTA agencies may explore as a beneficial option, with NICE as an example (18).

Timely assessments are relevant for NASs for unmet medical need, which is often the case for oncology drugs. In all six jurisdictions included in our study, the maximum delay for oncology drugs was much lower than for non-oncology drugs. However, median timelines for oncology drugs were lower only in two jurisdictions (FR, GER) in our study, both of which advise on the value-added extent of a medicine. It was not the case for ZIN, whose approach towards oncology and non-oncology drugs is consistent with regard to HTA outcomes; however, median timelines for HTA for oncology drugs at this agency are almost double those for non-oncology drugs.

Median timelines between regulatory approval and HTA recommendations differed substantially across six jurisdictions for drugs approved by EMA in 2007-2010 whilst for drugs approved by EMA in 2011-2013, the differences in median timelines were not as distinct. However for NASs approved by EMA in 2013, the longest median time in one jurisdiction (PL, 360 days) was three times longer than in the jurisdiction with the lowest median (GER, 120 days). The delays from regulatory approvals to NICE recommendations were substantial, with a median for all drugs of 392 days; however, there current plans are for the NICE appraisal process to start well before a new drug receives MA, meaning NICE draft guidance will be published before MA and final guidance will be published within 90 days after MA is granted (18).

NICE have also implemented an Abbreviated Technology Appraisal (ATA) to evaluate technologies of similar or better clinical outcomes and of similar costs or cost saving. This approach could bring value from both a patient access and budgetary perspective.

This study provides evidence for a future trend toward minimising timelines from MA to HTA recommendations. Timeliness is one of the key success factors for EU joint evaluations, for both relative effectiveness assessments and full HTA reports including additional economic aspects within EUnetHTA and this factor still seems to present a challenge for successful cooperation at EU level (13). In general, timelines from regulatory approval by EMA to HTA recommendations decreased noticeably over time in England, France and Poland, while in France, timelines increased from a median of 126 days for drugs approved by EMA in 2007 to a median of 261 days for drugs approved by EMA in 2013 and the Netherlands, where timelines increased from a median of 124 days for drugs approved by EMA in 2007 to a median of 163 days for drugs approved by EMA in 2013. In Scotland, timelines were more consistent over the analysed years with no extreme variations.

Classifications used to allow international comparison of HTA recommendations

In our study we developed and used trichotomous classification for HTA recommendations based on in-depth analysis of each country's specific new drug reimbursement processes. Other classifications used in previous research characterised HTA recommendations as favourable, favourable with restrictions and non-favourable (23) or a proposed classification of NICE recommendations: yes, yes with major restrictions, yes with minor restrictions, no (24). Almost all classifications published in literature could be easily translated into our trichotomous classification (25) (26), which takes into account the details of each system and allows consistent international comparison of HTA outcomes.

Study limitations

Our study is based on publicly available information. Drugs with less than four HTA outcomes were excluded from our study to avoid the substantial proportion of drugs not assessed by HTA agencies. Based on publicly available information we were able to calculate only overall timelines from MA to HTA outcomes without breaking timelines down into details such as the gap between MA and HTA submission, timeline from HTA submission to HTA outcome and sponsor time during the HTA process.

CONCLUSIONS

EU jurisdictions vary substantially in their approach to oncology and non-oncology drugs, with England, Poland and Scotland issuing more negative recommendations for oncology drugs, while France and in particular Germany, issuing more positive recommendations for oncology drugs. The Netherlands is the only jurisdiction applying a consistent approach across oncology and non-oncology drugs.

Timelines vary considerably across jurisdiction which can be a barrier for joint EU assessments. Both HTA outcomes and timelines can only be interpreted with in-depth understanding of jurisdiction-specific HTA processes. The ability to measure each component of timelines accurately also needs to be considered. However this is hindered by the perceived lack of transparency from HTA agencies on information such as date of submission of an application.

There are substantial differences in HTA outcomes across EU jurisdictions which could be explained by differences in HTA processes, criteria used by HTA agencies such as added value extent versus cost-effectiveness criteria. Other factors such as clinical trial end points, evidence requirements, interpretation of clinical and economic evidence, patient voice and use of appropriate comparators play a role.

Timelines from regulatory approvals to initial HTA recommendations also vary dramatically which impacts patients' access to new medicines in jurisdictions with

the longest timelines. Timelines can be considered as a key quality indicator for patients' access to new drugs. Poland has the longest timelines from regulatory approvals to HTA recommendations, with median values being more than three times longer than in Germany. Whilst these timelines negatively impact access to new drugs by Polish patients in need, they may be influenced by various factors. One of these factors may be pharmaceutical company delays, but this may be impossible to determine based on publicly available data.

EU international comparisons are crucial for envisaged joint production of HTA reports and even more importantly for the utilization of joint reports in the national decision-making processes for drug reimbursement. Based on our study results there is need for transparency in publicly available data including the starting date of HTA process. Timelines could potentially be explored in details in further research based on data provided by HTA agencies through benchmarking studies. Based on the analysis of the minimal access gap, we conclude that it is possible for HTA agencies to make recommendations on new drugs very soon after or approximately close to regulatory approval. Further investigation in regard to this could lead to a better understanding of the conditions that would enable a reduction in the access gap.

REFERENCES

1. Jonsson B. Technology assessment for new oncology drugs. Clin Cancer Res. 2013;19(1):6-11.
2. Rawlins MD. Crossing the fourth hurdle. Br J Clin Pharmacol. 2012;73(6):855-60.
3. Hutton J, McGrath C, Frybourg JM, Tremblay M, Bramley-Harker E, Henshall C. Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies (fourth hurdle systems). Int J Technol Assess Health Care. 2006;22(1):10-8.
4. Kanavos P. The impact of heath technology assessment: an international comparison. EuroObserver. 2010.
5. Banta D. What is technology assessment? Int J Technol Assess Health Care. 2009;25 (Supplement 1):7-9.
6. Lipska I, Hoekman J, McAuslane N, Leufkens H, Hovels AM. Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? Clin Pharmacol Ther. 2015;98(5):489-91.
7. Montgomery B. Review of Access to New Medicines: SMC Health SGDo; 2016 December 2016.
8. European Commission, DG SANCO. Strengthening of the EU cooperation on Health Technology Assessment (HTA). 2016. (https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/20161020_frep_en.pdf accessed 25th May 2017)
9. European Commission. Strategic discussion on European cooperation on HTA. Meeting and Discussion Report. October 2013 (http://ec.europa.eu/health//sites/health/files/technology_assessment/docs/hta_network_strategic_discussion_en.pdf accessed 27th June 2017)
10. EUnetHTA Joint Action 2 2012-2015 FINAL TECHNICAL REPORT Executive Summary. 2016. (http://eunethta.eu/sites/5026.fedimbo.belgium.be/files/EUnetHTAJA2_FinalTechnicalReport_Executive%20Summary_May2016.pdf accessed 27th June 2017)
11. European Commission, HTA Network. HTA NETWORK REFLECTION PAPER ON REUSE OF JOINT WORK IN NATIONAL ACTIVITIES 2015. (https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/reuse_jointwork_national_hta_activities_en.pdf accessed 27th June 2017)
12. Kristensen FB, Gerhardus A. Health technology assessments: what do differing conclusions tell us? BMJ. 2010;341:c5236.
13. Kleijnen S, Toenders W, de Groot F, Huic M, George E, Wieseler B, et al. European collaboration on relative effectiveness assessments: What is needed to be successful? Health Policy. 2015(0).
14. Office for Health Economics. Report Assesssing Trends in SMC Advice Decisions (October 2009 - September 2015) 2016. (https://www.ohe.org/publications/assessing-trends-smc-advice-decisions-october-2009-september-2015 accessed 27th June 2017)
15. Chamberlain C, Collin SM, Stephens P, Donovan J, Bahl A, Hollingworth W. Does the cancer drugs fund lead to faster uptake of cost-effective drugs? A time-trend analysis comparing England and Wales. Br J Cancer. 2014;111(9):1693-702.
16. Kleijnen S, Lipska I, Leonardo Alves T, Meijboom K, Elsada A, Vervolgyi V, et al. Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries. Ann Oncol. 2016.
17. Buxton M, Longworth L, Raftery J, Sculpher M, Towse A. Reforming the Cancer Drug Fund. BMJ : British Medical Journal. 2014;349.
18. Aggarwal A, Fojo T, Chamberlain C, Davis C, Sullivan R. Do patient access schemes for high-cost cancer drugs deliver value to society?—lessons from the NHS Cancer Drugs Fund. Ann Oncol. 2017.
19. Hirako M, McAuslane N, Salek S, Anderson C, Walker S. A Comparison of the Drug Review Process at Five International Regulatory Agencies. Drug Inf J. 2007;41(3):291-308.

20. Schelleman H, Dupree R, Kristensen FB, Goettsch W. Why we should have more collaboration on HTA in Europe: the example of sofosbuvir. Journal of Pharmaceutical Policy and Practice. 2015;8(1):O13.
21. Wilsdon; T, Serota A, for Charles River Associates conctracted by EFPIA, Medicines Australia and EuropaBio A comparative analysis of the role and impact of Health Technology Assessment. May 2011.
22. Ernst & Young, Young People Oncology Foundation Alivia. Access to innovative cancer drugs in Poland in comparison with selected European Union countries and Switzerland. 2015. https://www.alivia.org.pl/raport2015/05_05_2015_Raport_wersja_EN.pdf accessed 27th June 2017)
23. Pujolras LM, Cairns J. Why do some countries approve a cancer drug and others don't? Journal of Cancer Policy. 2015;4:21-5.
24. Raftery J. Review of NICE's recommendations, 1999-20052006 2006-05-25 21:59:06. 1266-8 p.
25. Nicod E, Kanavos P. Developing an evidence-based methodological framework to systematically compare HTA coverage decisions: A mixed methods study. Health Policy. 2016;120(1):35-45.
26. Context Matters. Global Variability in HTA Decisions Poses Challenges for Innovative Biopharmaceutical Research and Development. 2014.

SUPPLEMENTARY MATERIAL

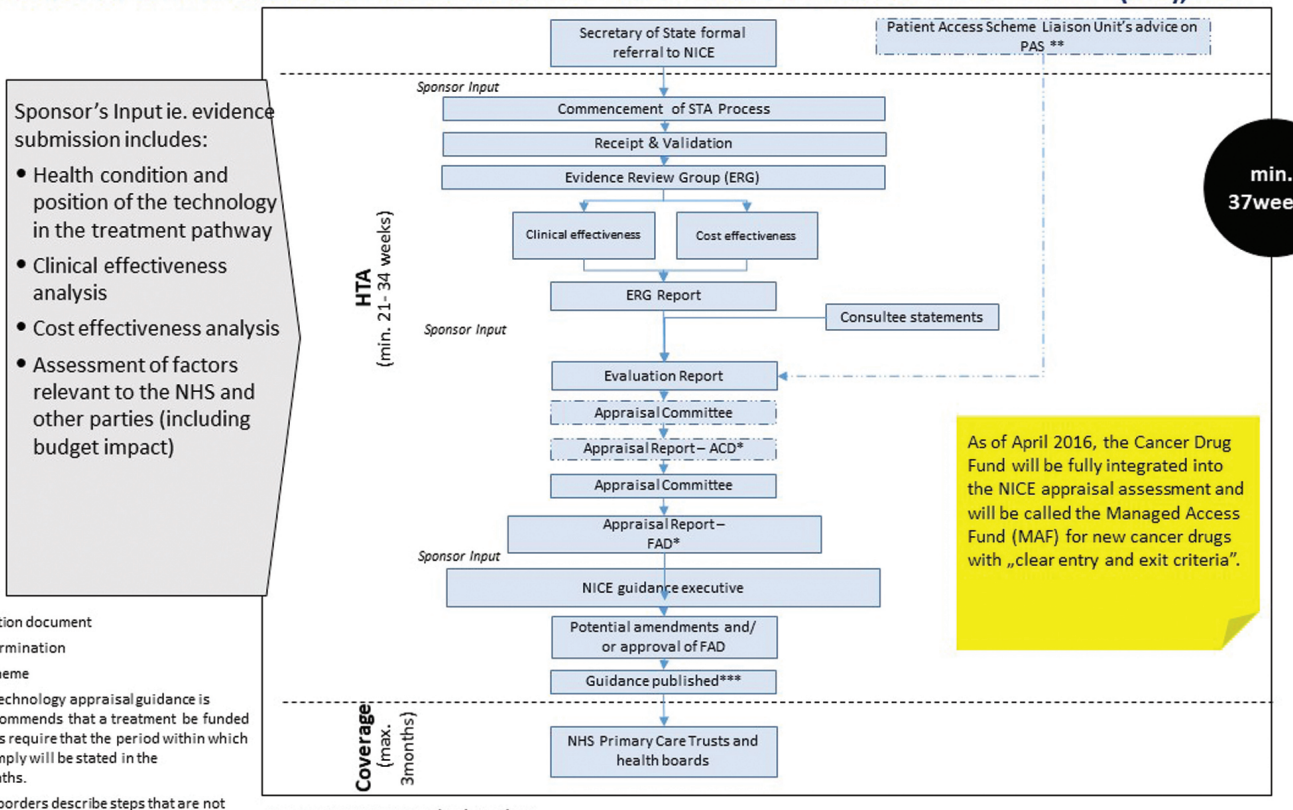
HTA processes in selected EU jurisdictions

We explored and mapped the details of HTA processes in the drug reimbursement decision-making process in order to classify new drugs assessments into a trichotomous system with three categories of HTA recommendations (positive/ positive with restrictions/ negative):

- England, NICE – National Institute for Health and Care Excellence
- France, HAS – French National Authority for Health
- Germany, IQWiG – the Institute for Quality and Efficiency in Health Care
- Netherlands, ZIN – the National Health Care Institute (former CVZ)
- Poland, AOTMiT – the Agency for Health Technology Assessment and Tariff System
- Scotland, SMC – Scottish Medicines Consortium at NHS National Services

1. England, NICE - National Institute for Health and Care Excellence

OVERVIEW OF A NEW DRUG'S APPROVAL PROCESS – SINGLE DRUG TECHNOLOGY ASSESSMENT (STA), NICE



* ACD – appraisal consultation document
FAD – final appraisal determination

** PAS – patient access scheme

***Compliance with NICE technology appraisal guidance is mandatory. When NICE recommends that a treatment be funded by the NHS, the Regulations require that the period within which the health service must comply will be stated in the recommendations as 3 months.

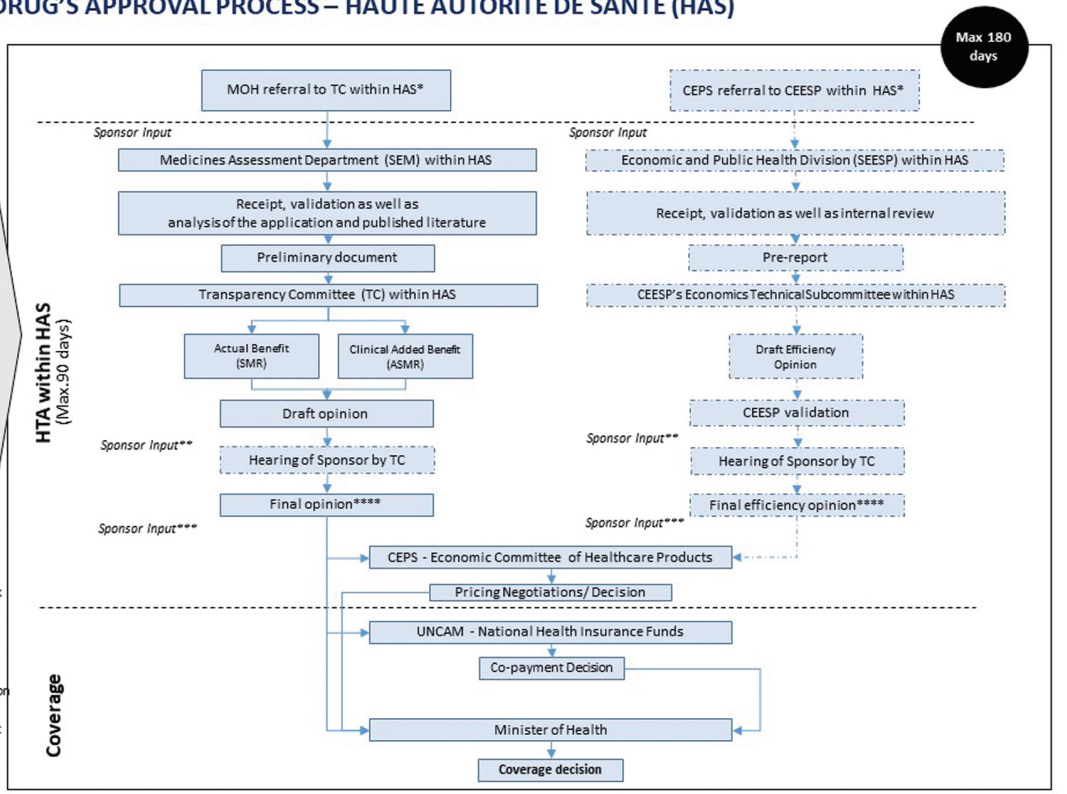
Legend: dotted blue lines/borders describe steps that are not relevant in all cases.

Sources: NICE, NHS, author's analysis

Data source http://www.nice.org.uk/

2. France, HAS - French National Authority for Health,

OVERVIEW OF A NEW DRUG'S APPROVAL PROCESS – HAUTE AUTORITÉ DE SANTÉ (HAS)



Sponsor's Input (medical technical dossier with TC):

- **scientific and clinical evidence ie. Indications, presentations, comparators, clinical efficiency and tolerance data, public health interest, population, SMR, ASMR, studies in process etc.**

Sponsor's Input (efficiency dossier with CEESP)***:**

- **General information on the product including commercialization and costs in Europe, efficiency and budget impact.**

*****As of October 2013, France requires manufacturers to provide an efficiency dossier for drugs that fulfill two conditions:

- The manufacturer claims an ASMR (drug) between I and III.
- The drug is likely to have significant impact on the health insurance budget (> €20 million in annual sales revenue during the second full year on the market).

* Minister's/ CEPS's referral is independent of the unscheduled work of the TC and CEESP ie. applications submitted by pharmaceutical companies and of referrals on the TC's own initiative.

** written comments and can ask to be heard by the Committee

*** material errors only

**** The TC opinion is being published immediately. The CEESP opinion is made publically available once the price negotiation is concluded.

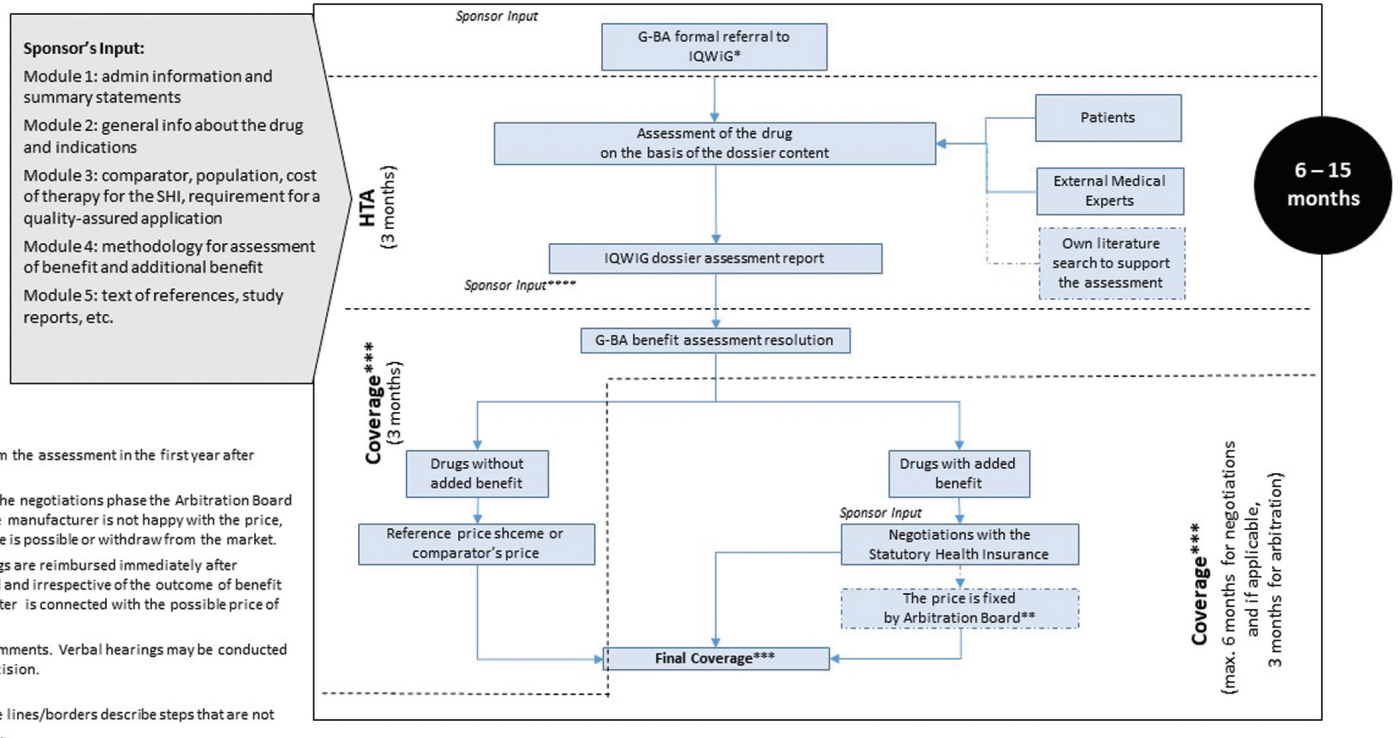
Legend: dotted blue lines/borders describe steps that are not relevant in all cases.

Sources: HAS, author's analysis

Data source http://www.has-sante.fr/portail/jcms/r_1455081/Home-page

3. Germany, IQWiG - the Institute for Quality and Efficiency in Health Care,

OVERVIEW OF A NEW DRUG'S APPROVAL PROCESS – DOSSIER ASSESSMENT PROCEDURE, IQWiG



* G-BA must perform the assessment in the first year after launch

** If no consent in the negotiations phase the Arbitration Board fixes the price. If the manufacturer is not happy with the price, appealing procedure is possible or withdraw from the market.

***In Germany drugs are reimbursed immediately after regulatory approval and irrespective of the outcome of benefit assessment. The latter is connected with the possible price of the product.

****3 weeks for comments. Verbal hearings may be conducted before the G-BA decision.

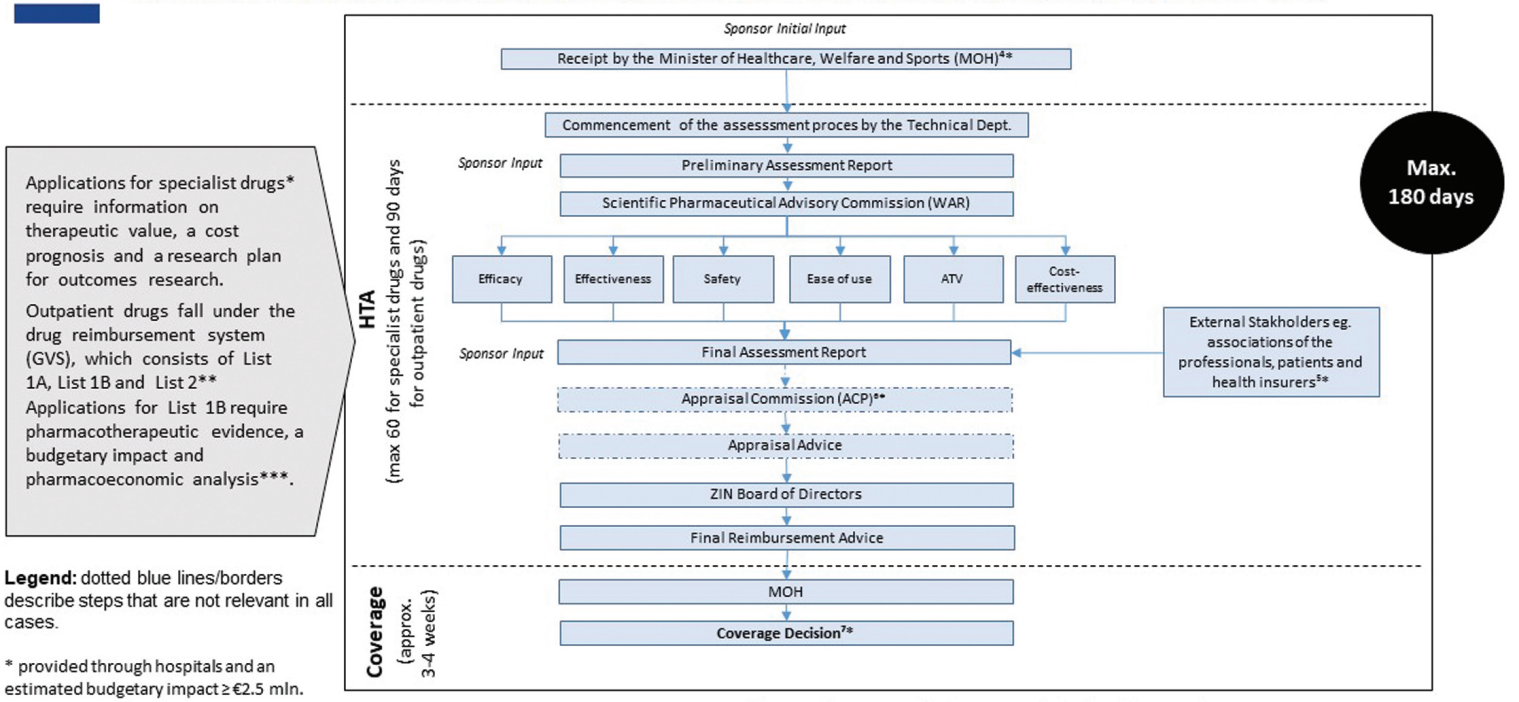
Legend: dotted blue lines/borders describe steps that are not relevant in all cases.

Sources: IQWiG; Requirement for benefit assessment in Germany and England, V.Ivandic, Health Economics Review, 2014; author's analysis

Data source https://www.iqwig.de/en/home.2724.html

4. Netherlands, ZIN – the National Health Care Institute (former CVZ)

OVERVIEW OF A NEW DRUG'S APPROVAL PROCESS IN THE NETHERLANDS, ZORGINSTITUUT (ZIN)



** List 1A: groups of therapeutically interchangeable drugs, List1B: non-interchangeable drugs and/or drugs with added therapeutic value, List 2: drugs restricted in reimbursement

*** Exemptions: orphan drugs, BI<€500,000 per year and HIV drugs

4* valid applications submitted before the 25th of a month will be included in the next month's assessment assignment

5* WAR determines which parties in the field will be invited.

6* Meets upon the Board's request. Issues advice based on societal considerations. In reality meets rarely.

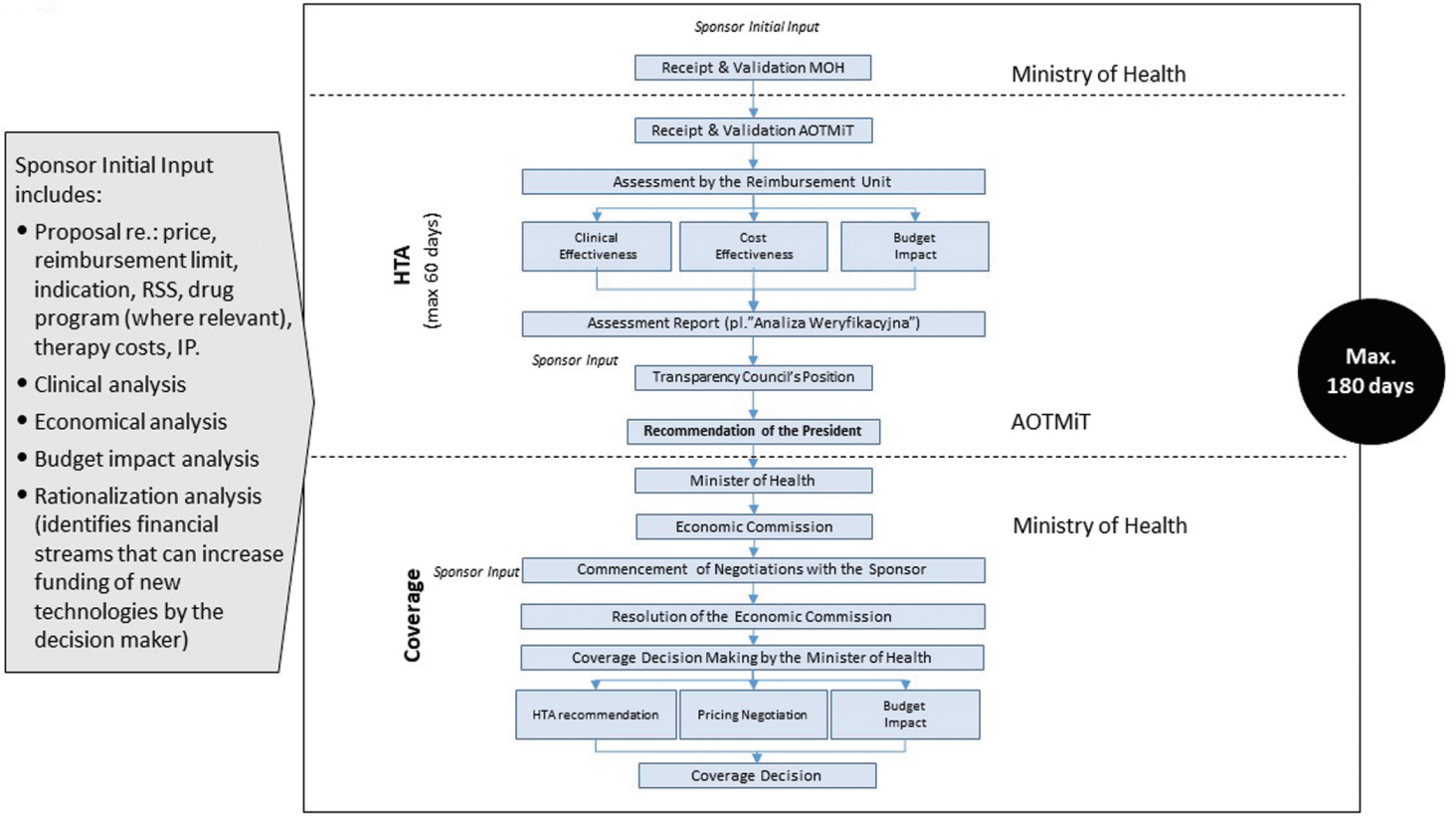
7* Coverage decisions are mandatory for the health insurers.

Sources: ZIN; 2014 Report: „Decision making in drug reimbursement" M. Franken; 2010 KCE Report 147: „Drug Reimbursement Systems"; CVZ 2010 Report: „Dutch Assessment Procedures for the Reimbursement of Outpatient Medicines", author's analysis

Data source https://www.zorginstituutnederland.nl/publications+in+english

5. Poland, AOTMiT - the Agency for Health Technology Assessment and Tariff System

OVERVIEW OF A NEW DRUG'S APPROVAL PROCESS IN POLAND, AOTMiT, MOH

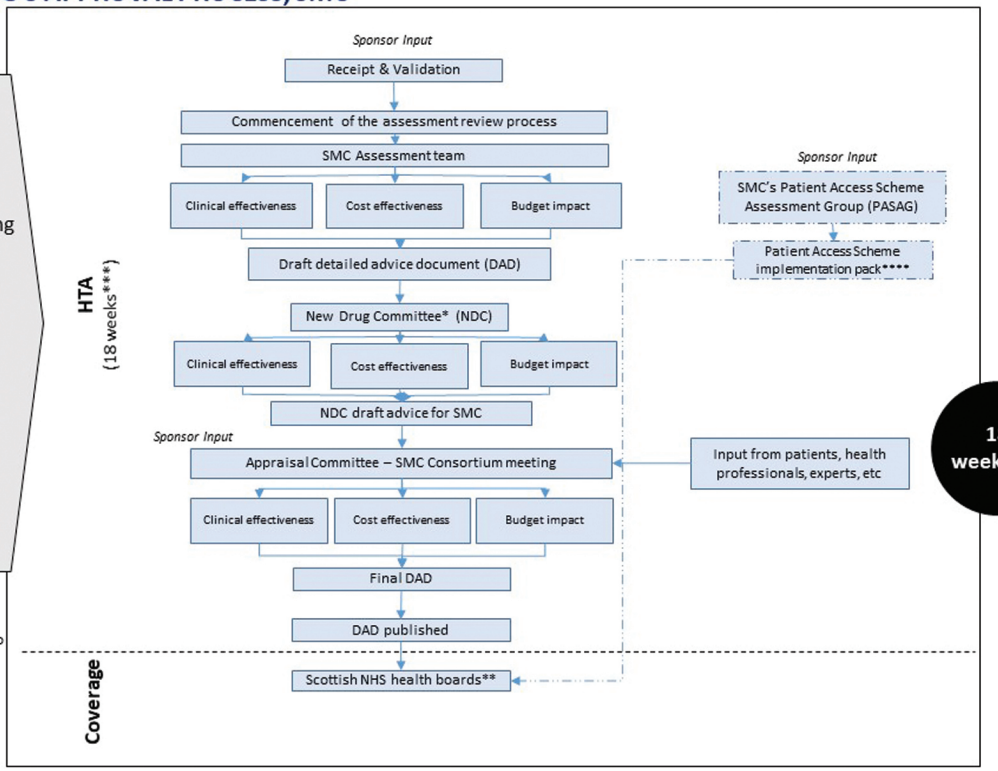


Sources: reimbursement law, law on health care services financed out of public funds, AOTMiT

Data source http://www.aotm.gov.pl/

6. Scotland, SMC - Scottish Medicines Consortium at NHS National Services

OVERVIEW OF A NEW DRUG'S APPROVAL PROCESS, SMC



* Scientific committee

** The SMC advice is issued to Scottish Health Boards but it is not mandatory and the final decision about the provision of drugs is made by the Health Boards themselves. Although the advice is not binding, doctors and individual clinicians are expected to take it into account and should only prescribe against it if they can justify their decision in light of evidence about a patient's particular needs or circumstances.

*** 22 weeks for end of life/ orphan medicines that require a PACE meeting.

****If medicine is accepted

Legend: dotted blue lines/borders describe steps that are not relevant in all cases.

Sources: SMC, NHS, author's analysis

Data source https://www.scottishmedicines.org.uk

chapter 3

BENCHMARKING HEALTH TECHNOLOGY ASSESSMENT AGENCIES – METHODOLOGICAL CHALLENGES AND RECOMMENDATIONS

Iga Lipska
Neil McAuslane
Tina Wang
Lawrence Liberti
Hubert G.M. Leufkens
Anke M. Hövels

Prepared for submission

ABSTRACT

Background

To enable increased collaboration and the development of reliance models among HTA agencies, quantitative and qualitative comparative information on HTA agencies' processes, practices and performance are needed as the platform on which to build trust in and across agencies.

Objectives

To identify and quantitate the common stages of the submission, assessment and appraisal of a new drug in an HTA agency recommendation process and the type of information required to enable comparative analysis; to provide benchmarking data that can be used to enable increased clarity regarding the differences and similarities across HTA agencies, understand performance within and across HTA agencies and identify areas in the processes of individual agencies in which time is spent and to encourage systematic measuring of the processes that occur during HTA assessment for recommending new drugs

Results

Data for 109 HTA reviews from five HTA agencies are analysed in this paper. Healthcare systems and HTA processes differed substantially across jurisdictions. However, there were no substantial differences in the HTA methodology applied by these jurisdictions. Our study shows considerable differences among the median timelines from assessment, via appraisal phase up to final HTA recommendation for the five agencies included in this analysis. In the group of agencies analysed in our study only one agency has more than 75% of its resources dedicated to HTA activities and this agency has the shortest median timelines.

Conclusions

It is feasible to find consensus among HTA agencies regarding the common milestones of the HTA review process in order to map jurisdiction-specific processes against agreed generic processes, along with the detailed characteristics of each agency that enables results to be interpreted in the right context. HTA agency benchmarking across jurisdictions has promising potential; however, timelines can't be used as a single measure to compare or measure performance of HTA agencies but only with in-depth understanding of jurisdiction specific HTA processes.

INTRODUCTION

All health technology assessment (HTA) agencies have the same or similar underlying objectives and obligations to ensure that the utilisation of health technologies, including new medicines, provides the best value for money (1). As the HTA environment becomes more globalised and new collaborative and integrated ecosystems develop, there needs to be a clear understanding of how the different process and practices within the environment are evolving. Indeed, in order to enable increased collaboration and the development of reliance models, quantitative and qualitative comparative information on HTA agencies' processes, practices and performance are needed as the platform on which to build trust in and across agencies.

There is a common understanding and general acceptance that HTA agencies should adhere to certain "key principles" including independence, transparency, inclusiveness, scientific basis, timeliness, consistency and legal framework. Drummond and colleagues proposed that these principles could be organised into four areas: the structure of HTA programmes, the methods of HTA, the processes of conduct of HTA and the use of HTA in decision making (2). The same group of researchers suggest that such key principles could be augmented and used to formulate audit questions to measure HTA agencies' performance (3).

On the other hand, there is also almost full agreement as to the existence of differences among HTA agencies in processes and methodologies for clinical and economic assessments as well as in national procedures (4). The challenge and the opportunity for agencies, companies and other stakeholders is the identification of truly comparative metrics to recognise similarities and differences among HTA agencies, because an understanding of all aspects of these agencies is necessary to appropriately interpret HTA information.

The move toward increased HTA transparency is unavoidable as collaborative networks grow and in fact, independent comparisons of HTA activities are already underway. Therefore, HTA organisations should facilitate open discussion of the scientific basis for their decisions, especially when diverse coverage decisions for the same new medicine occur across jurisdictions (5, 6). The most recent public consultation by the European Commission on strengthening EU cooperation on HTA revealed that transparency of the HTA process is seen as a relevant factor of very high or high importance (83% and 16% of survey replies respectively) (4).

As HTA agencies processes and practices have been mapped by different stakeholders, the main focus has been on outcomes, differences in outcomes and timelines (7, 8). Historically, agencies have been measured by divergent stakeholders including academics, pharmaceutical companies and consultancies. A set of 14 best practice principles were developed by Charles River Association (CRA) in 2011 (7) and then applied in the subsequent report of 2013 (8). These principles, which were mainly constructed around the revision of existing principles published by Drummond and colleagues (2, 3) and based on literature searches, demonstrated to some extent

the consensus between academia, payers and industry. More importantly, metrics were proposed that could be modified for each principle and used to compare the role of HTA in selected healthcare systems. The suggested 14 best practice principles were sub-grouped into four categories: scope and prioritisation, methods, process and impact (7).

The authors concluded that because of the variety of HTA across jurisdictions, it was a challenge to apply one set of best practice principles (7, 8). It should also be noted that HTA agencies have raised objections to some of the principles outlined in previous research (2, 7-9). However there was full agreement among agencies that "HTA should be timely" (2). The results of the European Commission public consultation showed that timely delivery of an assessment report is a relevant factor of very high, high and medium importance when carrying out HTAs (51%, 41% and 8% of replies respectively) (4). However timely HTA delivery does not depend only on the performance of HTA agencies, but rather is also impacted by both the quality and timing of submissions by pharmaceutical companies to HTA agencies.

According to a commonly used definition, *benchmarking* is evaluating something by a comparison with a standard. Benchmarking could also be considered as a continuous systematic process for comparing performance indicators across peer organisations for the purpose of organisational improvement. Over time, trends can be determined and improvements measured and thus best practice across agencies can be identified. Benchmarking can also be used by HTA agencies to support decisions on resource allocation.

Although HTA agencies are concerned because of differences in agency mandate and lexicon as well as in how decisions are made, the assessment and appraisal period for all agencies can be broken into component parts or a framework that can help identify similarities across agencies. This identification in turn enables the use of qualitative and quantitative comparative metrics to build fit-for-purpose processes and practices as well as improved HTA integration and truly supportive collaborative models.

This paper describes an HTA agency benchmarking methodology that was developed with active HTA agency participation to ensure its ability to enable comparative data to be collected and interpreted.

Objectives

The overall objective of this study was to provide a methodology for benchmarking HTA agencies. Specifically, the objectives were to

- Identify and quantitate
  - the common stages of the submission, assessment and appraisal of a new drug in an HTA agency recommendation process and
  - the type of information required to enable comparative analysis.

- Provide benchmarking data that can be used to
  - enable increased clarity regarding the differences and similarities across HTA agencies,
  - understand performance within and across HTA agencies and
  - identify areas in the processes of individual agencies in which time is spent.
- Encourage systematic measuring of the processes that occur during HTA assessment for recommending new drugs so as to
  - provide a methodology that will enable comparative analysis and
  - enable ongoing performance improvement initiatives.

METHODS

The methodology that was developed for this study is based on the premise that notwithstanding the apparent variances among the HTA processes of different agencies, these processes are made up of a set of basic stages or building blocks that allow meaningful comparisons. These milestones in the HTA deliberative process were identified and defined and the study designed based on previous research by Allen and associates that mapped the processes of current HTA agencies (10). Starting in 2012, the ten following agencies worked with the researchers to achieve an understanding of the different processes employed by each agency, highlighting areas of similarities and differences that were considered particularly important:

- AAZ – Agency for Quality and Accreditation in Health Care and Social Welfare (Agencija za kvalitetu i akreditaciju u zdravstvu i socijalnoj skrbi), Croatia
- CADTH – Canadian Agency for Drugs and Technologies in Health, Canada
- CONITEC – National Committee for Technology Incorporation (Comissão Nacional de Incorporação de Tecnologias), Brasil
- INESSS – National Institute of Excellence in Health and Social Services (Institut national d'excellence en santé et en services sociaux), Canada, Quebec
- INFARMED – National Authority for Medicines and Health Products (Autoridade National do Medicamento e Products de Saude), Portugal
- KCE – Belgian Health Care Knowledge Centre (Federaal Kenniscentrum voor de Gezondheidszorg), Belgium
- NICE – National Institute for Health and Care Excellence, UK England
- PBAC – Pharmaceutical Benefits Advisory Committee, Australia
- SMC – Scottish Medicines Consortium at NHS National Services, UK Scotland
- VASPVT – State Health Care Accreditation Agency at the Ministry of Health (Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba prie Sveikatos apsaugos ministerijos), Lithuania.

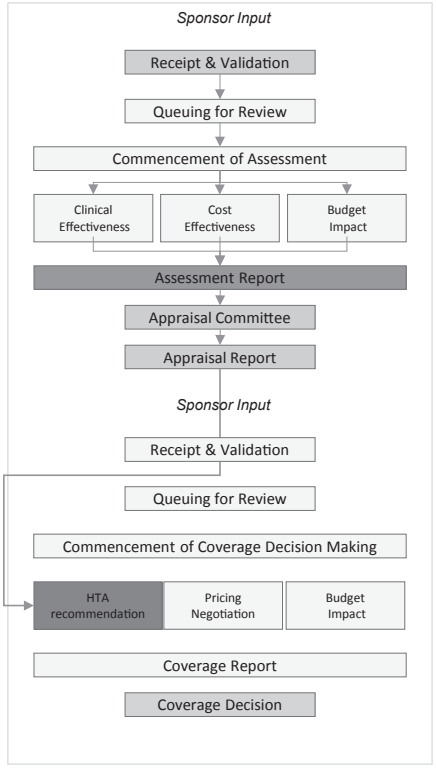
Our study was divided into three main phases.

Phase I – identification of common milestones across HTA agencies and the development of the generic process map

First, based on the information available in the public domain and on personal communication with individual HTA agencies, we developed HTA process maps for each jurisdiction participating in the study. Second, we designed a map of generic HTA process with common milestones (Figure 1). Third, the participating HTA agencies agreed upon this generic process and common milestones.

Phase II – the development of the questionnaire and its use in the pilot phase

In June 2012, an agency discussion meeting took place to scope the benchmarking project methodology and to seek agreement among HTA agencies. Built on prior CIRS work and experience in benchmarking regulatory agencies area (11),the questionnaire was developed in Excel by the main researcher (IL) through email and face-to-face consultation with HTA agencies and structured in two main parts, to collect information



Review milestones

Captured in the full study

	Review milestones	Date
1	Submission to HTA agency	Date
2	End of assessment phase	Date
3	Start of the appraisal phase	Date
4	End of appraisal phase	Date
5	Final HTA recommendation	Date
6	Minister of Health/s coverage decisions	Date

Figure 1. Agreement on common milestones for HTA review process.

on the organisational aspects as well as the assessment and appraisal process followed by the different agencies, evaluating resources, timelines and outcomes (Figure 2).

A pilot study was then conducted focused on collection of information on four individual products per agency that underwent single-technology assessment (STA), two of the most recent products that received a positive HTA recommendation from the agency (including positive recommendations with restrictions) and two of the most recent products that received a negative HTA recommendation. Based on the feedback received from HTA agencies during pilot phase the improved version of the questionnaire was prepared and sent to HTA agencies for their comments and feedback and amendments were made to the data collection tool and the questionnaire.

Phase III – the development of the final version of the questionnaire based on HTA agencies' feedback provided and data collection for the full study

The final version of the questionnaire was also divided into two main domains: general information and individual product information. The general information portion consisted of five main domains (Scope and remit, Resource and budget, Appraisal/ scientific committee, Transparency and Review procedures and processes), containing 51 questions. The individual product portion of the questionnaire consisted of four

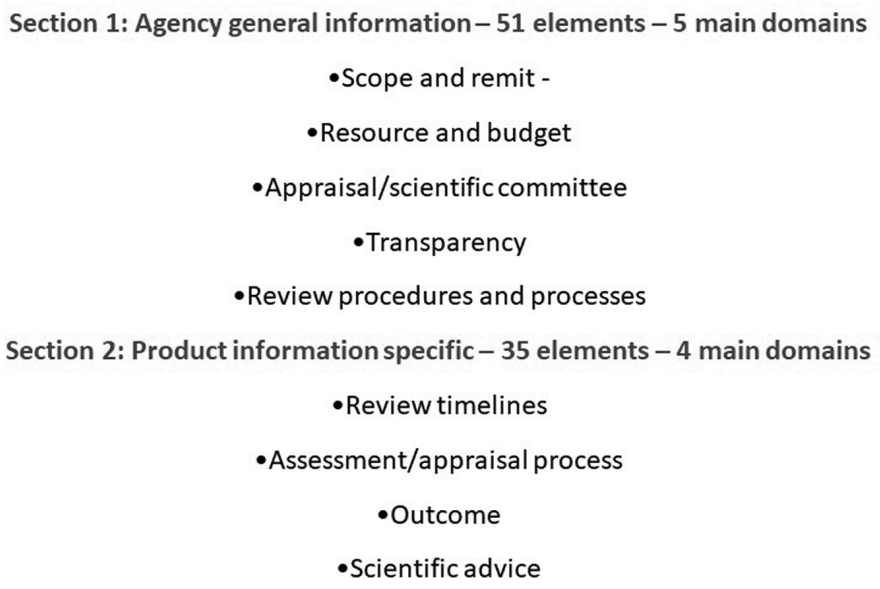


Figure 2. Outline of characteristics suggested to be collected to provide the necessary data for comparative purposes – based on agency input.

main domains (Review timelines, Assessment/appraisal process, Outcome and Scientific advice) containing in total 35 questions (and additionally space for comments was provided). The details of the questionnaire are provided in the Supplementary Material for this manuscript.

The final version of the questionnaire was discussed at a HTA agency meeting in June 2014 and subsequently distributed to select HTA agencies for the fully study. In the full study, we collected the information on individual products that have undergone STA including all new active substances (NASs) that were assessed and appraised by the participating HTA organisations in 2013 and that received HTA recommendation in 2013. Exclusion criteria were generics, major line extensions, vaccines, development of a marketed active substance without any change to formulation or indication/disease state, changes to labelling for reasons other than those relating to new indications/ disease states or new formulations, changes to manufacturing and control methods, applications where a completely new dossier was submitted from a new company for the same active substance and the same indication(s) as already approved for another company, applications from a new or additional name, or a change or name, for an existing compound. In general, HTA agencies provided data through completion of the questionnaire; however, some parts of the questionnaire were pre-filled by researchers based on the information available in the public domain and then reviewed and verified by the HTA agencies.

In this paper, we report on results of the questionnaire related to characteristics of five HTA agencies and the timelines and milestones in the appraisal and assessment phase. We calculated timelines based on the data verified and provided by HTA agencies. These five HTA agencies data are anonymised in this paper. For confidentiality reasons the data was collected under the condition that the agencies specific data will be presented anonymously and the focus of this paper is to evaluate the methodology not the specific agencies performance. This analysis focuses on a subset of questions included in our study questionnaire, namely questions 9 on the HTA submission date to the agency, questions 14-17 regarding details of assessment phase, questions 18-22 regarding details of appraisal phase and question 23 on the final date of HTA recommendation (all detailed questions on timelines are included in the individual product part of the questionnaire (Supplementary Material). Timelines were calculated for: individual HTA agencies, for all agencies, for HTA outcomes (positive, positive with restrictions, negative), for oncology vs non-oncology products. Based on our detailed questionnaire, pharmaceutical company time could be calculated during both the assessment and appraisal phase and even more importantly extracted from HTA agency time based on the detailed data provided by HTA agencies, which also allowed us to extract time taken by companies during assessment and appraisal phase.

RESULTS

In total, data for 109 HTA reviews from five HTA agencies are analysed in this paper. Three agencies are in Europe and four agencies defined themselves as independent from government. The size of HTA agencies varied considerably; however, four agencies consisted of more than 100 full- time employees (FTEs) and one agency had less than 100 FTEs. The total number of FTEs assigned to HTA activities at the agencies varied from 14 to 88, which interestingly translates into less than 25% of total FTEs of two of the agencies, between 50% to 75% for two agencies and more than 75% for one agency. Total agency budgets ranged from less than $ 2 million to almost $ 115 million. Three agencies declared to outsource HTA-related activities to universities or academic groups and four agencies to individual independent contractors or consultancy companies (Figure 3). Median time from HTA submission to HTA recommendation varied between 99 and 862 days (Figure 3).

Agencies		A	B	C	D	E
Median time (days) from HTA Submission to HTA recommendation		862	268	209	147	99
Internal resources	Size of the agency	Over 100 FTEs	Over 100 FTEs	Over 100 FTEs	Over 100 FTEs	Less than 100 FTEs
	Number of internal HTA FTEs	21	50.75	66	88	**14.3**
External resources	Universities/ Academic centres/ academic groups	Yes	Yes	Yes	N/A	No
	Individual independent contractors	Yes	Yes	Yes	N/A	Yes
	Consultancy companies/ consultancy groups	No	No	Yes	N/A	No
	Governmental agencies	No	No	No	N/A	No
	Hospitals/health service providers	No	N/A	N/A	N/A	No

Figure 3. Resources for HTA-related activities vs median time of HTA process.

Detailed timelines

Overall, median time form regulatory approval to HTA recommendation was approximately 220 calendar days, with the median time from regulatory approval to HTA submission being approx. 70 days (Figure 4). The median time for the assessment phase was 14 days and for HTA appraisal phase 100 days, with company median time being 11 and 10 days during the assessment and appraisal phases respectively. However these timelines differ considerably across various HTA agencies

Figure 5 presents detailed timelines and breakdown of the processes for two agencies, with extreme values for median time from HTA submission to HTA recommendation (99 and 862 days for Agency E and Agency A respectively). We compared details of where time was spent from HTA submission to HTA recommendation, based on agreed milestones. The median time from HTA submission to the end of HTA assessment phase is 60 and 442 days for agency E and A respectively and the median time of the appraisal phase also differs substantially, from 12 to 358 days for Agency E and A respectively. The median time from the end of appraisal phase to HTA recommendation equals only 3 days for Agency E while for Agency A it is 39 days.

In Figure 6, the time between submission to the HTA agency and final recommendation is presented for individual products and also for oncology vs. non-oncology products. The median time between submission and final recommendation was 149 days for all products and 146 versus 149 days for oncology versus non-oncology

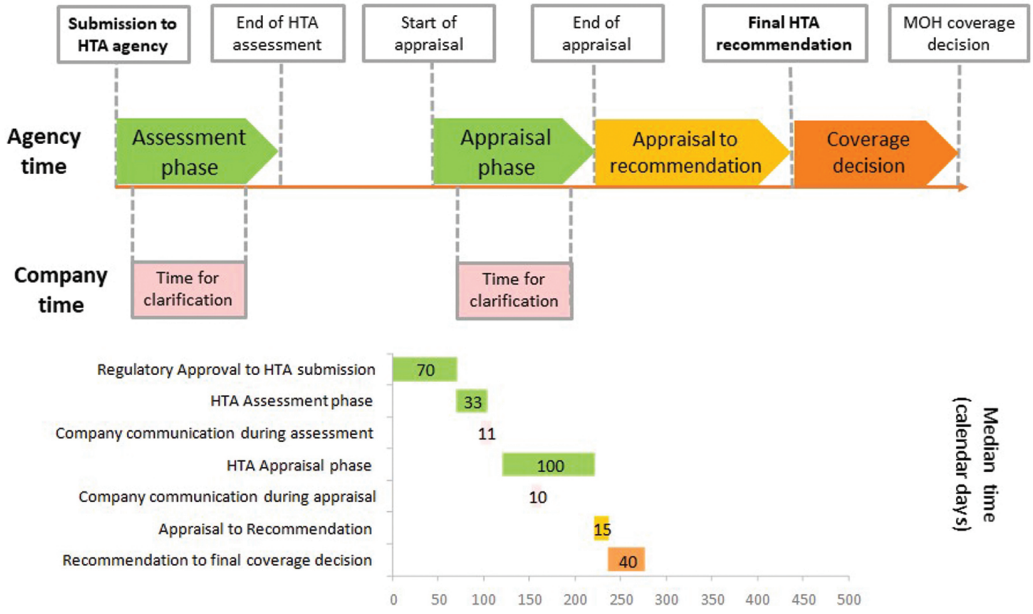


Figure 4. Agreement on common milestones vs. median time.

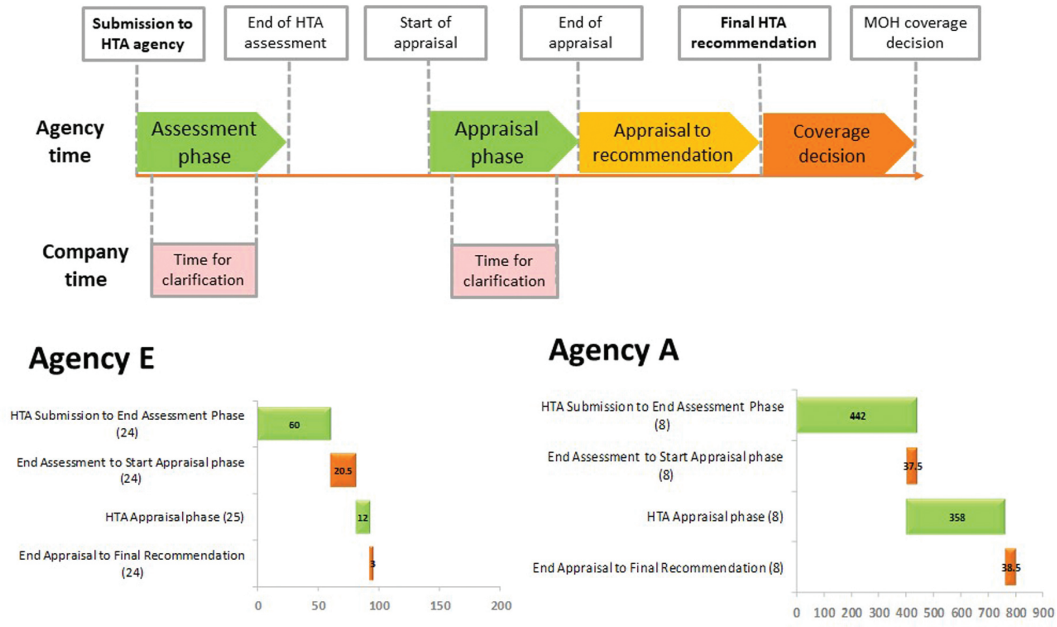


Figure 5. Comparison – Where Time is Spent between HTA Submission and Final Recommendation.

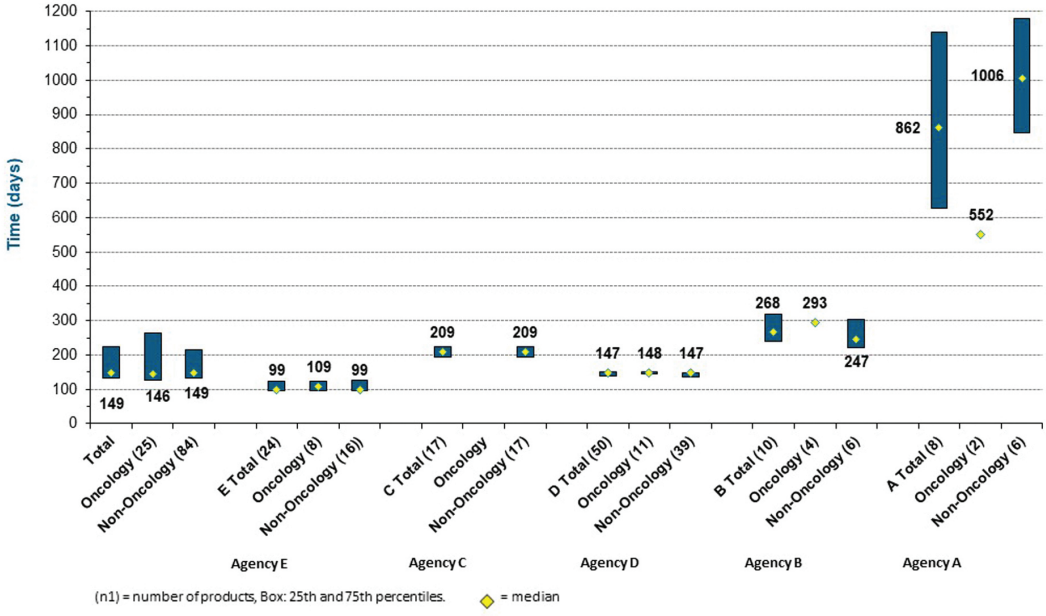


Figure 6. Time between "Submission to HTA Agency" and "Final recommendation by HTA Agency", analyzed by oncology vs non-oncology and by HTA agency.

products respectively. Three agencies (agency E, D and B) had consistent median times across oncology and non-oncology products, varying from 109 to 293 days for oncology products and from 99 to 247 days for non-oncology products. One out of five analysed agencies did not evaluate oncology products within the time period of data collection. Importantly, for one agency, timelines were much longer compared with the other four agencies, with median time for all products being 862 days and there was considerable difference in the median time for oncology vs. non-oncology products (552 and 1006 days respectively).

In Figure 7, the timelines between HTA submission and HTA recommendation are illustrated according to HTA outcome (positive, positive with restrictions and negative) and by therapeutic area (oncology vs non-oncology). The median time for positive HTA outcome varied from 109 days for oncology products and 146 days for non-oncology products (however only four oncology products from two agencies and 17 non-oncology products from four agencies have positive HTA outcome). Median time for a positive with restrictions HTA outcome varied from 148 to 171 days for oncology and non-oncology products respectively (only four products from three agencies are included in oncology group and 34 from all five agencies in non-oncology group). As for negative HTA outcomes, the median time for both oncology and non-oncology products are almost the same (148 and 149 days respectively; 17 oncology products from three agencies and 33 non-oncology products from four agencies are included).

Figure 8 presents timelines for each agency by HTA outcome. Even for the agency with shortest timelines (99 days for all products) the median time for negative HTA outcome was considerably longer (123 days) compared with positive and positive with restrictions HTA outcomes (which was almost the same at 95 and 96 days respectively). For two agencies (agency C and D) the median times were very consistent across different HTA outcomes (however, there were no positive HTA outcomes included in this study for agency C). For the two remaining agencies (agency B and A) there were considerable differences in the median time across different HTA outcomes (208, 260 and 315 days respectively for positive, positive with restrictions and negative HTA outcomes for agency B and 767 and 975 days for positive and negative HTA outcomes respectively in case of agency A).

DISCUSSION

This study presents a methodology to benchmark HTA agencies and considers its potential for future use. We showed that by mapping HTA processes, identifying common milestones and the scope of required information required at submission, HTA agencies can be compared and timelines measured.

Healthcare systems and HTA processes differ substantially across jurisdictions. (12) However, there are no substantial differences in the HTA methodology applied by

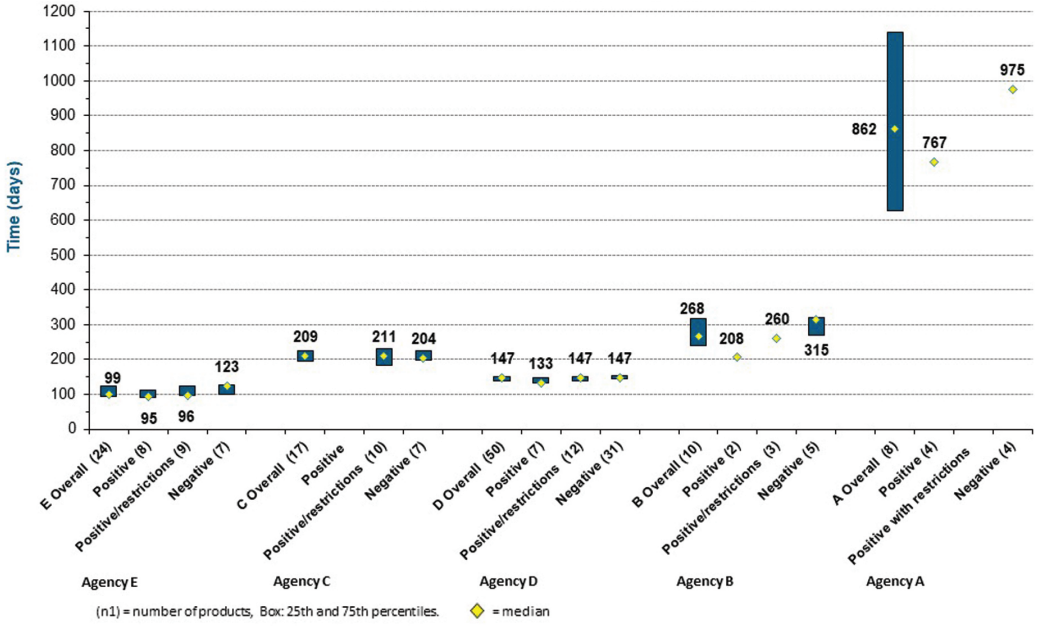


Figure 8. Time between "Submission to HTA Agency" and "Final recommendation by HTA Agency", analyzed by HTA outcome and by agency.

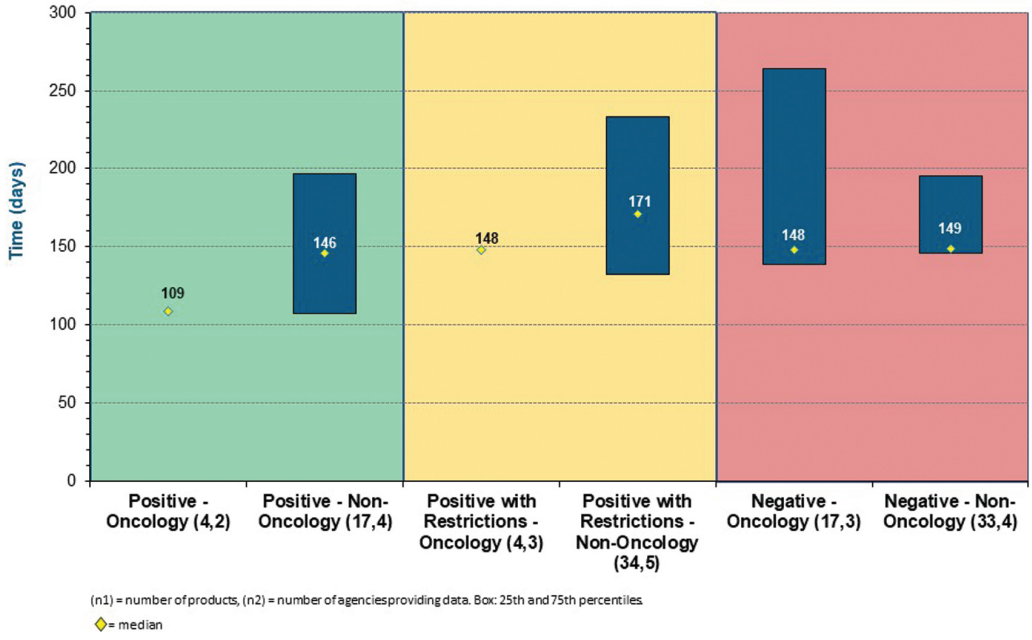


Figure 7. Time between "Submission to HTA Agency" and "Final recommendation by HTA Agency", analyzed by outcome and therapeutic area (oncology vs non-oncology).

these jurisdictions (13). Considering this wide variety of healthcare systems and HTA processes and outcomes we propose that HTA processes can be mapped and common milestones identified and agreed upon and thus understood and compared across HTA agencies. In fact, HTA agencies are currently being compared by external groups (7, 8); however, these analyses are often criticised by HTA agencies due to the lack of comparable bases. The methodology developed for this study could be used to provide comparative analysis across agencies to external stakeholders as well as within and across HTA agencies for their self-improvement.

Study limitations

This study has some limitations that are worth noting. First, the number of agencies studied was low, since inclusion was based on data completeness. Another limitation of this study is the use of a trichotomous system of HTA recommendations (positive, positive with restrictions, negative), which is a simplification necessary to allow comparison of HTA recommendations. This system was used in previous publications (chapter 3).

As the study covers international comparison the use of the English language for the questionnaire was considered to be the most universal. Considerable effort was dedicated to the precise and unambiguous formulation of questions for the study in consideration of the participation of those for whom English was not a native language. This issue, which may require additional study, was also raised by Drummond and colleagues in their research.(3).

The lack of assessment of the quality of industry submissions is another limitation of this study. Benchmarking is commonly associated with measuring quantitative metrics such as time, process, resource and cost, but it is also possible to use qualitative measures in a systematic fashion to assess more difficult-to-measure parameters such as quality. However, whilst we consider that quality is an extremely important parameter, as the quality of an industry submission to an HTA agency can substantially impact timeliness of the HTA processes, it was considered to be outside of the scope of this research.

Has an international standard or HTA best practice already been set and implemented?

There have been an impressive number of internationally recognised initiatives to develop standards for best practise in HTA as well as HTA practical tools. Best practise in undertaking and reporting HTA has already been proposed by research groups in Europe over the recent decades (14). Also some steps have been taken to establish internationally recognised good practices in HTA (15). Consensus seems to have been reached around the practical tools and methods in the field of HTA in Europe (16) including the HTA Core Model, composed of nine domains, which was developed within the European Network for HTA (EUnetHTA) after broad consultation and

agreement among stakeholders(17). In addition, standardised reporting has been achieved for rapid relative effectiveness assessments (REAs) of new pharmaceuticals to be used for European collaboration (13, 18, 19) and as previously mentioned, key principles for the improved conduct of HTA for resource-allocated decisions was developed by Drummond and associates (2).

The implementation

The implementation of HTA best practice into real healthcare system settings and thus the objective and reliable comparison of HTA agencies' outcomes and performance has yet to be resolved. Such comparisons are of great value for both internal and external stakeholders: public opinion could be informed and agencies could self-improve through the objective measure of their performance. In addition, results from a regulatory agency benchmarking study can be used to provide an evidence base to request resources from health authorities and agencies could improve processes by learning from other agencies more effective and efficient ways to undertake the review (11, 20).

Common milestones for HTA review process

Our study shows that HTA agencies can agree on common milestones for the HTA review processes. The process maps and our study conclusions can be taken further to support the design of procedures in newly established HTA agencies and the improvement of processes in existing HTA agencies. Henshall indicated that the description and in-depth understanding of decision-making systems is an underestimated aspect of the approach taken by Drummond and associates. (21). Others suggested great consideration should be given to the context and stakeholders (22). We emphasise in our study that in order to compare HTA agencies and measure and interpret timelines, an in-depth understanding across agencies of HTA processes and the numerous factors behind those processes is needed.

Timelines of HTA processes

Timelines of HTA processes are measurable but are not a measure themselves and should be always interpreted with a full understanding of the HTA processes. In their key principles on HTA Drummond and associates indicate that "HTA should be timely" which is considered to be the agreed principle within broader subgroup of key principles regarding the use of HTA in decision making (2). This key principle is followed by three more precise audit questions regarding timely manner: (a) Does the HTA organisation have a defined time period for conducting HTAs/producing recommendations? (b) Does the HTA organisation adhere to the agreed timelines? (c) Does the organisation have a mechanism to update its HTAs/recommendations within a given time period? (3). We argue that time is one indicator that can be

measured precisely based on the data provided by HTA agencies with common milestones identified. For this purpose, a subset of questions refers to detailed timelines in our study questionnaire (Supplementary Material).

There is a general trade-off between the robustness of HTA process and timeliness. For example, the stakeholder involvement in the development of recommendations by the National Institute of Health and Care Excellence (NICE) is thorough but typically very resource and time consuming.

Our study shows considerable differences among the median timelines from assessment, via appraisal phase up to final HTA recommendation for the five agencies included in this analysis. Obviously, the resources available for HTA-related activities impact timelines: in the group of agencies analysed in our study only one agency has more than 75% of its resources dedicated to HTA activities and this agency has the shortest median timelines. This was the only agency in the study where HTA processes constitute the core activities of the organisation, while for the remaining four agencies, HTA activities are only part of broader scope of the organisations' activities. This is particularly true for two of the agencies for which the percentage of FTEs dedicated to HTA activities is less than 25% and where the median timelines of the whole HTA process are the longest.

There are several factors that can impact timelines. First, long median timelines could be explained by the HTA processes in place in agencies; for example extensive stakeholder involvement (including patients, clinicians and pharmaceutical companies) in the processes, public consultation of draft documents or the appeal procedure available in case of negative HTA outcome. In addition, the frequency of appraisal committee meetings can also affect timelines, especially during the appraisal phase. In some organisations committees meet several times per month and in some, several times per year. Third, delays can also be caused by pharmaceutical company strategy; for example, if a particular market is not a priority for a company, providing additional evidence or clarifications to an HTA agency could take longer. Finally, it could be speculated that the processes may be deliberately prolonged due to financial issues such as healthcare system sustainability, especially in the case of very expensive drugs in countries with limited resources. This clearly impacts patients' access to new and expensive drugs but also supports financial stability in healthcare and delays assessments that could later be based on decisions already made by other jurisdictions.

Timelines by HTA outcome

Our study shows that median time of HTA processes (from HTA submission to HTA recommendation) is the shortest for oncology products with positive HTA outcome while the median time is the longest for non-oncology products with restricted HTA outcome. However, the median time for oncology products across different HTA outcomes median time is the shortest for positive HTA outcomes, considerably longer for HTA restrictions and exactly the same for negative HTA outcome. For non-oncology

products the differences across various HTA outcomes are not as substantial, which could potentially be explained by public health priorities in given jurisdictions with regards to oncology.

Our study shows that median times of HTA processes analysed by HTA outcomes are consistent for three agencies and differ considerably for the remaining two agencies, the shortest being for products with positive HTA outcomes and the longest for products with negative HTA outcomes. These results might indicate that the timelines for three jurisdictions were consistent because of consistent processes regardless of the outcomes, whilst timelines for negative outcomes for two of the agencies were potentially longer because of stakeholder involvement and public consultation of draft documents. Although longer HTA timelines can delay patients' access to medicines, it is worth noting that time can be also spent on stakeholders' involvement, depending on the various HTA processes in place, pharmaceutical company input such as additional evidence submission, comments and communication and patient group and clinicians involvement.

Previous research on developing a systematic framework for describing and comparing different features of HTA agencies (23) found considerably more differences than similarities across HTA agencies and countries. Based on our study results we conclude that irrespective of differences existing between HTA agencies and jurisdictions, HTA processes can be compared based on agreed common milestones.

CONCLUSIONS

Our study shows that it is feasible to find consensus among HTA agencies regarding the common milestones of the HTA review process in order to map jurisdiction-specific processes against agreed generic processes, along with the detailed characteristics of each agency that enables results to be interpreted in the right context. Such benchmarking studies should be performed systematically and be based on the data provided directly by HTA agencies; however, data on common milestones should be available in the public domain to make HTA processes more transparent.

HTA agency benchmarking across jurisdictions has promising potential; however, timelines can't be used as a single measure to compare or measure performance of HTA agencies but only with in-depth understanding of jurisdiction specific HTA processes.

REFERENCES

1. Sorenson C, Drummond M, Kanavos P. Ensuring value for money in health care. The role of health technology assessment in European Union. . Copenhagen2008.
2. Drummond M. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care. 2008;24:3:244-58.
3. Drummond M, Neumann P, Jonsson B, Luce B, Schwartz JS, Siebert U, et al. Can we reliably benchmark health technology assessment organisations? Int J Technol Assess Health Care. 2012;28(2):159-65.
4. Commission; E, SANCO D. Strengthening of the EU cooperation on Health Technology Assessment (HTA). 2016.
5. Schelleman H, Dupree R, Kristensen FB, Goettsch W. Why we should have more collaboration on HTA in Europe: the example of sofosbuvir. Journal of Pharmaceutical Policy and Practice. 2015;8(1):O13.
6. Kristensen FB, Gerhardus A. Health technology assessments: what do differing conclusions tell us? BMJ. 2010;341:c5236.
7. Wilsdon; T, Serota A, for Charles River Associates conctracted by EFPIA P, Medicines Australia and EuropaBio A comparative analysis of the role and impact of Health Technology Assessment. 2011 May 2011.
8. Wilsdon; T, Fiz; E, Haderi; A, EFPIA rbCRAfPa. A comparative analysis of the role and impact of Health Technology Assessment: 2013 Final report CRA Project No. D19197-00. 2014.
9. Neumann PJ, Drummond MF, Jonsson B, Luce BR, Schwartz JS, Siebert U, et al. Are Key Principles for improved health technology assessment supported and used by health technology assessment organisations? Int J Technol Assess Health Care. 2010;26(1):71-8.
10. Allen N, Pichler F, Wang T, Patel S, Salek S. Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. Health Policy. 2013;113(3):305-12.
11. Hirako M, McAuslane N, Salek S, Anderson C, Walker S. A Comparison of the Drug Review Process at Five International Regulatory Agencies. Drug Inf J. 2007;41(3):291-308.
12. Oortwijn W, Broos P, Vondeling H, Banta D, Todorova L. Mapping of health technology assessment in selected countries. Int J Technol Assess Health Care. 2013;29(4):424-34.
13. Kleijnen S, George E, Goulden S, d'Andon A, Vitre P, Osinska B, et al. Relative effectiveness assessment of pharmaceuticals: similarities and differences in 29 jurisdictions. Value Health. 2012;15(6):954-60.
14. Velasco M, Perleth M, Drummond M, Gurtner F, Jorgensen T, Jovell A, et al. Best practice in undertaking and reporting health technology assessments. Working group 4 report. Int J Technol Assess Health Care. 2002;18(2):361-422.
15. Goodman C. Toward international good practices in health technology assessment. Int J Technol Assess Health Care. 2012;28(2):169-70.
16. Kristensen FB, Lampe K, Chase DL, Lee-Robin SH, Wild C, Moharra M, et al. Practical tools and methods for health technology assessment in Europe: structures, methodologies, and tools developed by the European Network for Health Technology Assessment, EUnetHTA. Int J Technol Assess Health Care. 2009;25 Suppl 2:1-8.
17. Lampe K, Mäkelä M, Garrido MV, Anttila H, Autti-Rämö I, Hicks NJ, et al. The HTA Core Model: A novel method for producing and reporting health technology assessments. Int J Technol Assess Health Care. 2009;25(S2):9-20.
18. Kleijnen S, Pasternack I, Van de Casteele M, Rossi B, Cangini A, Di Bidino R, et al. Standardized reporting for rapid relative effectiveness assessments of pharmaceuticals. Int J Technol Assess Health Care. 2014;30(5):488-96.
19. Kleijnen S, Toenders W, de Groot F, Huic M, George E, Wieseler B, et al. European collaboration on relative effectiveness assessments: What is needed to be successful? Health Policy. 2015(0).

20. McAuslane N, Leong J, Liberti L, Walker S. The Benefit-Risk Assessment of Medicines. Therapeutic Innovation & Regulatory Science. 2017:216847901769626.
21. Henshall C. Describe decision-making systems, assess health technology assessment reports. Int J Technol Assess Health Care. 2012;28(2):168.
22. Sampietro-Colom L. Consider context and stakeholders. Int J Technol Assess Health Care. 2012;28(2):166-7.
23. Schwarzer R, Siebert U. Methods, procedures, and contextual characteristics of health technology assessment and health policy decision making: comparison of health technology assessment agencies in Germany, United Kingdom, France, and Sweden. Int J Technol Assess Health Care. 2009;25(3):305-14.

SUPPLEMENTARY MATERIALS

Supplementary Material Questionnaire for HTA agencies benchmarking study

The draft questionnaire was developed by the Centre for Innovation in Regulatory Science (CIRS) through consultation with HTA agencies (via email exchange and at face-to-face meetings). The final version of the questionnaire was developed by CIRS in cooperation with HTA agencies.

The questionnaire is composed of two main parts: the first part containing general information on the HTA organisation and the second part containing information on individual products assessed and appraised by the HTA agency.

The general information portion consisted of five main domains (Scope and remit, Resource and budget, Appraisal/scientific committee, Transparency and Review procedures and processes), containing 51 questions.

The individual product portion of the questionnaire consisted of four main domains (Review timelines, Assessment/appraisal process, Outcome and Scientific advice) containing in total 35 questions (and additionally space for comments was provided).

The questionnaire was designed in Excel and distributed to HTA agencies. For each of the questions, agencies used drop down (pre-defined) lists or provided relevant answers in the answer field as specified. For information on individual products, single worksheets were automatically generated for each individual product when the HTA agency declared how many products for which they wanted to provide data. The structure and details of the questionnaire are presented below.

Part I: General information on HTA organisations

AGENCY INFORMATION	Question
Agency identifier	1. Please indicate the full name of the agency (free text prefilled)
	2. Please indicate jurisdiction (free text prefilled)
Scope and remit	3. Please indicate the remit of the agency
	a. Drug technologies (yes/no)
	b. New Active Substances only (yes/no)
	c. Non-drug technologies (yes/no)
	d. Surgical interventions (yes/no)
	e. Health prevention programmes (yes/no)
	f. Medical devices (yes/no)
	g. Dental procedures (yes/no)
	h. Others (please specify)

Part I: (continued)

AGENCY INFORMATION	Question
	4. Indicate the main activities that are covered by the agency a. Health policy (yes/no) b. Marketing authorisation/product licence (yes/no) c. Health Technology Assessment - original reports (yes/no) d. Health Technology Assessment - review submissions from the industry (yes/no) e. Health Technology Assessment-original reports AND submissions from industry (yes/no) f. Patient information (yes/no) g. Product safety (yes/no) h. Pricing (yes/no) i. Clinical trials advice (yes/no) j. Other, please specify (free text)
Type of agency	5. Indicate which of the following best describes this agency (yes/no) a. Independent from government b. Operates within administrative structure of the government
	6. Date of establishment of the current agency (free text date) a. Date of establishment of single-technology review (free text date) i.e. Common Drug Review
Size of agency	7. Please provide information on internal staff numbers a. Total staff in the agency full-time employees (FTEs) (free text numbers) b. Number of full-time employees (FTEs) assigned to HTA activities (free text numbers)
	8. Please provide information on agency assessors conducting specialised reviews a. Number of reviewers (FTEs) for industry submissions for New Active Substances (NASS) (free text numbers) b. Number of reviewers (FTEs) for industry submissions for Major Line Extensions (MLEs) (free text numbers) c. Number of reviewers (FTEs) for industry submissions for New Active Substances (NASs) AND Major Line Extensions (MLEs) in total (free text numbers) d. Number of reviewers (FTEs) for industry submissions for Devices (free text numbers) e. Number of reviewers (FTEs) for Industry submissions for other health technologies (free text numbers)

Part I: (continued)

AGENCY INFORMATION	Question
	9. Please indicate the professional background and numbers of the agency staff assigned to the review and assessment of industry submissions

Question 9 table	Number Employed as assessors (Degree/Expertise)			
	Total	With PhD or PharmD	With MS	Other
Physicians				
Physicians with additional education/expertise in health economics				
Physicians with additional education/expertise in project management				
Statisticians				
Pharmacists				
Pharmacists with additional education/expertise in health economics				
Pharmacists with additional education/expertise in project management				
Health Economists				
Other scientists				
Project Managers				
Administrative staff				
Others				

a. Please indicate the number of the administrative agency staff assigned to the review and assessment of industry submissions (as equivalent of FTEs)?

External resources

10. Does the agency outsource any HTA-related activities (yes/no)

If YES please indicate to what external organisations:

a. Universities/academic centres/academic groups (yes/no)
b. Consultancy companies/consultancy groups (yes/no)
c. Governmental agencies (yes/no)
d. Individual independent contractors (yes/no)
e. Hospitals/health service providers (yes/no)
f. Others (please specify)

Part I: (continued)

AGENCY INFORMATION	Question
	11. What types of HTA-related activities are outsourced? a. Full HTA reports (yes/no) b. Rapid HTA reports (yes/no) c. Critical review of manufacturer's submissions (yes/no) d. Educational activities related to HTA (yes/no) e. Others (yes/no)
	12. If YES please specify what % of HTA-related activities budget is are designated for outsourced work (free text %)
Agency's budget	13. Please indicate whether the following data are in the public domain (yes/no) a. agency total budget (yes/no) b. agency total budget allocated to HTA activities (yes/no)
	14. Please indicate agency total budget (local currency; free text numbers)
	15. Please indicate agency total budget allocated to HTA activities (local currency; free text numbers)
Fee structure (year 2013)	16. Are fees charged to sponsors for the review and assessment of applications for drugs (yes/no) If YES please provide the following information: a. Fee for review and assessment of NAS (local currency; free text numbers) b. Fee for review and assessment of generics (local currency; free text numbers) c. Fee for review and assessment of major line extension (local currency; free text numbers) d. Fee for review and assessment of other technologies please specify (local currency; free text numbers)
	17. Does the agency charge a fee for scientific advice? (yes/no) If YES please provide the following information: a. Fee for scientific advice in local currency (free text numbers)
	18. Please provide the following information in relation to the way the agency is funded a. Funded entirely by the statutory health insurance (yes/no) b. Self funded entirely from fees (yes/no) c. Other please specify (free text) d. Partially funded from different sources (please give proportions of total budget below): i) % statutory health insurance (free text %) ii) Fees (free text %) iii) Other - please specify (free text %)

Part I: (continued)

AGENCY INFORMATION	Question
Committee procedure	19. If the appraisal procedure includes obtaining the information from Appraisal/Scientific Committee of internal and/or external experts please complete the following a. Name of the Committee (free text) b. Number of Committee Members (free text numbers) c. Name of additional Committees if applicable (free text) d. Number of additional Committee Members (free text numbers) 20. Who nominates the members? a. Ministry of Health (yes/no) b. Chair of the HTA organisation (yes/no) c. Other (please specify) 21. Briefly outline the committee members selection process (free text) 22. Committee Members' professional discipline (free text)

Question 22 table	Committee Members' professional discipline (Degree/Expertise)			
	Total	With PhD or PharmD	With MS	Other
Physicians				
Statisticians				
Pharmacists				
Health Economists				
Other scientists				
Project Managers				
Lay representatives / public members				
Others				

23. Committee Members' years of experience/years in the Committee (numerical value)

Committee Members' years of experience/years in the Committee (Degree/Expertise)

Years of experience in the Committee

Less than 1 year

Between 1-2 years

Between 3-5 years

Between 6-10 years

Over 11 years

Total number of members in the Committee

Part I: (continued)

AGENCY INFORMATION	Question
	24. How frequently does the Committee meet? (multiple choice) a. Once per week b. Once per month c. Other (please specify)
	25. Are the Committee meetings open to the following groups: a. Public (yes/no) b. Industry (yes/no) c. Patient groups (yes/no) d. Media (yes/no) e. Other (please specify)
	26. For NAS and major line extensions (MLE) applications does the Committee review a. Once per week b. Once per month c. Other (please specify)
	27. Is there defined voting procedure for the Committee? (yes/no)
	28. Does the Committee review: a. The complete dossier (yes/no) b. Assessment reports from the reviewers (yes/no) c. The complete dossier AND assessment reports from the reviewers (yes/no) d. Other documents (please specify)
Transparency	29. What priority does your agency assign to being open and transparent in relationships with the public, professions and industry? (yes/no) a. High priority b. Medium priority c. Low priority d. Please comment (free text)
	30. What are the main drivers for establishing transparency? Please indicate the top three incentives for assigning resources to activities that enhance the openness of the HTA system (yes/no) a. Political will b. Press and media attention c. Public attention d. Industry attention e. Patients/Patient Interest Group concerns f. Need to increase confidence in the system g. Other (please specify)

Part I: (continued)

AGENCY INFORMATION	Question
	31. Please indicate which of the following information items about the assessment and appraisal processes are available to the public (yes/no) a. Assessment and appraisal times b. Review documents c. Appraisal documents d. Executive summary documents e. HTA recommendation documents f. Conflict of interest disclosure documents of the Committee members g. Conflict of interest disclosure documents of HTA Agency management h. Conflict of interest disclosure documents of HTA Agency staff i. The Committee meeting dates j. Standard operational procedures (SOPs) followed for assessments/appraisals k. HTA guidelines l. The list of technologies being assessed and reviewed
	32. If the agency publishes the list of technologies being assessed and reviewed, how often is it updated? (yes/no) a. Daily b. Weekly c. Monthly d. Quarterly e. Once a year f. Less than once a year g. When key milestones are reached
	33. Is the agency website available in English? (yes/no option)
	34. If NO - which local language(s) is the agency website available? (free text)
	35. Are companies able to follow the progress of their own applications? (yes/no)
Transparency	36. If YES please indicate the mechanisms available to industry (yes/no) a. Electronic access to the status of application b. E-mail contact c. Telephone contact d. Meetings e. Other, please specify

Part I: (continued)

AGENCY INFORMATION	Question
	37. Is there an electronic system for tracking applications? (yes/no)
	38. If YES please indicate whether it has the following activities
	a. Tracing applications that are under review and identifying the stage in the process (yes/no)
	b. Signalling that target review dates have been exceeded (yes/no)
	c. Recording the terms of the HTA recommendation once issued (yes/no)
	d. Archiving information on applications in a way that can be searched (yes/no)
	39. Is such system currently being developed (yes/no)?
	40. If your answer to 37d is NO - are there plans to introduce such a system? (yes/no option)
	a. If so, please give target date for implementation (free text date)
Procedures and processes	41. Are there HTA guidelines available in the Agency?(yes/no)
	42. Are there standard operational procedures available in the Agency? (yes/no)
	43. Are there defined assessment and appraisal processes? (yes/no)
	44. Is there any patient advocacy group engaged in the review process? (yes/no)
	45. How are patients engaged in the review process? (yes/no)
	a. Not engaged
	b. Able to write submissions like any other stakeholder
	c. Defined patient representative group
	d. Participating in the decision making process (eg. seats on the board)
	46. Are there criteria for priority setting? (yes/no)
	47. Is there any topic selection process implemented in your organisation? (yes/no)
	48. Are there explicit criteria for topic selection? (yes/no)
	49. Does the agency give scientific advice to the industry? (yes/no)
	a. If yes, is advice available before submission to regulatory agency (yes/no)
	b. If yes, is advice available before submission to HTA organisation/agency (yes/no)
	c. If yes, is advice available after marketing authorisation (yes/no)
	50. Are there any guidelines implemented concerning scientific advice? (yes/no)
	51. Is scientific advice issued in parallel with the regulatory agency? (yes/no)

Part II: Information on individual products

PRODUCT INFORMATION	Question
Product 1 - please provide product specific information in this section	
Product identifier and characteristics of the product	1. Drug INN (free text) 2. Drug ATC Class (free text) 3. Brand Name (free text) 4. Name of manufacturer (free text) 5. Indication approved by Regulatory Agency 6. Indication in question for HTA process 7. Innovation status (yes/no) a. First in class b. First in treatment c. First in indication d. Follow-on drug
Regulatory approval	8. Regulatory Agency approval date/Marketing Authorisation Approval date (Free text Date) (date that is applicable for jurisdiction in question)
Assessment, appraisal and decision-making phase on individual product	9. Submission date to the HTA Agency (Free text Date) (date that the agency records the submission) 10. Assessments performed in the Agency or used by the Agency (yes/no) a. Clinical analysis b. Economic analysis c. Budget impact analysis d. Subpopulations in label e. Other (please specify) (free text) 11. Patient advocacy or other groups solicited for consultation? (yes/no) 12. Patient advocacy or other group's consultation received? (yes/no) 13. If YES please provide name(s) of group(s) consulted (free text) 14. Date of the end of assessment phase (free text date) 15. Any time for clarification given to the industry during assessment phase? (yes/no) 16. Exact time for clarification given to the industry during assessment phase a. Date the questions were sent to the company (free text – dates) b. Date of the sponsor's response (free text – dates) 17. Procedure implemented to stop the time of the assessment phase if industry is asked for clarification/"stop the clock" procedure? (yes/no)

Part II: (continued)

PRODUCT INFORMATION	Question
	18. Starting date of the appraisal phase (free text date)
	19. Date of the end of the appraisal phase (free text date)
	20. Any time for clarification given to the industry during appraisal phase? (yes/no)
	21. Exact time for clarification given to the industry during appraisal phase
	a. Date the questions were sent to the company (free text – dates)
	b. Date of the sponsor's response (free text – dates)
	22. Procedure implemented to stop the time of the appraisal phase if industry is asked for clarification/"stop the clock" procedure? (yes/no)
	23. Date of final HTA recommendation (free text date)
	24. Types of data used to develop HTA recommendation (yes/no)
	a. Systematic Review on safety/efficacy/effectiveness (yes/no)
	b. Meta-analysis (yes/no)
	c. Randomised Clinical Trials RCTs (yes/no)
	d. Prospective studies (yes/no)
	e. Registries (yes/no)
	f. Clinical guidelines (yes/no)
	g. Input from clinical professionals (yes/no)
	h. Evidence submission from manufacturer (yes/no)
	i. Cost minimasation analysis (yes/no)
	j. Cost effectiveness/utility analysis (yes/no)
	k. Cost benefit analysis (yes/no)
	l. Critique/review of manufacturer's pharmocoeconomic evaluation (yes/no)
	m. Input from patients (yes/no)
	25. Please indicate if the HTA recommendation/conclusion was:
	a. Positive (yes/no)
	b. Positive with restrictions (eg. population, indication) (yes/no)
	c. Negative (yes/no)
	26. Main reasons for approval, including restrictions (free text)
	27. Main reasons for deny (free text)
	28. Date of Minister of Health's/payer's/health insurance institution's final reimbursement/coverage decision if more than one, indicate date of first decision (free text date)

Part II: (continued)

PRODUCT INFORMATION	Question
	29. Please indicate if the MoH's/payer's/health insurance institution's final reimbursement/coverage decision was: a. Positive (yes/no) b. Positive with restrictions (eg. population, indication) (yes/no) c. Negative (yes/no)
	30. Was this drug subject to special or priority review (e.g. orphan drug, oncological drug)? (yes/no) a. If YES please provide details (free text)
	31. Has scientific advice been given on this particular product? (yes/no)
	32. If so please indicate the date of the scientific advice (free text date)
	33. If so has scientific advice been followed by the sponsor? (yes/no) a. Fully b. Partially c. Not at all
	34. Have there been any additional consultations required for this particular product? (yes/no) a. If YES – please specify (free text)
	35. Has any pre-submission advice been given on this particular product? (yes/no) a. If YES – please specify (free text)
Comments	Comments relating to this Product

part B

HTA RECOMMENDATIONS – FOCUS ON ONCOLOGY

chapter 4

DOES CONDITIONAL APPROVAL FOR NEW ONCOLOGY DRUGS IN EUROPE LEAD TO DIFFERENCES IN HEALTH TECHNOLOGY ASSESSMENT DECISIONS?

Iga Lipska
Jarno Hoekman
Neil McAuslane
Hubert G.M. Leufkens
Anke M. Hövels

Published: Clin Pharmacol Ther. 2015 Nov;98(5):489-91

INTRODUCTION

An early access pathway of conditional approval for potentially beneficial medicines is available within the European regulatory framework. However marketing authorization does not necessarily result in recommendations for public funding by health technology assessment agencies (HTA). As conditional approval goes along with less than complete data on benefits and risks of a treatment option for a high medical need, this raises the question how HTA decision making is affected by these uncertainties.

The Conditional Marketing Authorization (CMA) procedure was implemented in the European regulatory system in 2006 for certain categories of medicinal products with the potential to address unmet medical needs in seriously debilitating, life-threatening or rare diseases including cancer. CMA can be granted on the basis of less than complete clinical data than is required for Standard Marketing Authorization (SMA), with the condition that sponsors meet specific study obligations in the post-approval phase.

Previous research suggests that currently CMA is used by the European regulator and industry at the end rather than the beginning of the marketing authorization (MA) process, and is not necessarily resulting in earlier access (1). Moreover, one concern by industry which may contribute to not requesting CMA upfront is a perception that CMA decreases the likelihood of reimbursement.

The question as to whether CMA has an impact on recommendations for reimbursement by national HTA bodies could be considered from the perspective of two scenarios: firstly, use of the CMA pathway results in a higher proportion of positive regulatory HTA recommendations because of high unmet medical need. Secondly, use of the CMA pathway results in a lower proportion of positive recommendations due to the less than complete data and the precautionary reluctance to pay for uncertainty. This is explicitly an HTA dilemma, as generally the requirements for reimbursement or funding otherwise are not the same as those for MA decision making due to the emphasis that HTA bodies place on features as therapeutic benefit, relative effectiveness, cost-effectiveness, and in some systems also, budget impact (2).

In order to substantiate this question we compared HTA recommendations of six national HTA agencies in Europe for oncology medicinal products approved in the period 2007-2012 (N=25), stratified for standard (SMA, i.e. N=17) or conditional marketing authorization (CMA, i.e. N=8). Selection of six European jurisdictions was done taking into account geographical distribution in EU, availability of information on HTA recommendations in public domain and a defined official role of HTA recommendations in decision making process on drug reimbursement. All anticancer drugs with initial oncology indication approved by EMA between 1st of January 2007 and 31st December 2012 with both CMA and SMA were included in this study. Therefore the results are likely to be representative for CMA approvals post 2012. For more details about methods and data see Supplementary Materials (Annex 1).

RESULTS

In Figure 1 the outcomes of HTA decision making for the 25 oncology products, i.e. 8 CMA compared to 17 SMA, by the 6 European HTA bodies are summarized. We observed overall little to no differences between recommendations of HTA bodies by pathway. Only minor differences were observed within each individual jurisdiction or when aggregating all recommendations over 6 HTA bodies. None of these differences were statistically significant. Thus, HTA bodies that came to more positive decisions on products approved through a SMA pathway, did the same on CMA products. This was also the case for negative decision making or proportions of products where HTA review was still pending. Our initial hypotheses of expected differences, i.e. the two scenarios of relative more positive HTA decisions due to the recognized high medical need, or relative more negative HTA decisions due to the high level of uncertainties in the data, are not supported by this analysis.

DISCUSSION

Bringing promising oncology products to patients requires careful weighing of available data to justify appropriate decision making on marketing authorization, and consequently, access in terms of reimbursement or other forms of funding. These are multifaceted decisions and regulatory CMA schemes have been developed to increase the uptake of these products in clinical practice under certain, strictly defined, conditions. The study results suggest that use of these schemes for oncology products does not affect the likelihood that a product is recommended for reimbursement. This suggest that HTA bodies balance data completeness and medical needs in such a way that the prospect of a possible clinical benefit for high unmet medical need ameliorates some of the concerns over the availability of less than complete data. However, there seem to be some apparent similarities in the way regulatory and the individual HTA bodies weigh the data, their limitations and uncertainties, giving the prospect of a possible clinical benefit for high unmet medical need.

We observed differences in outcomes between the individual HTA bodies which are most likely linked to institutional differences in national legal requirements, HTA criteria used and systems of weighing benefits and risks of new oncology products. This suggests that the individual HTA bodies have their own institutional dynamics and logics that to a certain degree operate independently from the products they review.

Other factors also influence HTA recommendations (e.g. initial MA indication, evidence availability at time of decision, therapeutic area, other interventions, HTA guidelines). However in this research we only investigated the impact of conditional and standard MA on HTA recommendations which could be considered a limitation of the study. As the results showed similarity of outcome irrespective of pathway, this could suggest that these factors potentially influence both groups equally. However

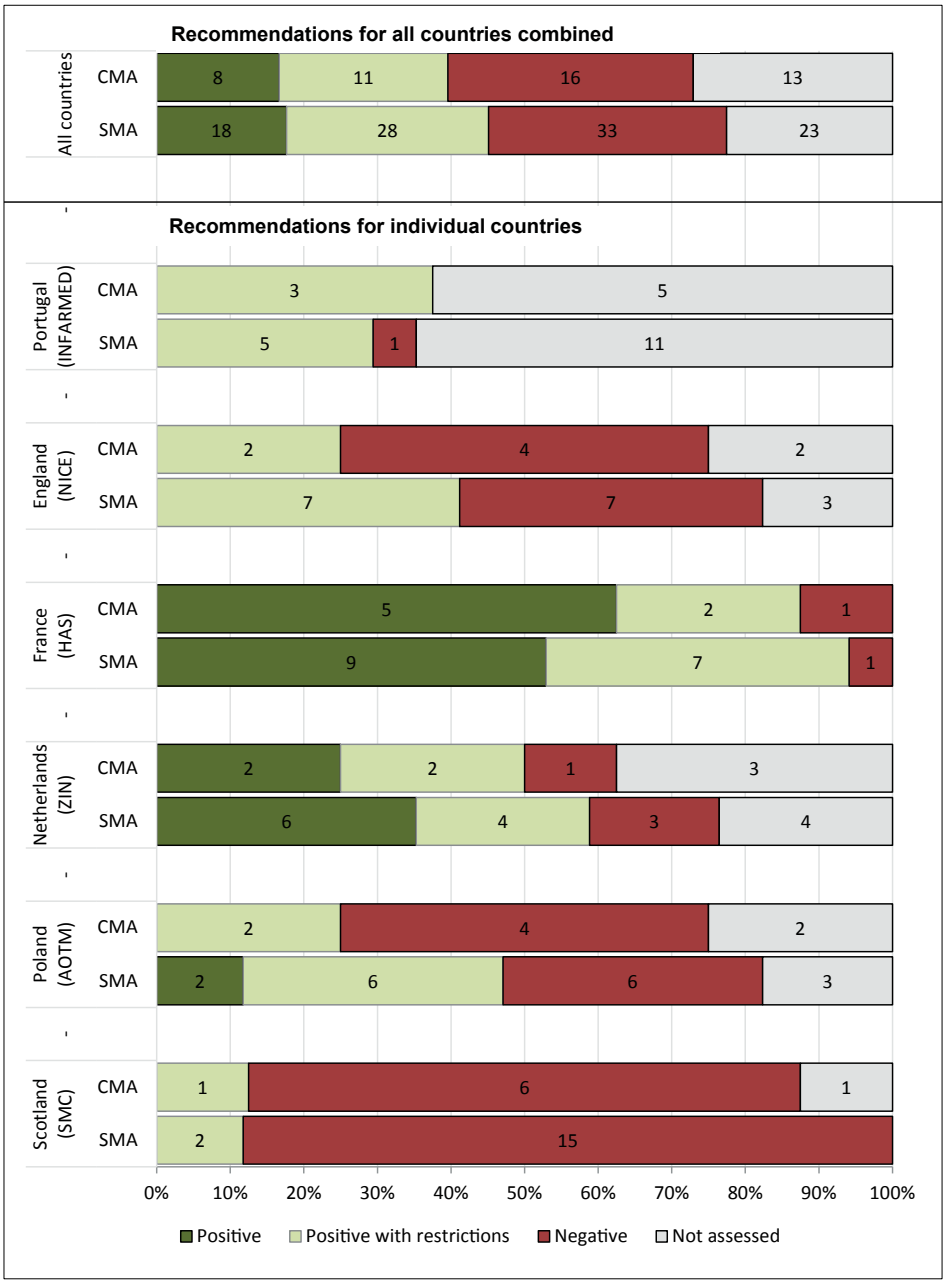


Figure 1. Health technology assessment outcomes for conditional marketing authorization versus standard marketing authorization for all jurisdictions included in the study (total and per jurisdiction).

additional research on other factors influencing HTA recommendations needs to be considered.

Given that we did not find an association between regulatory approval status and HTA decisions there seems to be a need for more effective alignment between regulatory and HTA bodies as recognized by many authors and research groups (3). Such alignment may become a critical feature throughout the whole product lifecycle of a medicine.

More cooperation between regulatory and HTA bodies is particularly needed to ensure that there is alignment on which medicines can be considered to fulfill high unmet medical need and that the clinical evidence requirements for CMA as requested in post-marketing obligations will be sufficient for both regulatory approval and HTA recommendation. In fact, to create common understanding of unmet medical need, early dialogue and scientific advice is needed with participation from all stakeholders including regulators, HTA bodies, patients and industry. Based on such understanding more informative choices can be made regarding the route of regulatory review at the beginning of the development process.

Another key aspect in regulatory-HTA interactions is the need for both parties to agree on the necessary post-marketing commitments by the sponsor to provide comprehensive post-approval data to confirm the original positive benefit-risk balance. This collaboration is especially important to ensure that the studies required as condition for CMA can also be conducted if reimbursement is needed or used for other additional requirements for data by HTA bodies, (i.e. relative effectiveness assessment). Therefore, input from HTA bodies in designing such CMA studies would be a welcome addition.

There are numerous initiatives to align regulatory and HTA activities better of which the most influential in Europe is the collaboration between EMA and EUnetHTA. The latter was established to create an effective and sustainable network of HTA organizations across Europe and consists of government appointed HTA organizations from Europe. Due to joint effort of the network partners some major methodological developments have been proposed in the field of HTA. EUnetHTA and EMA meet biannually, and have provided parallel scientific advice to medicines developers on multiple occasions. The model could become a key success factor in providing early patient access to drugs while ensuring that post-marketing obligations are defined in such a way as to also satisfy criteria for reimbursement.

The already initiated continuous cooperation between EMA and EUnetHTA provide some initiatives in this direction resulting among others in the improvement of European Public Assessment Reports published by EMA to meet HTA bodies' needs (4).

In its recently published new draft guidelines on scientific application and practical arrangements on CMA EMA advices the applicant to consider requesting parallel scientific advice from HTA bodies prior to submission of CMA application (5).

Novel performance based coverage schemes have been proposed and are currently under consideration internationally although not widely used. Potentially these models could recognise also the evolving nature of data availability over time which could result in adaptive coverage decisions.

In conclusion, we found similar variability in HTA decision making between conditional and standard approved oncology products through the Centralized European regulatory system. The higher level of less than complete data in conditional approved oncology products did essentially not result in large differences in the way the HTA bodies included in this study treat such dossiers. Nevertheless, improved alignment between regulatory and HTA authorities remains important.

CONFLICT OF INTEREST DISCLOSURE

The authors declare that there are no conflicts of interest associated with this manuscript.

AUTHOR CONTRIBUTIONS

IL: wrote manuscript, designed research, performed research, analyzed data
JH: designed research, analyzed data, wrote manuscript
NM: wrote manuscript
HGML: wrote manuscript
AH: performed research, wrote manuscript

REFERENCES

1. Hoekman J, Boon WPC, Bouvy JC, Ebbers H, De Jong JP, De Bruin ML. Use of the conditional marketing authorisation for oncology drugs in Europe. Clin Pharm Ther, in press, doi:10.1002/cpt.174.
2. Garrido MV, Kristensen FB, Palmhoj Nielsen C, Busse R. Health Technology Assessment and Health Policy-Making in Europe. Current status, challenges and potential. World Health Organization, European Observatory on Health Systems and Policies, Copenhagen, 2008.
3. Bergmann, L. et al. Actual developments in European regulatory and health technology assessment of new cancer drugs: what does this mean for oncology in Europe? Ann. Oncol. 25, 303-306 (2014).
4. Berntgen, M., Gourvil, A., Pavlovic, M., Goettsch, W., Eichler, H-G., Kristensen, F.B. Improving the contribution of regulatory assessment reports to Health Technology Assessments—A collaboration between the European Medicines Agency and the European network for Health Technology Assessment. Value Health. 17, 634–641 (2014).
5. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/07/WC500190555.pdf (accessed 30th July 2015)

SUPPLEMENTARY MATERIALS

Annex 1 - Jurisdictions and NASs included in the study

Data were collected on all New Active Substances (NASs) approved by EMA for an initial oncology indication in years 2007-2012. We included NASs with both conditional and standard MA. Other regulatory pathways were excluded from analysis. First recommendations by HTA organizations in six European jurisdictions were included: 1) Agencja Oceny Technologii Medycznych i Taryfikacji, Poland (AOTMiT, former AOTM),2) Haute Autorite de Sante, France (HAS),3) Autoridade National do Medicamento e Products de Saude, Portugal (INFARMED),4) National Institute for Health and Care Excellence, England, UK (NICE), 5) Scottish Medicines Consortium, Scotland, UK (SMC),6) Zorginstituut, The Netherlands (ZIN, former CVZ). All data was collected from publicly available information on the websites of EMA and the six HTA organizations: http://www.ema.europa.eu/ema/; http://www.aotm.gov.pl; http://www.has-sante.fr; http://www.infarmed.pt ; http://www.nice.org.uk/; https://www.scottishmedicines.org.uk ; http://www.zorginstituutnederland.nl.

We included 6 European jurisdictions in our study taking into account geographical distribution in EU, availability of information on HTA recommendations in public domain and the defined official role of HTA recommendations in decision making process on drug reimbursement.

All anticancer drugs with initial oncology indication approved by EMA between 1st of January 2007 and 31st December 2012 with both CMA and SMA were included in this study. The starting date was based on the actual implementation date of European legislation on CMA which in practice took effect from 2007 (as EMA guideline on the scientific application and practical arrangements necessary to implement the European regulation on CMA was published for public consultation in December 2006). The end of that period was decided based on the time interval needed for HTA bodies to develop and publish HTA recommendations for new drugs approved by EMA.

As the data was collected at the end of 2014, a 2 year period was considered a reasonable time interval between the EMA approval and HTA recommendations being issued across all 6 jurisdictions to avoid a high proportion of the drugs still pending HTA outcome.

Common name	ATC code	Active substance	Brand name	EMA number	EMA approval year	EMA approval type*
Abiraterone	L02BX03	Abiraterone acetate	Zytiga	EMEA/ H/C/002321	2011	SMA
Axitinib	L01XE17	Axitinib	Inlyta	EMEA/ H/C/002406	2012	SMA
Azacitidine	L01BC07	Azacitidine	Vidaza	EMEA/ H/C/000978	2008	SMA

Common name	ATC code	Active substance	Brand name	EMA number	EMA approval year	EMA approval type*
Cabazitaxel	L01CD	Cabazitaxel	Jevtana	EMEA/ H/C/002018	2011	SMA
Catumaxomab	L01XC09	Catumaxomab	Removab	EMEA/ H/C/000972	2009	SMA
Decitabine	L01BC08	Decitabine	Dacogen	EMEA/ H/C/002221	2012	SMA
Degarelix	L02BX02	Degarelix	Firmagon	EMEA/ H/C/000986	2009	SMA
Eribulin	L01XX41	Eribulin	Halaven	EMEA/ H/C/002084	2011	SMA
Everolimus	L01XE10	Everolimus	Afinitor	EMEA/ H/C/001038	2009	SMA
Gefitinib	L01XE02	Gefitinib	Iressa	EMEA/ H/C/001016	2009	SMA
Ipilimumab	L01XC11	Ipilimumab	Yervoy	EMEA/ H/C/002213	2011	SMA
Lenalidomide	L04AX04	Lenalidomide	Revlimid	EMEA/ H/C/000717	2007	SMA
Nilotinib	L01XE08	Nilotinib	Tasigna	EMEA/ H/C/000798	2007	SMA
tegafur/ gimeracil / oteracil	L01BC53	Tegafur / gimeracil / oteracil	Teysuno	EMEA/ H/C/001242	2011	SMA
Temsirolimus	L01XE09	Temsirolimus	Torisel	EMEA/ H/C/000799	2007	SMA
Vemurafenib	L01XE15	Vemurafenib	Zelboraf	EMEA/ H/C/002409	2012	SMA
Vinflunine	L01CA05	Vinflunine	Javlor	EMEA/ H/C/000983	2009	SMA
brentuximab vedotin	L01XC12	Brentuximab vedotin	Adcetris	EMEA/ H/C/002455	2012	CMA
Crizotinib	L01XE16	Crizotinib	Xalkori	EMEA/ H/C/002489	2012	CMA
Lapatinib	L01XE07	Lapatinib	Tyverb	EMEA/ H/C/000795	2008	CMA
Ofatumumab	L01XC10	Ofatumumab	Arzerra	EMEA/ H/C/001131	2010	CMA
Panitumumab	L01XC08	Panitumumab	Vectibix	EMEA/ H/C/000741	2007	CMA
Pazopanib	L01XE11	Pazopanib	Votrient	EMEA/ H/C/001141	2010	CMA
Pixantrone	L01DB11	Pixantrone dimaleate	Pixuvri	EMEA/ H/C/002055	2012	CMA
Vandetanib	L01XE	Vandetanib	Caprelsa	EMEA/ H/C/002315	2012	CMA

*SMA = Standard marketing authorization; CMA = conditional marketing authorization.

Annex 2 – Distribution of HTA recommendations in total and per jurisdiction

HTA outcomes for conditional marketing authorization (CMA) vs standard marketing authorization (SMA) by jurisdiction

HTA recommendations	SMC Scotland		AOTMiT Poland		ZIN Netherlands		HAS France		NICE England		INFARMED Portugal	
	CMA	SMA	CMA	SMA	CMA	SMA	CMA	SMA	CMA	SMA	CMA	SMA
Positive	0 (0%)	0 (0%)	0 (0%)	2 (12%)	2 (25%)	6 (35%)	5 (62,5%)	9 (53%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Positive with restrictions	1 (12,5%)	2 (12%)	2 (25%)	6 (35%)	2 (25%)	4 (23,5%)	2 (25%)	7 (41%)	2 (25%)	7 (41%)	3 (37,5%)	5 (29%)
Negative	6 (75%)	15 (88%)	4 (50%)	6 (35%)	1 (12,5%)	3 (18%)	1 (12,5%)	1 (6%)	4 (50%)	7 (41%)	0 (0%)	1 (6%)
Not assessed	1 (12,5%)	0 (0%)	2 (25%)	3 (18%)	3 (37,5%)	4 (23,5%)	0 (0 %)	0 (0%)	2 (25%)	3 (18%)	5 (62,5%)	11 (65%)
Total	8	17	8	17	8	17	8	17	8	17	8	17

chapter 5

RELATIVE EFFECTIVENESS ASSESSMENTS OF ONCOLOGY MEDICINES FOR PRICING AND REIMBURSEMENT DECISIONS IN EUROPEAN COUNTRIES

Sarah Kleijnen
Iga Lipska
Teresa Leonardo Alves
Kim Meijboom
Ahmed Elsada
Volker Vervölgyi
Anne d'Andon
Angela Timoney
Hubert G.M. Leufkens
Anton de Boer
Wim Goettsch

Published: Ann Oncol. 2016 Sep;27(9):1768-75

ABSTRACT

Introduction

There is a debate on the added clinical value of new, expensive, anticancer treatments. Among European decision makers, the relevance of commonly used endpoints in trials, especially overall survival (OS), progression-free survival (PFS) and quality of life (QoL) varies, leading to the available evidence being valued differently.

Objective

To study the extent to which the value of endpoints for cancer medicines is weighted differently among European decision makers.

Materials and methods

We compared guidelines and relative effectiveness assessments (REAs) of medicines for pricing or reimbursement decisions in England, France, Germany, Netherlands, Poland and Scotland. Anticancer medicines that received marketing authorisation in Europe between 2011-2013 with at least four national REAs were evaluated. A total of 79 REAs were included.

Results

The number of REAs included per jurisdiction varied between 7 (The Netherlands) and 18 (Germany). OS data were included in all REAs and were the preferred endpoint by health technology assessment (HTA) agencies, but these data were not always mature or robust. QoL data were included in only 54% of the REAs, with a limited impact on the recommendations. PFS data were included in 70% of the REAs, but the extent to which HTA agencies find PFS relevant varied.

Conclusion

European decision making on relative effectiveness of anticancer medicines is affected by a gap in requested versus provided clinical evidence. OS and QoL are relevant to patients, but conclusive data on these endpoints are not always available, mainly because the regulator is willing to accept greater clinical uncertainty. At the same time HTA agencies perceive the relevance of PFS differently. A multi-stakeholder debate would be essential to align concrete robust evidence requirements in oncology and a common definition for clinical relevance, which will benefit patients and society in general.

INTRODUCTION

New anticancer medicines promise an improved prognosis for patients with life-threatening diseases. However, most of them are modestly effective while very expensive (1). This dilemma frequently leads to a multi-stakeholder debate about the value of such medicines entering the European market.

Unlike the centralised European marketing authorisation decision, each member state independently makes its own reimbursement decisions. One of the most important criteria for reimbursement decisions is usually the comparative efficacy and/or effectiveness of the new treatment with existing options (2,3). This comparison is often referred to as a relative efficacy/effectiveness assessment (REA) and is performed by health technology assessment (HTA) agencies. Other relevant factors in reimbursement decisions include ethical, social, budget-impact and cost-effectiveness considerations (3).

Evidence from case studies suggests that HTA agencies value commonly used clinical endpoints for anticancer medicines differently (4,5). Generally, the potential benefits of a new treatment come down to its effect on overall survival (OS) and/or quality of life (QoL), or their surrogates (6). Examples of surrogates are disease-free survival (DFS) in the curative setting, and progression-free survival (PFS) in the non-curative setting.

PFS is the length of time during and after the treatment that a patient lives with the disease but it does not get worse.. The increasing use of PFS as a primary endpoint in anticancer trials is debated due to doubts about its clinical meaningfulness (7,8). Advanced colorectal and advanced ovarian cancer seem to be the only two tumour types for which evidence suggests that PFS may be accepted as surrogate for OS (7). But even for these indications, the validity of this association in contemporary oncology with novel therapies is being questioned (7). It is also debated whether PFS can measure a direct clinical benefit in the advanced setting (9). This would be the case if it provides a duration in which patients experience less symptoms, clinical consequences of the disease and/or improved quality of life (5).

A comparison of pazopanib assessments for advanced/ metastatic renal cell carcinoma, found that some HTA agencies considered an increase in PFS to be patient relevant, whereas other agencies considered it only relevant in absence of OS data and when supported by improved QoL (4). In addition, a study comparing appraisals of breast cancer and colorectal cancer medicines across five HTA agencies found that HTA agencies interpreted the PFS benefit differently (5).

Greater harmonisation in assessing clinical endpoints for anticancer medicines is important to patients, healthcare providers and payers to guide appropriate treatment decisions. The objective of this research is to study the role of OS, PFS and QoL data in REAs informing pricing or reimbursement decisions in European jurisdictions, by a) studying whether data on these endpoints are included, and b) studying the impact of these data on recommendations.

METHODS

Research design

We conducted a retrospective comparative cross-sectional analysis of publicly available HTAs of anticancer medicines that received marketing authorisation between 2011 and 2013.

Selection of HTA jurisdictions

Of the 29 EU jurisdictions (UK divided into England and Scotland), nine had publicly available reports from HTA organisations involved in assessing medicines for pricing or reimbursement decisions. From these, three were excluded. Belgium was excluded as only a limited number of reports were publicly available; Portugal and Ireland were excluded as only a few brief summaries were available, providing insufficient information to inform this study. We present the six jurisdictions included and their respective HTA agencies in Table 1.

HTA guidelines

National HTA guidelines assessing medicines were obtained from the relevant HTA agencies' websites. If no national guideline was available, grey literature was searched.

Selection of medicines and reports

Of all new active substances approved by the EMA from 1 Jan 2011 to 31 Dec 2013 to treat malignant diseases (n=26), we included only those medicines for which four or more HTA reports were published before April 2015 by different HTA agencies for the first indication approved (n=14). A total of 72 HTA reports for these 14 medicines were included. When an HTA report included separate analyses and/or recommendations for individual (sub)indications, we included each (sub)indication separately. Although the 12 reports from Germany's Institute for Quality and Efficiency in Health Care (IQWiG) included 25 (sub)indications with separate recommendations, we excluded 7 indications because data were missing. One report from the France's National Authority for Health (HAS) included two indications with separate recommendations. The final data set included 79 HTAs. We present a flowchart of the selection process in Figure 1.

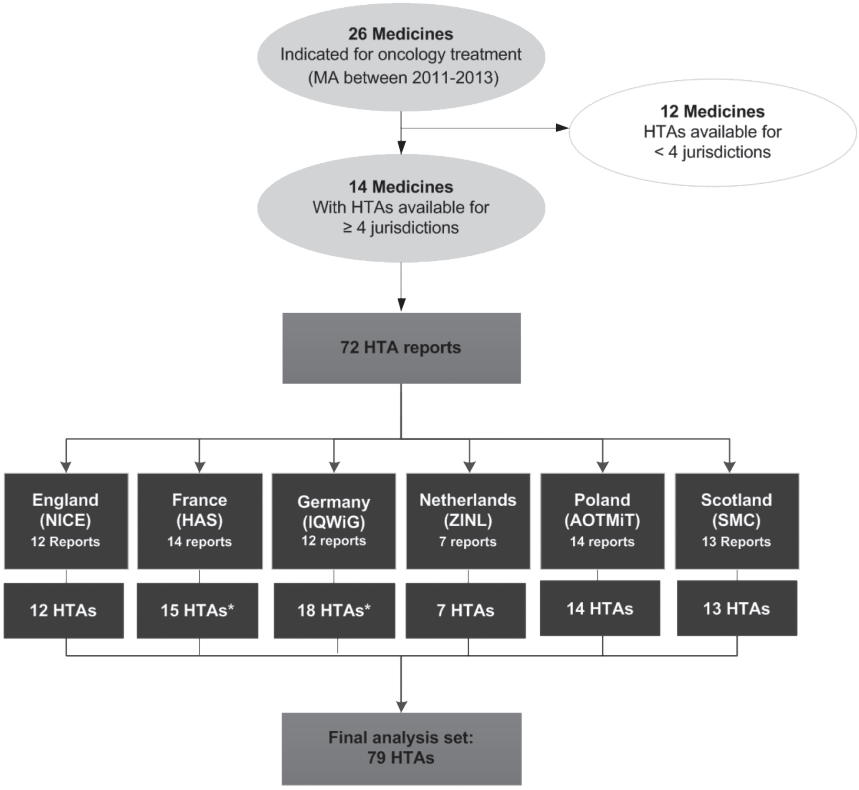
Data collection

To collect data from the assessments, we developed a structured data collection form (DCF) including 32 questions, 14 open-ended and 18 categorical. The DCF and a description of its development are presented in Supplementary Table 1 and 2 (S1 and S2). This article focuses on a subset of questions in the DCF that are related to the research questions.

Table 1. Overview of Health Technology Assessment agencies included in the study

Jurisdiction	England	France HAS	Germany	Netherlands	Poland	Scotland
HTA organisation	NICE	HAS	IQWiG	ZIN	AOTMiT	SMC
Section in report about relative effectiveness assessment	Evidence for clinical effectiveness[a]	Clinical added value (ASMR)	Early benefit assessment	Pharmaco therapeutic assessment	Clinical efficacy[a]	Clinical effectiveness issues[a]
Section in report used to identify impact of endpoint on recommendation	Summary of Appraisal Committee's key conclusions	Transparency Committee Conclusions and Summary & discussion section of the Analysis of Data	Executive summary of added benefit assessment and Extent and probability of added benefit	Letter to Ministry of Health, Welfare and Sports and Judgement medicines committee Discussion/ Extrapolation/ Conclusion section	Justification of recommendation	Advice and Summary of clinical effectiveness issues
Other criteria (besides relative effectiveness) taken into account by agency in recommendation	Cost-effectiveness	Cost-effectiveness for claimed ASMR I–III and/or high budget-impact	None	Cost-effectiveness for premium pricing, budget impact	Cost-effectiveness, budget-impact	Cost-effectiveness
Recommendation is used as basis for	Funding decision	Reimbursement & pricing decision (positive list)	Pricing decision (reference pricing, price negotiations with social insurance)	Reimbursement & pricing decision[b]	Reimbursement & pricing decision (positive list)	Funding decision by Health Boards

[a] No separate REA recommendation; [b] Pricing decision is only applicable to outpatient medicines, for which a positive list is in place
Abbreviations: AOTMiT=Agencja Oceny Technologii Medycznych i Taryfikacji; HAS= Haute Autorité de Santé ; HTA=Health technology assessment; IQWiG= Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; MA=Market authorisation; NICE=National Institute for Health and Care Excellence; REA=relative effectiveness assessment; SMC=Scottish Medicines Consortium; ZIN= Zorginstituut Nederland;

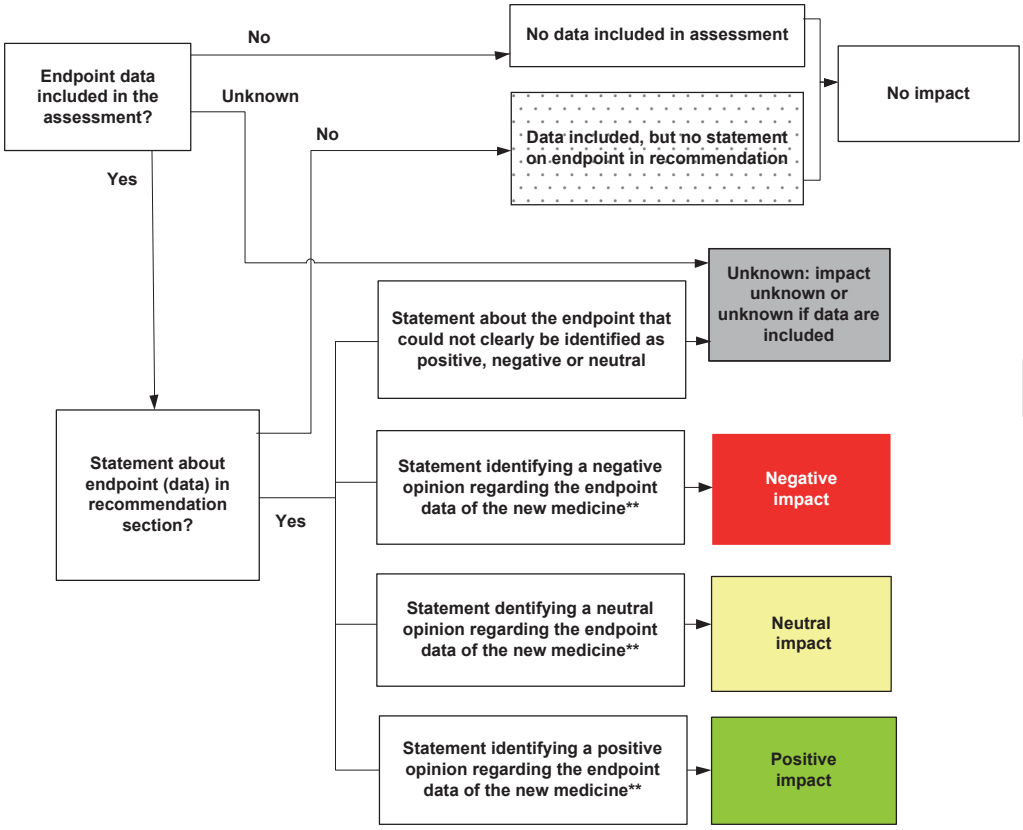


* When an HTA report included separate analysis and/or recommendations for several (sub)indications, each (sub)indication was included as a separate assessment.

Abbreviations: AOTMiT=Agencia Oceny Technologii Medycznych i Taryfikacji; HAS= Haute Autorité de Santé ; HTA=Health technology assessment; IQWiG= Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; MA=Market authorisation; NICE=National Institute for Health and Care Excellence; REA=relative effectiveness assessment; SMC=Scottish Medicines Consortium; ZIN= Zorginstituut Nederland.

Figure 1. Flow-chart: selection of medicines and health technology assessments

As the study focuses on relative effectiveness rather than cost effectiveness, we extracted statements about the endpoints from the clinical sections of the reports and from the overall recommendations or discussion sections (Table 1). QoL data had to be collected with validated QoL instruments. To capture the impact of the clinical endpoints on the recommendations, we categorised the extracted statements as *positive*, *neutral*, *negative*, *unknown* (impact unknown or unknown if data are included) or *no impact* (not included/not identified). Statements were classified as neutral if it indicated that no change/difference is shown vs a comparator. We present the algorithm for the categorisation in Figure 2.



* The impact was classified as unknown in case of multiple comparators with different impact values and it was not possible to choose a single most relevant comparator (e.g. England, axitinib and afatinib). In addition, for some Polish reports it is unknown whether endpoint data are included due to confidential (sensored) sections.
** Based on direct statement in recommendation/discussion on endpoint OR indirect statement (e.g superior efficicacy) that is clearly related to a specific endpoint

Figure 2. Algorithm used to determine the impact of the endpoint data on recommendation

We abstracted data between April and May 2015 and invited an expert panel consisting of one representative from each of the six agencies who are or have been involved in producing HTAs. Their role was to validate the algorithm used to categorise the impact of the endpoint and to clarify pending issues.

Data analysis

We used descriptive statistics to present the data and qualitatively analysed statements to compare what agencies regard as clinically relevant in the context of trial endpoints, and why these judgements may differ.

RESULTS

HTA guidelines

Information in the guidelines on endpoints is presented in Supplementary Table 3 (S3). In general, all HTA guidelines preferred clinically and patient relevant endpoints relating to morbidity, mortality and QoL. Surrogate endpoints are not favoured, but used when supporting information is provided about the relationship between the surrogate and patient-relevant endpoints. Most guidelines do not specify whether PFS is considered a surrogate or patient-relevant endpoint. A French consensus statement by clinical experts indicates that PFS in metastatic disease is relevant only in certain settings. On the contrary, a German report on surrogate endpoints in oncology concluded that PFS should not be considered a valid surrogate for OS in colorectal and breast cancer.

The guidelines from England and Scotland make special provisions for life-extending treatments at the end of life, which can result in a higher valuation of the clinical benefit offered by treatment reflected in a higher cost-effectiveness threshold.

HTAs included and recommendation outcomes

We list all assessed medicines and recommendation outcomes in Table 2. The number of HTAs included per jurisdiction varied between 7 (The Netherlands) and 18 (Germany). 27% (21/79) of the assessments had a negative/lesser benefit recommendation, but the percentage varies considerably per jurisdiction (6-69%). Overall, few medicines were rejected primarily for clinical reasons (4/79 recommendations), whereas 10/79 were rejected primarily because of cost/cost-effectiveness issues. For 7/79 assessments the rejection was based on the clinical and cost/cost-effectiveness profile. For France, Germany and The Netherlands, negative/lesser benefit recommendations were based solely on the clinical profile, whereas they were mainly based on the cost/cost-effectiveness profile or both (clinical and cost/cost-effectiveness profile) for England, Scotland and Poland.

Endpoint data included in REAs

Figure 3 details the endpoints included in the REAs and their impact on the recommendations. OS data were included by all agencies in all REAs, but the data are not always mature. Germany did not include PFS data in any of the REAs. In the other jurisdictions, PFS data were included in 80-100% of the REAs. QoL data are frequently lacking, and inclusion varies, from 29% (Poland) to 67% (England). Where QoL data were not included, this was either because the data were not collected, or the quality was considered insufficient. Safety data were included by all jurisdictions for all medicines.

Table 2. List of medicines included and outcome of recommendations that inform pricing and/or reimbursement decisions

Abbreviated indication	Medicine (generic name)	England	France	Germany	Netherlands	Poland	Scotland
Bone metastases from solid tumours	1. denosumab	✓(Optimised)	✓ (minor)[a] ± [a]	Not assessed	±	×, ©&€	Not assessed
Breast cancer	2. eribulin	×, €	✓ (minor)	± [b] ± [b]	✓	×, ©&€	×, €
	3. pertuzumab	Not assessed	✓ (moderate)	✓ (major)[c]	Not assessed	✓	×[d], €
Colorectal cancer	4. aflibercept	×, ©&€	±	✓ (minor)	Not assessed	✓	×[e], €
Gastric cancer	5. tegafur / gimeracil / oteracil	Not assessed	×, ©	Not assessed	×, ©	×, ©	✓ (with restrictions)
Melanoma	6. ipilimumab, 2nd line Tx	✓[g]	✓ (minor)[f]	✓ (considerable)	✓	✓	×[h], ©&€
	7. vemurafenib	✓[g]	✓ (moderate)	✓ (considerable)[i]	✓	✓	×[h], €
	8. dabrafenib	✓	±	±	Not assessed	✓	✓ (with restrictions)[j]
Non-small-cell lung cancer	9. afatinib	✓	±	✓ (major)[k] ✓ (minor)[k] ± [k] ×, ©	Not assessed	✓	✓
	10. crizotinib	×, €	✓ (moderate)	±	Not assessed	×, ©&€	×[h], €
Prostate cancer	11. cabazitaxel	×, €	✓ (minor)[l]	✓ (considerable)[m] ✓ (minor)[m]	✓	×, ©&€	×, ©&€

Table 2. (continued)

Abbreviated indication	Medicine (generic name)	England	France	Germany	Netherlands	Poland	Scotland
	12. abiraterone, after Tx with Taxane	✓[g]	✓ (moderate)	✓considerable)[n]	±	✓	x[o], €
	13. enzalutamide	✓[g]	✓ (moderate)	✓ (considerable)[p] ✓ (major)[p]	Not assessed	✓	✓ (with restrictions)
Renal-cell carcinoma	14. axitinib	✓ (Optimised) [g]	✓ (minor)	✓ (considerable)[q]	Not assessed	✓	x[h], €
	# assessments	12	15	18	7	14	13
	n x/ % x	4 / 33%	1 / 7%	1 / 6%	1 / 14%	5 / 36%	9 / 69%

Legend:
✓ Recommended/ Added benefit
± No added benefit proven (GE)/ similar therapeutic value (NL, FR)
x Not recommended (EN, PO, SC)/ lesser benefit (FR,GE,NL)
© Clinical profile (benefit, harms) was the primary reason for negative recommendation
€ Costs/cost-effectiveness was the primary reason for negative recommendation
©&€ Clinical profile (benefit, harms) & costs/cost-effectiveness were the primary reason for negative recommendation

Abbreviations: Tx=treatment
[a] HAS recommended that denosumab provides a minor improvement in actual benefit (level IV) in patients with breast cancer or prostate cancer with bone metastases but does not provide an improvement in actual benefit (level V) in patients with other types of solid tumours with bone metastases.
[b] Eribulin was assessed for two subgroups: Patients for whom treatment with taxanes or anthracyclines is no longer an option vs patients for whom repeated treatment containing an anthracycline or a taxane is an option.
[c] IQWIG assessed two separate subpopulations of which only one was included in the analysis: HER2-positive metastatic breastcancer (hint of major added benefit)
[d] The same indication was reassessed in 2014, for which an updated efficacy analysis was added. But the recommendation remained negative due to an insufficiently robust economic analysis and the high treatment cost in relation to the health benefits.
[e] The medicine was reassessed by SMC for the same indication. The reassessment included the same clinical data. However, the recommendation changed from negative to positive due to a Patient Access Scheme that improved the cost-effectiveness of the medicine.

Table 2. (continued)

[f] Ipilibumab was assessed by HAS in 2011 and 2012 for the same indication, both assessments resulting in a minor incremental added benefit recommendation.
[g] NICE end-of-life criteria were met (life expectancy < 24 months, extension to life of at least an additional 3 months and ≤ 7000 patients in England. The criteria were introduced in 2009
[h] The medicine was reassessed by SMC for the same indication. The reassessment in included the same clinical data, however, the recommendation changed from negative to positive with limitations due to a Patient Access Scheme that improved the cost-effectiveness of the medicine
[i] Vemurafenib was assessed by IQWIG in 2012 and 2013 for the same indication both resulting in a considerable added benefit recommendation. For the reassessment the manufacturer submitted additional data cut-offs, however the data were not included by IQWIG due to increased risk of bias.
[j] meets SMC end of life criteria (life expectancy ≤ 36 months). The criteria were introduced in 2014.
[k] Afatibin was assessed by IQWIG for 6 different subpopulations of which 4 were included in the analysis: 1) non-pretreated patients with ECOG PS 0 to 1 and an EGFR mutation Del19 (Indication of a major AB) 2) non-pretreated patients with ECOG PS 0 to 1 and an EGFR mutation L858R, Age<65 (Hint of a minor AB) 3)) non-pretreated patients with ECOG PS 0 to 1 and an EGFR mutation L858R, Age≥ 65 (AB not proven) 4) non-pretreated patients with ECOG PS 0 to 1 and other EGFR mutations (Indication of LB).
[l] Cabazitaxel was reassessed by HAS for the same indication in 2012. New data were included in the reassessment (2012) resulting in a change of the recommendation from minor improvement in actual benefit to moderate improvement in actual benefit.
[m] Cabazitaxel was assessed by IQWIG for 3 different subpopulations: 1) Best supportive care population, age < 65 year (considerable added benefit) 2) Best supportive care population,, age ≥ 65 years (hint of added benefit) 3) Docetaxel retreatment population. The third subpopulation was excluded from the dataset as IQWIG did not conduct an analysis because no data were available.
[n] IQWIG assessed two separate subpopulations of which one was included in the analysis: Best supportive care population (considerable added benefit)
[o] Abiterone was assessed twice by SMC for the same indication in 2012, with the same clinical data. However, the recommendation changed from negative to positive due to a Patient Access Scheme that improved the cost-effectiveness of abiterone
[p] Enzalutamide was assessed by IQWIG for 2 different subpopulations: 1) patients without visceral metastases (Hint of a major added benefit), 2) patients with visceral metastases (Hint of a considerable added benefit)
[q] IQWIG assessed two separate subpopulations of which one was included in the analysis: 1) cytokine population (hint of a considerable added benefit)

Impact of endpoint data on recommendations

OS and safety data had an impact on the recommendation in 94% and 86% of the REAs respectively. The impact of OS data was mainly positive (48%/94%) or neutral (35%/94%), whereas that of safety data was mainly negative (39%/86%) or neutral (34%/86%). PFS data had an impact in 56% of the recommendations, but this varied highly between jurisdictions, from 0% in Germany to 85% in Scotland. The impact of PFS data was mainly positive (35%/56%). The influence of QoL data seems rather limited as only 41% of the recommendations were affected by QoL data, with the impact being mainly neutral (19%/41%) or positive (16%/41%).

In Supplementary Table 4 (S4) we present the impact of the endpoints for all medicines per jurisdiction in detail. In at least two instances (cabazitaxal and crizotinib), the impact differed between jurisdictions because of how the clinical relevance of the effect size of OS or PFS was interpreted. For example, the effect size of cabazitaxal for prostate cancer (2.4 month OS gain, HR=0.70) was considered a major added benefit (Germany), or a slight benefit against a high risk of adverse events (Poland). It was explicity stated in REAs that the PFS gain was considered clinically relevant by multiple jurisdictions for pertuzumab for breast cancer (18.5 vs 12.4 months, HR=.62), crizotinib for lung cancer (7.7 vs 3 month, HR=.49), vemurafenib for melanoma (5.3 vs. 1.6 months, HR=.26) and afatinib for lung cancer (11.1 vs 6.9 months, HR=.58).

DISCUSSION

The costs of new anticancer medicines are high, although their clinical value is sometimes disputed (10,11), resulting in a debate as to whether or not these medicines should be routinely available in public healthcare systems in the EU. Recently Harten et al. (12) found that the prices of anti-cancer medicines varied substantially among 15 European states. Other studies reported that the reimbursement of anti-cancer medicines varied among European countries (5,13,14). For countries in which health care is financed by general taxation, such as the UK, technologies are more likely to be reimbursed the lower their incremental cost-effectiveness ratio is (13). However, the correlation between cost effectiveness and reimbursement is not as evident in countries such as France and Germany, where decisions are based on clinical evidence (13). Despite cost effectiveness being the principal driver of decisions in some European countries, the relative effectiveness of a medicine is the most commonly shared decision-making criterion across all countries (3).

This study adds to the existing knowledge by focusing on differences in the assessment of clinical endpoints in REAs for anticancer medicines across European HTA agencies. It highlights the existing evidence gap between the ideal situation (preferred type of evidence as requested by HTA agencies) and the reality (actual evidence provided). OS and QoL are considered preferred patient-relevant endpoints,

but conclusive data on these endpoints are not always available. Nevertheless, for QoL, the lack of evidence does not seem to negatively impact the recommendations. The cross-country variation we found in valuing clinical endpoints was most striking for PFS data.

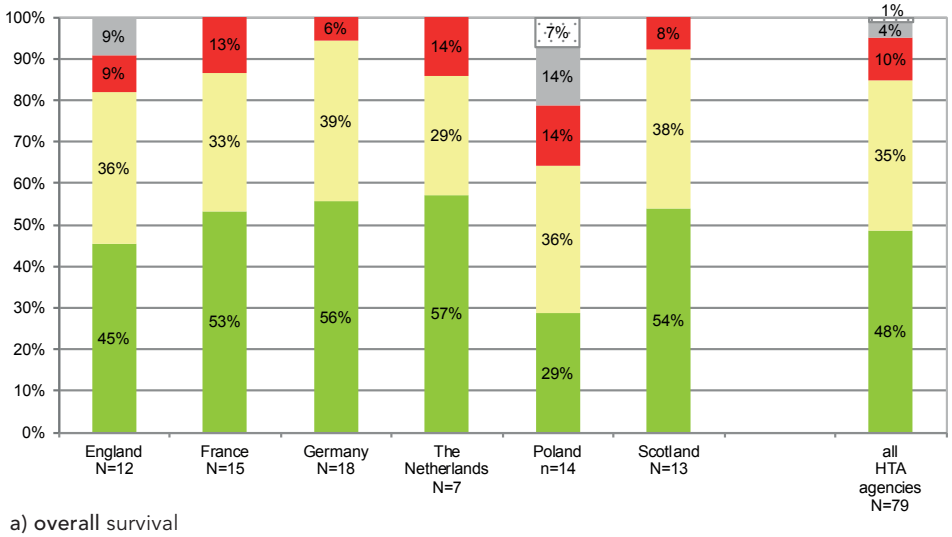
The variation we found in relevance of PFS data, reflects the ongoing debate about the increasing reliance on PFS in to demonstrate a clinical benefit for regulatory purposes (7,9). Granting early access to novel therapies based on PFS data can benefit patients who need life-extending therapies, but this runs the risk of reimbursing therapies that later prove not as effective or safe as initially thought (15). We were unable to identify a formal position of HTA agencies about the relevance of PFS from the publicly available data, except for Germany where PFS is explicitly considered to be of limited influence (16). Interestingly, the German position does not lead to more negative recommendations than the other jurisdictions.

For the other jurisdiction, the HTA guidelines suggest that PFS is generally seen as a surrogate endpoint, which confirm previous research (5,17,18). But as the HTA agencies are reluctant to discard the data despite weak evidence on surrogacy of PFS for OS (7, 19), it could be speculated that the agencies may expect a PFS gain to be relevant to patients (17). Considerations that may be relevant are the size of the PFS gain, the indication and stage of disease, and existing treatments or other supporting evidence. For example, evidence suggests that granting access for lung cancer drugs that prolong PFS by more than 3 months is robustly beneficial (15). But the researchers also stress that this is likely to vary considerably among indications. We think that reporting the considerations about each endpoint, and explicitly stating whether PFS is seen as a surrogate or patient-relevant endpoint in the HTA reports, as in German reports, would increase transparency and facilitate harmonisation.

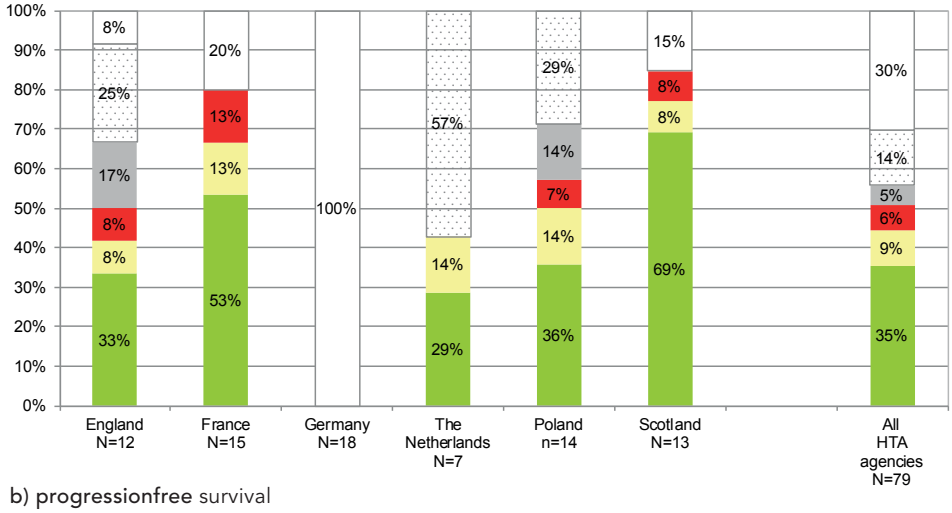
In addition, recent initiatives by clinicians to define clinical relevance (6,20) are a step forward. The European and American society for oncology have independently standardised approaches to grade the net health benefit, taking into account the clinical and safety results of medicines, compared to available treatments (6,20). This seems to be an important step towards consistent, transparent and informed decision-making in a field of rapid development such as that of oncology treatments.

This study shows that the consideration of endpoint data varies between HTA jurisdictions. Further divergences are also seen between HTA bodies and drug regulatory agencies (5) because the regulator is willing to accept a higher degree of clinical uncertainty to expedite access to therapies. Currently, the development of anticancer drugs is designed to meet drug licensing requirements, and do not specifically accommodate the requirements of HTA. A multi-stakeholder debate would be essential to align concrete robust evidence requirements in oncology and standardise the definition of 'relevant clinical benefit', which will benefit patients and society in general.

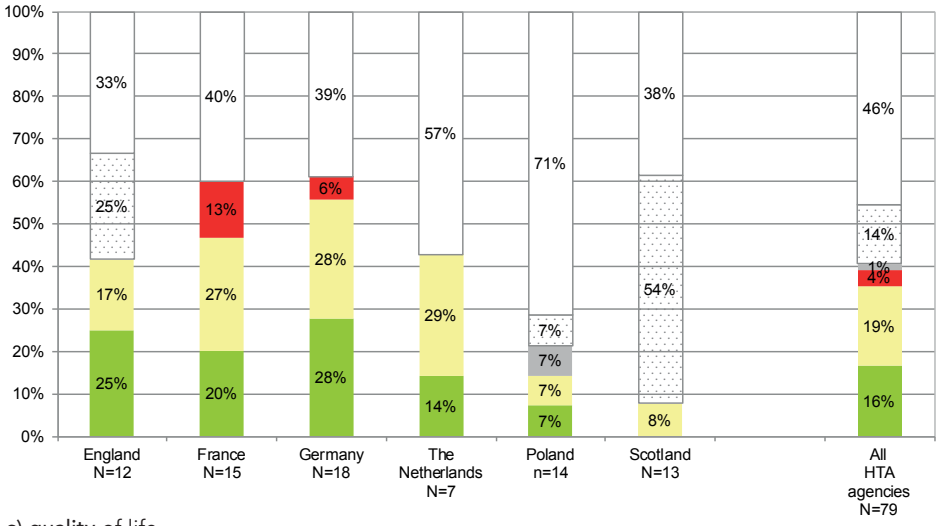
Figure 3. The impact of the endpoints on the recommendations: a) overall survival; b) progressionfree survival; c) quality of life and d) safety.



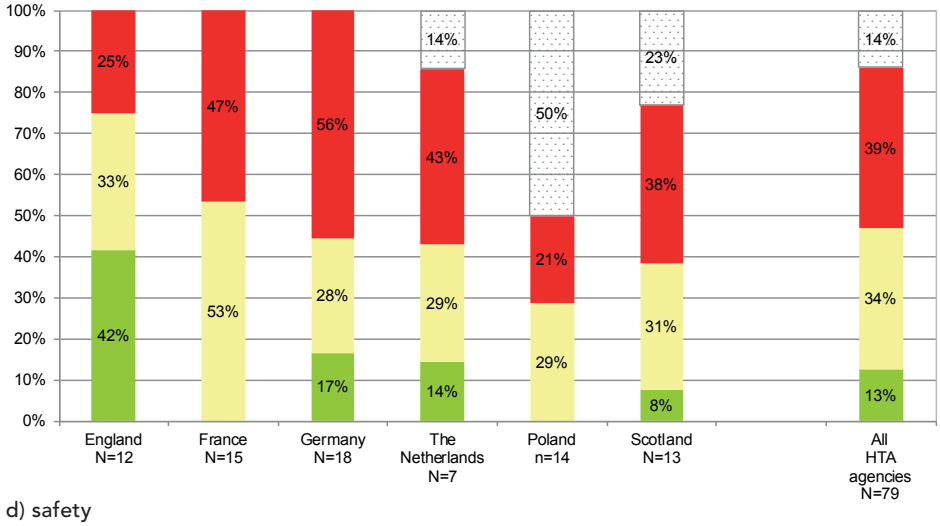
a) **overall** survival



b) **progressionfree** survival



c) **quality** of life



d) safety

Legend:

- No data included in assessment
- Data included, but no statement on endpoint in recommendation
- Unknown: impact unknown or unknown if data are included
- Negative impact
- Neutral impact
- Positive impact

Limitations

This study has some limitations. First, this study's results simplify real-world decision making. We focused on REAs but other factors such as cost-effectiveness (e.g Scotland) can influence the recommendations. Moreover, our research is based on publicly available information, but other factors that are not reported may have had an influence in these complex decision-making processes. Secondly, we compared a limited number of HTA jurisdictions, although this is mitigated by their diversity, as we included both jurisdictions where cost-effectiveness is and is not relevant. Thirdly, interpreting value statements in the HTA reports is subjective. To standardise the interpretation, we introduced a decision algorithm with a quality control procedure, and consulted HTA experts to reduce possible misinterpretation.

CONCLUSIONS

European decision making on relative effectiveness of anticancer medicines is affected by a gap in requested clinical evidence versus the evidence that is actually available. OS and QoL are relevant to patients, but conclusive data on these endpoints are not always available, mainly because the regulator is willing to accept a higher degree of clinical uncertainty. At the same time HTA agencies perceive the relevance of PFS differently. A multi-stakeholder debate would be essential to align concrete robust evidence requirements in oncology and a collectively shared definition for clinical relevance, which will benefit patients and society in general.

REFERENCES

1. Sorensen S. Valuing end-of-life care in the United States: the case of new cancer drugs. Health Econ Pol Law 2012; 7:411-430.
2. Sorenson C. Use of comparative effectiveness research in drug coverage and pricing decisions: a six-country comparison. Issue Brief (Commonw Fund) 2010;91:1–14.
3. Kleijnen S, George E, Goulden S, et al. Relative effectiveness assessment of pharmaceuticals: similarities and differences in 29 jurisdictions. Value Health 2012; 15:954-960.
4. Kleijnen S, Fathallah M, Van der Linden MW, et al. Can a joint assessment provide relevant information for national/local relative effectiveness assessments? An in-depth comparison of pazopanib assessments. Value Health 2015;18:663-672.
5. Shah KK, Mestre-Ferrandiz J, Towse A, Smyth EN. A review of health technology appraisals: case studies in oncology. Int J Technol Assess Health Care 2013; 29:101-109.
6. Cherny NI, Sullivan R, Dafni U, et al. 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 2015; 26:1547-1573.
7. Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: A systematic review of trial-level meta-analyses. JAMA Intern Med 2015;175:1389-1398.
8. Robinson AG, Booth CM, Eisenhauer EA. Progression-free survival as an end-point in solid tumours--perspectives from clinical trials and clinical practice. Eur J Cancer 2014; 50: 2303-2308.
9. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012;30:1030-1033.
10. Light DW, Lexchin J. Why do cancer drugs get such an easy ride? BMJ 2015 23;350:h2068.
11. Sobrero AF, Pastorino A, Sargent DJ, Bruzzi. Raising the bar for antineoplastic agents: how to choose threshold values for superiority trials in advanced solid tumors. Clin Cancer Res. 2015 1;21:1036-1043.
12. van Harten WH, Wind A, de Paoli P, et al. Actual costs of cancer drugs in 15 European countries. Lancet Oncol. 2016 Jan;17(1):18-20.
13. Lim CS, Lee YG, Koh Y, Heo DS. International comparison of the factors influencing reimbursement of targeted anti-cancer drugs. BMC Health Serv Res. 2014 Nov 29;14:595.
14. Mihajlović J, Dolk C, Tolley K, et al. Reimbursement of targeted cancer therapies within 3 different European health care systems. Clin Ther. 2015 Feb 1;37(2):474-80.
15. Lakdawalla DN, Chou JW, Linthicum MT, et al. Evaluating Expected Costs and Benefits of Granting Access to New Treatments on the Basis of Progression-Free Survival in Non-Small-Cell Lung Cancer. JAMA Oncol. 2015 May;1(2):196-202.
16. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Afatinib. November 2015. Berlin, Germany. Available at https://www.g-ba.de/downloads/40-268-3424/2015-11-05_AM-TL-XII_Afatinib_2015-05-15-D-163_TrG.pdf Accessed 7 December 2015.
17. Chabot I, Rocchi A. Oncology drug health technology assessment recommendations: Canadian versus UK experiences. Clinicoecon Outcomes Res 2014;6:357-367.
18. EUnetHTA. Endpoints used in relative effectiveness assessment of pharmaceuticals: Surrogate Endpoints. Available at http://www.eunethta.eu/outputs/methodological-guideline-rea-pharmaceuticals-surrogate-endpoints Accessed 7 December 2015.
19. Institute for Quality and Efficiency in Healthcare. Validity of surrogate endpoints in oncology: executive summary. 2011.
20. Ellis LM, Bernstein DS, Voest EE et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014; 32:1277-1280.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Methods for developing Data Collection Form

Methods for developing the Data Collection Form
A structured data collection form (DCF) was developed and used to collect data from the assessments. The DCF was divided into three sections: i. general information ii. methods used in the assessment and impact of the endpoints on the recommendation iii. outcome of the assessment. The DCF was tested and improved in two subsequent rounds. In both rounds, data abstraction was done independently by all four researchers for three assessment reports. In each round, three reports were selected based on their dissimilarities such as different jurisdictions, different indications, availability of comparator, orphan medicine status and availability of OS data. However, at this stage, the selection was limited to reports available in a common language for all researchers (English). After both rounds, the answers of the four researchers were compared and the inter-rater agreement was calculated[1,2]. For the open-ended questions, the inter-rater agreement was evaluated by a fifth independent researcher. At the end of each round, discrepancies in the responses were discussed by the four researchers and the DCF was further adapted. The inter-rater agreement increased from 0.68 in the first round to 0.72 in the second round, indicating an improvement of the agreement in the validation phase and substantial agreement between researchers (an inter-rater agreement of 1 indicates a perfect agreement)[2]. The agreement was lowest for the subjective questions that required researchers to 'value' the impact of the endpoints on the recommendation based on the statements in the reports. To further improve the consistency among the researchers' values for these specific questions, a decision algorithm was developed (see Figure 2) and frequently used statements were identified (see Supplementary Table 2). In addition, a quality check was conducted by the first author (i.e. check for errors and consistency), and any disagreements were discussed until consensus was reached among researchers about the impact of the endpoint.
Final Data Collection Form
i. General information about report
1. Topic
2. Country
3. URL of report
4. Date of data extraction
5. Date of HTA recommendation
ii. Methods used in the assessment
6. Which indication was under assessment?

[1] Shrout PE, Fleiss JL. Intraclass Correlations: Uses in Assessing Rater Reliability. Psychological Bulletin 1979, Vol. 86, No. 2, 420-428.

[2] Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics 1977, Vol. 33, No. 1, pp. 159-174.

Supplementary Table 1. (continued)

Final Data Collection Form
7. Goal of treatment (three options): a) extend life (improves morbidity or mortality) b) improve symptoms or QoL c) other e.g. provide prophylaxis
Comparators
8. Which comparator(s) was/were presented in the analysis of the assessment (included in the direct/indirect comparison)?
9. Which other possible comparators are identified by the HTA organization?
Overall surival (OS)
10. Are OS data included? (Y?N) *If no, please move on to question 14*
11. Is OS the primary or secondary endpoint in the pivotal study? Primary/secondary/not available
12. What was the effect size of OS in the overall population? Please answer question below per effect size a) Δmonths (e.g. 8 vs 5.2) b) HR c) CI of HR (p-value) d) Interventions compared (e.g. drug A vs B)
13. If available, which OS effect size(s) is/are mentioned in the assessment for subpopulation? Please answer question below per effect size a) subpopulation b) Δmonths (e.g. 8 vs 5.2) c) HR d) CI of HR (p-value) e) Interventions compared (e.g. drug A vs B)
14. What was the impact of endpoint for decision making? (see end of table for answer options)
Progression free survival (PFS)
15. Are PFS data included? (Y?N) *If no, please move on to question 21*
16. Is PFS the primary of secondary endpoint in the pivotal study? Primary/secondary
17. What was the effect size of PFS in the overall population? Please answer question below per effect size a) Δmonths (e.g. 8 vs 5.2) b) HR c) CI of HR (p-value) d) Interventions compared (e.g. drug A vs B)
18. If available, which PFS effect size(s) is/are mentioned in the assessment for subpopulation? Please answer question below per effect size a) subpopulation b) Δmonths (e.g. 8 vs 5.2) c) HR d) CI of HR (p-value) e) Interventions compared (e.g. drug A vs B)

Supplementary Table 1. (continued)

Final Data Collection Form
19. Which criteria were used to assess the PFS? a) RECIST (solid tumours), b) Other (please provide criteria in comments section), c) Not identified
20. Was PFS accepted as relevant endpoint? a) Acceptable (+): if there was an explicit statement about it b) Not acceptable (-): if there was an explicit statement about it c) Not identified (?): no explicit statement on the acceptability of the endpoint
21. What was the impact of endpoint for decision making? (see end of table for answer options)
Quality of life (QoL)
22. Are QoL data included in the assessment? Y/N (*if no, move on to question 25*)
23. Are generic and/or disease-specific quality of life data included? a) Generic, b) Disease-specific c) Generic and disease-specific d) unknown
24. What were the results? Please answer the questions below per QoL instrument, a) what is the name of the QoL instrument? b) interventions compared(e.g. drug A vs B) c) was there a statistical significant difference (if yes, please provide the effect size in the comment) yes/no/not available d) are the results applicable to the overall population? (if yes please provide subpopulation in comment) yes/no/not available
25. What was the impact of the endpoint for decision making? (see end of table for answer options)
Safety
26. Are safety data included in the assessment? Y/N
27. What was the impact of the endpoint for decision making? (see end of table for answer options)
Other endpoint measures
28. Are data presented on any other endpoints? Y/N If yes, provide the endpoint measures in the comments section
29. Was any other endpoint measure mentioned in the recommendations section? Y/N If yes, provide the statement in the comments section
iii. Outcome of the assessment
30. What was the final recommendation? a) positive (including conditional reimbursement/listing with limitations etc) or added benefit b) equal benefit or added benefit not proven c) egative or lesser benefit
31. In case of negative recommendations, what was the primary reason for the negative recommendation? a) clinical b) cost/cost-effectiveness c) both (clinical and cost/cost-effectiveness) d) other
32. In case there was a subgroup defined in the recommendation section, please specify the subgroup

Supplementary Table 1. (continued)

Final Data Collection Form
Q 14, 21, 25, 27
What was the impact of the endpoint for decision making? a) Positive impact: Statement in the recommendations section identifying a positive opinion regarding the endpoint data of the new medicine b) Negative impact: statement in the recommendations section identifying a negative opinion regarding the endpoint c) Neutral impact: statement in the recommendations sections identifying a neutral opinion regarding the endpoint d) Impact unknown: statement in the recommendations sections that cannot clearly be identified as positive, negative or neutral or if it is unknown whether data on the endpoint are included e) Not identified: no statement on the endpoint on the recommendations section f) Not included: Endpoint data were not included in the assessment

Supplementary Table 2. Categorisation of terminology used to describe the impact of the endpoint (data) on the recommendation

Endpoint	Typical wordings in report	Categorisation
OS & PFS	The results are considered 'clinically relevant' 'relevant clinical gain' 'clinically meaningful' or 'improvement of OS/PFS'	Positive
All endpoints	A statement about a significant difference was considered clinically relevant unless indicated differently	Positive
Safety	Adverse events profile is 'tolerable/acceptable/ generally manageable/safe' or 'less harm'	Positive
Safety	'Similar adverse events in therapeutic class'	Neutral
All endpoints	'No change/no difference shown vs comparator'	Neutral
Safety	Considerable adverse events' or 'Adverse events profile is NOT tolerable/acceptable/ generally manageable/ safe' or 'greater harm'	Negative
All endpoints	In case no data on a specific endpoint were included, the impact of the endpoint has been scored as 'not included' as the endpoint did not impact the recommendation.	Not included

Supplementary Table 3. Information contained in Agency guidelines about the use of endpoints

Jurisdiction (agency)	Reference	Information included about endpoints
England (NICE)	National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. NICE article [PMG9]. London, United Kingdom. URL: http://www.nice.org.uk/article/pmg9/chapter/Foreword	**2.2 Components of the scope** 2.2.8 As far as possible, the scope identifies principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is, they measure health benefits and adverse effects that are important to patients and/or their carers. The clinical outcome measures usually quantify an impact on survival or health-related quality of life that translates into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness. **3. Evidence** 3.1.2 The evaluation of effectiveness requires quantification of the effect of the technology under appraisal and of the relevant comparator technologies on survival, disease progression and health-related quality of life so that this can be used to estimate QALYs. **4.3. Patient and carer groups** 4.3.1. The Institute invites submissions from all patient and carer groups involved in the appraisal. 4.3.2 These written submissions may provide perspectives from patients and carers on: · the experience of having the condition, or in the case of carers, the experience of caring for someone with the condition · the experience of receiving care for the condition in the healthcare system · the experience of having specific treatments for the condition · the outcomes of treatment that are important to patients or carers (which may differ from the outcomes measured in the relevant clinical studies and the aspects of health included in generic measures of health-related quality of life) · the acceptability of different treatments and modes of treatment · their preferences for different treatments and modes of treatment · their expectations about the risks and benefits of the technology. **6.2 Appraisal of the evidence** 6.2.9 In the reference case, the Committee will regard all QALYs as being of equal weight. However, when considering the overall health benefits, the Appraisal Committee can accept analysis that explores a QALY weighting that is different from that of the reference case when a technology appraisal concerns a 'life extending treatment at the end of life', or in other circumstances when instructed by the NICE board.

Supplementary Table 3. (continued)

Jurisdiction (agency)	Reference	Information included about endpoints
		6.2.10 In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met: · the treatment is indicated for patients with a short life expectancy, normally less than 24 months and there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment and · the technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England. In addition, the Appraisal Committees will need to be satisfied that: · the estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and · the assumptions used in the reference case economic modelling are plausible, objective and robust. 6.2.11 When the conditions described in section 6.2.10 are met, the Appraisal Committee will consider: · the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age and · the magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost effectiveness of the technology to fall within the normal range of maximum acceptable ICERs. 6.2.12 Treatments approved following the application of the 'end-of-life' criteria listed in section 6.2.10 will not necessarily be regarded or accepted as standard comparators for future appraisals of new treatments introduced for the same condition. Second and subsequent extensions to the marketing authorisations for the same product will be considered on their individual merits.
Germany (IQWIG)	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. General Methods version 4.1. 2013. Cologne, Germany. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf	**3.1.1 Definition of patient-relevant medical benefit and harm** As the benefit of an intervention should be related to the patient, this assessment is based on the results of studies investigating the effects of an intervention on patient-relevant outcomes. In this connection, "patient-relevant" refers to how a patient feels, functions or survives [44]. Consideration is given here to both the intentional and unintentional effects of the intervention that in particular allow an assessment of the impact on the following patient-relevant outcomes to determine the changes related to disease and treatment:

Supplementary Table 3. (continued)

Jurisdiction (agency)	Reference	Information included about endpoints
		1) mortality 2) morbidity (symptoms and complications) 3) health-related quality of life As supplementary information, consideration can be given to the time and effort invested in relation to the disease and the intervention, as well as treatment satisfaction of patients. However, a benefit or added benefit cannot be determined on the basis of these outcomes alone […] […] In accordance with §35b SGB V, the following outcomes related to patient benefit are to be given appropriate consideration: increase in life expectancy, improvement in health status and quality of life, as well as reduction in disease duration and adverse effects. These dimensions of benefit are represented by the outcomes listed above; for example, the improvement in health status and the reduction in disease duration are aspects of direct disease-related morbidity; the reduction in adverse effects is an aspect of therapy-related morbidity….. 3.1.2 Surrogates of patient-relevant outcomes […] Surrogate endpoints are therefore normally considered in the Institute's benefit assessments only if they have been validated beforehand by means of appropriate statistical methods within a sufficiently restricted patient population and within comparable interventions (e.g. drugs with a comparable mode of action). A surrogate endpoint can be regarded as valid if the effect of an intervention on the patient-relevant outcome to be substituted is explained to a sufficient degree by the effect on the surrogate endpoint [27,541]. The necessity to evaluate surrogate endpoints may have particular relevance within the framework of the early benefit assessment of drugs (see Section 3.3.3), as regulatory approval procedures primarily investigate the efficacy of a drug, but not always its patient-relevant benefit or added benefit […] 3.2.4 Patient-reported outcomes The patient-relevant dimensions of benefit outlined in Section 3.1.1 can also include patient-reported outcomes (PROs). In addition to health-related quality of life and treatment satisfaction, PROs can also cover other dimensions of benefit, for example, disease symptoms. As in the assessment of quality of life and treatment satisfaction, instruments are required that are suitable for use in clinical trials [160]. In the selection of evidence (especially study types) to be considered for the demonstration of an effect, the same principles as with other outcomes usually apply [183]. This means that also for PROs (including health-related quality of life and treatment satisfaction), RCTs are best suited to demonstrate an effect.

Supplementary Table 3. (continued)

Jurisdiction (agency)	Reference	Information included about endpoints
		As information on PROs is subjective due to their nature, open studies in this area are of limited validity. The size of the effect observed is an important decision criterion for the question as to whether an indication of a benefit of an intervention with regard to PROs can be inferred from open studies. Empirical evidence shows a high risk of bias for subjective outcomes in open studies [555]. This should be considered in their interpretation (see also Sections 7.1.4 and 7.3.4). However, situations are conceivable where blinding of physicians and patients is not possible. In such situations, if possible, other efforts are required to minimize and assess bias (e.g. blinded documentation and assessment of outcomes). Further aspects on the quality assessment of studies investigating PROs are outlined in [183].
	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. [A10-05] Validity of surrogate endpoints in oncology (Rapid report). November 2011. Cologne, Germany. URL: https://www.iqwig.de/download/A10-05_Executive_Summary_v1-1_Surrogate_endpoints_in_oncology.pdf	The report concludes that PFS is a surrogate endpoint that should only be included in assessments if the effect of the treatment on PFS predicts the effect the treatment has on the patient-relevant endpoint (overall survival). This is considered proven, when validated by means of appropriate statistical methods within a sufficiently restricted patient population and within comparable interventions (e.g. drugs with a comparable mode of action). A surrogate endpoint can be regarded as valid if the effect of an intervention on the patient-relevant endpoint to be substituted is explained to a sufficient degree by the effect on the surrogate endpoint.
The Netherlands (ZIN)	Ministry of Health, Welfare and Sport and College voor zorgverzekeringen. Dutch Assessment Procedures for the Reimbursement of Outpatient Medicines. ZN2011023491. Diemen 2010, The Netherlands. URL: http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/publications-in-english/2010/1003-dutch-assessment-procedures-for-	Appendix 2: Assessment criteria of the CFH […] Intended effects should, preferably, be expressed in clinically relevant outcome parameters that are noticeable for the patient, such as degree of morbidity, mortality and/or quality of life. Clinically relevant outcome parameters are often not yet available at the moment of assessment (e.g., for preventative cardiovascular medicines). Such clinical studies tend to provide only surrogate (also known as intermediary) outcome parameters. In such cases, surrogate outcome parameters (e.g., a laboratory result, or a physical characteristic) form the only useable parameters for assessing intended effects. It should be mentioned that a demonstrable relationship must exist between this surrogate parameter and a clinically relevant outcome parameter. Surrogate outcome parameters are not always noticeable by patients. In order to establish relevant outcome measures, the CFH can use the guidelines of the EMA and the treatment guidelines of care-providers […]

Supplementary Table 3. (continued)

Jurisdiction (agency)	Reference	Information included about endpoints
	the-reimbursement-of-outpatient-medicines/Dutch+Assessment+Procedures+for+the+Reimbursement+of+Outpatient+Medicines.pdf	[…] Very little research is undertaken that explicitly focuses on quality of life. However, the added value of a medicine may actually be expressed in the form of an improved quality of life. Consequently, it is always worthwhile mentioning relevant data on this aspect. Firm conclusions cannot always be determined based on the Dutch results of research in which quality of life is a secondary parameter. When comparing the different unintended effects, especially the serious adverse events and the adverse events that occur with the highest frequency will be regarded. A serious adverse event is defined as a side effect that leads to mortality, a life threatening situation, invalidity or a disability, admission to hospital or lengthening the period of hospitalisation. Experience in using a medicine is important because it provides greater clarity about its intended effects, the risk of unexpected unintended effects, its applicability and the ease of use. More experience provides prescribers and patients with more confidence in the therapeutic value of a medicine […]
	College voor zorgverzekeringen. Specialist drugs package management. ZN2013077869. December 2013. Diemen, The Netherlands URL: https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/publications-in-english/2013/1312-specialist-drugs-package-management/1312-specialist-drugs-package-management/Specialist+drugs+package+management.pdf	Therapeutic value: Weighing up the value of the relevant properties of a drug (favourable and unfavourable effects, experience, ease of use and applicability) that together determine the drug's place within therapy. The therapeutic value is a comparison with the standard or usual care for the indication concerned. The outcome of therapeutic value is formulated as therapeutic added value, comparative value or lower value (in comparison with the standard treatment).
Scotland (SMC)	Scottish Medicines Consortium. Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF). October 2014. Glasgow, United Kingdom. URL: https://www.scottishmedicines.org.uk/Submission_Process/Submission_guidance_and_forms/Templates-Guidance-for-Submission/Templates-Guidance-for-Submission	Provide details of whether trials have directly measured health outcomes such as mortality, survival, incidence of disease, morbidity, functional performance, quality of life or whether surrogate markers have been measured e.g. reduction in blood pressure. Provide details of any association between surrogate markers and health benefits or disadvantages to patients. For drugs designated as orphan medicinal products for the indication(s) under review, provide a detailed explanation of the relevance of surrogate markers and the theoretical basis for this selection. This should also be related to quality of life data. Provide details of differences between the patient populations included in the studies, which provided evidence of clinical benefits and adverse effects compared to the Scottish population likely to receive the drug in clinical practice.

Supplementary Table 3. (continued)

Jurisdiction (agency)	Reference	Information included about endpoints
	Scottish Medicines Consortium. Supplement on medicines for end of life and very rare conditions. 2014. Glasgow, United Kingdom. URL: https://www.scottishmedicines.org.uk/Submission_Process/Submission_guidance_and_forms/Templates-Guidance-for-Submission/Templates-Guidance-for-Submission	2. Categorisation […] End of life medicine: A medicine used to treat a condition at a stage that usually leads to death within three years with currently available treatments […] 3.2. Evaluation of medicines with end of life or orphan status Submissions are assessed by NDC according to standard process. If NDC's draft advice for an end of life medicine or a medicine with orphan status is 'not recommended', the pharmaceutical company will be offered the opportunity to request a PACE meeting and will have the option to submit a brief statement for consideration at the PACE meeting at the same time as they provide comments on the NDC Detailed Advice Document (DAD). A copy of the template for the company PACE statement can be found on the SMC website. This statement should focus on additional information covering factors that may not be fully captured within conventional clinical and economic assessment, such as unmet need, severity of the condition and added value of the medicine for the patient and family / carers, place in therapy and also details of any sub-groups whom the medicine may specifically benefit […]
France (HAS)	EUnetHTA Joint Action Work Package 5. EUnetHTA JA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals. Background review version 5B. July 2011. Diemen, The Netherlands. URL: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Final%20version%20of%20Background%20Review%20on%20Relative%20Effectiveness%20Assessment%2Bappendix.pdf	All endpoints are included, however outcomes related to mortality and/or morbidity are preferred. Surrogate endpoints are included if no other endpoints are available and if they are considered clinically relevant. Quality of life data are included if the instrument is validated and appropriate to the specific disease.

Supplementary Table 3. (continued)

Jurisdiction (agency)	Reference	Information included about endpoints
	Rima de Sahb-Berkovitch et al. Assessing Cancer Drugs for Reimbursement: Methodology, Relationship between Effect Size and Medical Need. Thérapie 2010 Juillet-Août; 65 (4): 373–377	5. Conclusion and recommendations In assessing cancer drugs for reimbursement, the Transparency Commission requested data on overall survival. In fact, overall survival (OS) is not always the ideal primary endpoint. Progression-Free Survival (PFS) for metastatic situations or Disease-Free Survival (DFS) in adjuvant situations are wholly relevant endpoints in slowly progressing diseases or when salvage treatments are available. However, in early lines of treatment, insofar as the ultimate therapeutic objective of a cancer drug is to prolong survival, if PFS is chosen as the primary endpoint, OS should still be taken as a secondary endpoint with monitoring of survival. Its interpretation may often raise questions, particularly when, for obvious ethical reasons, second-line treatments have been administered. As for response rate alone, it is not accepted as an endpoint in assessment for reimbursement by the Transparency Commission, except in malignant blood diseases. Effect size is assessed using actuarial survival curves of the product versus the comparator. This information is often processed using median survival, but in the absence of an ideal parameter, the recommendation is to use several parameters: hazard ratio, median overall survival or progression-free survival and survival rate at a given time t. Apart from the endpoints, assessing cancer drugs for reimbursement is no different from other therapeutic classes. The attempt by the working group to determine an effect size threshold for the granting of reimbursement did not succeed because it would depend on medical need, the comparator and progress in knowledge in the field in question. (...)
Poland (AOTMiT)	The Regulation of the Minister of Health of 2 April 2012 on the minimum requirements to be satisfied by the analyses accounted for in the applications for reimbursement and setting the official sales price and for increasing the official sales price of a drug, a special purpose dietary supplement, a medical device,	§4 1. The clinical analysis referred to [...] shall include: [...] 4c) effectiveness and safety parameters constituting the objects of the trial; [...] [...] 3.5) characteristics of every trial included in the review in a tabular form with the account for following: [...] f) a list with all parameters subject to assessment in the trial; [...] [...] 3.6) a specification of the results obtained in each of the trials to the extend compliant with the criteria referred to in §1.4.c) in a tabular form.

Supplementary Table 3. (continued)

Jurisdiction (agency)	Reference	Information included about endpoints
	which do not have a reimbursed counterpart in a given indication as well as the Reimbursement Law from 2012 do not specify the effect sizes. URL: http://www.aotm.gov.pl/www/assets/files/wytyczne_hta/2012/Regulation_MoH_minimum_requirements_03042012_eng.pdf	
	Agency for Health Technology Assessment. Guidelines for conducting Health Technology Assessment (HTA). Version 2.1. Warsaw, April 2009. URL: http://www.aotm.gov.pl/www/assets/files/wytyczne_hta/2009/Guidelines_HTA_eng_MS_29062009.pdf	2.1.4. Health outcomes The clinical analysis should evaluate the health effects which represent clinically significant Endpoints*, playing an important role in a given disease, i.e.: · deaths, · cases or recoveries, · quality of life, · adverse effects (divided into serious and non-serious) · and/or medical events The endpoints in the clinical analysis should: · efer to the assessed disease and its course, · reflect the most important aspects of the health problem and at the same time allow to detect the possible differences between the interventions compared, · be essential for reasonable decision taking (critical points of a given health problem). If no clinical trials with patient oriented clinically significant endpoints have been found, surrogates can be assessed as the outcomes. In this case it is recommended to present the relationship between the surrogates used and the clinically significant endpoints in the analysis. If the results of clinical assessment are obtained using scales or questionnaires, information on their validation and the clinical significance of the outcomes should be presented. * patient oriented clinically important endpoint (clinically important endpoint, clinically relevant endpoint, patient important outcome, patient-oriented endpoint)–a parameter/outcome, a change of which as a result of treatment would make the treatment preferred for the patients. It reflects the treatment effects: life prolonging, improving the patient's well-being or allowing to live without disease complications or treatment.

Supplementary Table 4. Impact of endpoints per medicine

1. Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours

	England/Wales	France 1[a]	France 2[b]	Germany	The Netherlands	Poland[c]	Scotland
Comparator	zoledronic acid	zoledronic acid	zoledronic acid	Not assessed	zoledronic acid	zoledronic acid	Not assessed
Impact of endpoint:							
OS	Neutral	Neutral	Negative		Neutral	Negative	
PFS	Not included	Not included	Not included		Not identified	Not identified	
QoL	Neutral	Not included	Not included		Neutral	Not identified	
Safety	Neutral	Neutral	Neutral		Neutral	Not identified	
Recommendation	Optimised	ASMR IV	ASMR V		STV	Negative	
Primary reason negative recommendation						Clinical and cost/cost-effectiveness	

Abbreviations: ASMR= Clinical added value rating (I-V); STV= Similar therapeutic value.
[a] Breast cancer or prostate cancer with bone metastases
[b] Other types of solid tumours with bone metastases
[c] Bone metastases from prostate cancer

Supplementary Table 4. (continued)

2. **Eribulin** for patients with breast cancer who have received at least two chemotherapeutic regimens for locally advanced or metastatic disease. Prior therapy should have included an anthracycline and a taxane, unless patients were not suitable for these treatments

	England/Wales[a]	France	Germany 1[c]	Germany 2[d]	The Nether-lands	Poland[e]	Scotland
Comparator	Treatment of physician's choice (TPC)	TPC	capecitabine/ vinorelbine	taxanes / anthracyclines	TPC	TPC	TPC
Impact of endpoint:							
OS	Not identified	Positive	Positive	Neutral	Positive	Neutral	Positive
PFS	Not identified	Neutral	Not included	Not included	Neutral	Neutral	Negative
QoL	Not included	Not included	Not included	Not included	Not included	Not included	Negative
Safety	Negative	Neutral	Negative	Negative	Negative	Not identified	Neutral
Recommendation	Not recom-mended	ASMR IV	No AB proven	No AB proven	ATV	Negative	Not recom-mended
Primary reason negative recommendation	Cost-effective-ness					Clinical and cost/cost-effectiveness	Cost-effective-ness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V); ATV= Added therapeutic value.
[a] Indication assessed less specific: treatment of locally advanced or metastatic breast cancer
[c] Prior therapy should have included an anthracycline and a taxane. Patients for whom treatment with taxanes or anthracyclines is no longer an option
[d] Prior therapy should have included an anthracycline and a taxane. Patients in whom further treatment with taxanes is still possible
[e] Indication assessed less specific: treatment of locally advanced and methastatic breast cancer (after two treatment lines)

Supplementary Table 4. (continued)

3. Pertuzumab (in combination with trastuzumab and docetaxel) for treatment of patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease

	England/Wales	France	Germany*	The Netherlands	Poland	Scotland
Comparator	Not assessed	Placebo + trastuzumab/docetaxel	Placebo + trastuzumab &taxane (docetaxel, paclitaxel)	Not assessed	Placebo + trastuzumab /docetaxel	Placebo + trastuzumab /docetaxel
Impact of endpoint:						
OS		Positive	Positive		Positive	Positive
PFS		Positive	Not included		Positive	Positive
QoL		Neutral	Not included		Not included	Not identified
Safety		Negative	Negative		Not identified	Negative
Recommendation		ASMR III	Major AB		Positive	Not recommended
Primary reason negative recommendation						Cost-effectiveness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V).
* Patients with Human Epidermal Growth Factor Receptor 2 (HER2)-positive metastatic breast cancer

Supplementary Table 4. (continued)

4. Aflibercept (in combination with irinotecan/ 5-fluorouracil/ folinic acid (FOLFIRI) chemotherapy) for metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen

	England/Wales*	France	Germany	The Netherlands	Poland	Scotland
Comparator	Placebo+FOLFORI	Placebo+FOLFORI	Placebo+FOLFORI	Not assessed	Placebo+FOLFORI	Placebo+FOLFORI
Impact of endpoint:						
OS	Negative	Positive	Positive		Not identified	Neutral
PFS	Negative	Positive	Not applicable		Not identified	Positive
QoL	Not included	Not included	Not included		Not included	Not included
Safety	Negative	Negative	Negative		Not identified	Negative
Recommendation	Not recommended	ASMR V	Minor AB		Positive	Not recommended
Primary reason negative recommendation	Clinical and cost/ cost-effectiveness					Cost-effectiveness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V).
* Indication assessed: metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy

Supplementary Table 4. (continued)

5. Tegafur/gimeracil/oteracil in combination with cisplatin for the treatment of advanced gastric cancer

	England/Wales	France	Germany	The Netherlands	Poland	Scotland
Comparator	Not assessed	5-Fluorouracil + cisplatin	Not assessed	Triplet therapy*	5-Fluorouracil + cisplatin	5-Fluorouracil + cisplatin
Impact of endpoint:						
OS		Negative		Negative	Unknown	Neutral
PFS		Negative		Unknown	Unknown	Neutral
QoL		Negative		Unknown	Not included	Not included
Safety		Unknown		Unknown	Neutral	Neutral
Recommendation		Lesser benefit		LTV	Negative	Accepted with restrictions
Primary reason negative recommendation		Clinical effectiveness		Clinical effectiveness	Clinical effectiveness	

Abbreviations: LTV=lesser therapeutic value
* Combination treatment of epirubicin, cisplatin or oxaliplatin and 5-fluorouracil

Supplementary Table 4. (continued)

6. Ipilimumab for advanced melanoma in adults who have received prior therapy

	England/Wales	France	Germany	The Netherlands	Poland	Scotland
Comparator	Ipi + gp100 vs ipi alone vs gp100 alone	Ipi + gp100 vs ipi alone vs gp100 alone	Ipi + gp100 vs ipi alone vs gp100 alone	Ipi + gp100 vs ipi alone vs gp100 alone	ipi + gp100 vs gp100	Ipi + gp100 vs ipi alone vs gp100 alone
Impact of endpoint:						
OS	Positive	Positive	Positive	Positive	Positive	Positive
PFS	Not identified	Not included	Not included	Not identified	Not identified	Not included
QoL	Not identified	Neutral	Neutral	Not included	Not included	Not included
Safety	Neutral	Negative	Negative	Negative	Negative	Negative
Recommendation	Recommended	ASMR IV	Considerable AB	ATV	Positive	Not recommended
Primary reason negative recommendation						Clinical and cost/ cost-effectiveness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V); ATV= Added therapeutic value.

Supplementary Table 4. (continued)

7. **Vemurafenib** for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma

	England/Wales*	France	Germany	The Netherlands	Poland	Scotland
Comparator	Dacarbazine	Dacarbazine	Dacarbazine	Dacarbazine	Dacarbazine	Dacarbazine
Impact of endpoint:						
OS	Positive	Positive	Positive	Positive	Positive	Positive
PFS	Positive	Positive	Not included	Positive	Positive	Positive
QoL	Not included	Negative	Neutral	Not included	Not included	Not identified
Safety	Positive	Negative	Negative	Neutral	Not identified	Not identified
Recommendation	Recommended	ASMR III	Considerable AB	ATV	Positive	Not recommended
Primary reason negative recommendation						Cost-effectiveness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V); ATV= Added therapeutic value.
* locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

Supplementary Table 4. (continued)

8. Dabrefenib for adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma

	England/Wales*	France	Germany	The Netherlands	Poland	Scotland
Comparator	Vemurafenib	Dacarbazine	Dacarbazine	Not assessed	Vemura-fenib	Dacarbazine, vemurafenib
Impact of endpoint:						
OS	Neutral	Neutral	Neutral		Neutral	Neutral
PFS	Neutral	Negative	Not included		Neutral	Positive
QoL	Not identified	Neutral	Neutral		Not included	Neutral
Safety	Positive	Negative	Negative		Neutral	Neutral
Recommendation	Recommended	ASMR V	No AB proven		Positive	Accepted with restrictions

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V).
* locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

Supplementary Table 4. (continued)

9. **Afatinib** for treatment of EGFR-TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer with activating EGFR mutation(s)

	England /Wales[*]	France	Germany 1[e]	Germany 2[f]	Germany 3[g]	Germany 4[h]	The Netherlands	Poland	Scotland
Comparator	Erlo/gefitinib,pemetrexed or gemcitabine + cisplatin	Peme-trexed or gemcitabine + cisplatin	Pemetrexed + cisplatin	Pemetrexed + cisplatin	Pemetrexed + cisplatin	Pemetrexed + cisplatin	Not assessed	Erlotinib, gefitinib,	Pemetrexed or gemcitabine + cisplatin, TKI inhibitors
Impact of endpoint:									
OS	Neutral	Neutral	Positive	Neutral	Neutral	Negative		Unknown	Negative
PFS	Unknown	Positive	Not included	Not included	Not included	Not included		Unknown	Positive
QoL	Not identified	Positive	Positive	Positive	Negative	Neutral		Unknown	Unknown
Safety	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral		Not identified	Unknown
Recommendation	Recommended	ASMR V	Major AB	Minor AB	No AB proven	Lesser benefit		Positive	Accepted
Primary reason negative recommendation						Clinical effectiveness			

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V).
[*] patients with locally advanced or metastatic non-small cell lung cancer with EGFR mutation(s)
[e] non-pretreated patients with ECOG PS 0 to 1 and EGFR mutation Del19
[f] non-pretreated patients with ECOG PS 0 to 1 and EGFR mutation L858R and age <65
[g] non-pretreated patients with ECOG PS 0 to 1 and EGFR mutation L858R and age ≥ 65
[h] non-pretreated patients with ECOG PS 0 to 1 and other EGFR mutations

Supplementary Table 4. (continued)

10. **Crizotinib** for adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

	England/Wales	France	Germany*	The Netherlands	Poland	Scotland
Comparator	Chemotherapy (docetaxel or pemetrexed)	Chemotherapy (docetaxel or pemetrexed)	Chemotherapy (docetaxel or pemetrexed)	Not assessed	Chemotherapy (docetaxel or pemetrexed)	Chemotherapy (docetaxel or pemetrexed)
Impact of endpoint:						
OS	Neutral	Neutral	Neutral		Neutral	Neutral
PFS	Positive	Positive	Not included		Negative	Positive
QoL	Positive	Positive	Positive		Not included	Not included
Safety	Positive	Neutral	Negative		Not identified	Negative
Recommendation	Not recommended	ASMR III	No AB proven		Negative	Not recommended
Primary reason negative recommendation	Cost-effectiveness				Clinical and cost/ cost-effectiveness	Cost-effectiveness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V).
* indication assessed: patients with previously treated ALK-positive advanced NSCLC in whom chemotherapy is indicated (in particular, these can be patients with Eastern Cooperative Oncology Group [ECOG] performance status 0, 1, and, if applicable, 2)

Supplementary Table 4. (continued)

11. Cabazitaxel (+ prednis(ol)on) for metastatic hormone-refractory prostate cancer (mHRPC) in patients previously treated with a docetaxel-containing treatment regimen

	England/Wales*	France	Germany 1 Age≥65 years	Germany 2 Age<65 years	The Netherlands	Poland	Scotland
Comparator	mitoxantron+ prednis(ol)on	mitoxantron+ prednis(ol)on	mitoxantron+ prednis(ol)on	mitoxantron+ prednis(ol)on	mitoxantron+ prednis(ol)on	mitoxantron+ prednis(ol)on	mitoxantron+ prednis(ol)on
Impact of endpoint:							
OS	Positive	Positive	Positive	Positive	Positive	Negative	Positive
PFS	Positive	Positive	Not included	Not included	Positive	Not identified	Positive
QoL	Not included	Not included	Not included	Not included	Neutral	Not included	Negative
Safety	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Recommendation	Not recom-mended	ASMR IV	Considerable AB	Minor AB	ATV	Negative	Not recom-mended
Primary reason negative recommen-dation	Cost-effectiveness					Clinical and cost/ cost-effective-ness	Clinical and cost/ cost-effective-ness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V); ATV= Added therapeutic value.

Supplementary Table 4. (continued)

12. **Abiraterone** (+prednis(ol)on) for metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients who have received prior chemotherapy containing a taxane

	England/Wales	France	Germany	The Netherlands	Poland	Scotland
Comparator	placebo+ prednis(ol)on(e)	placebo+ prednis(ol)on(e)	placebo+ prednis(ol)on(e)	placebo+ predni-s(ol)on(e) (direct), carbazi-taxel (indirect)	placebo+ prednis(ol)on(e)	placebo+ prednis(ol)on(e)
Impact of endpoint:						
OS	Positive	Positive	Positive	Neutral	Positive	Positive
PFS	Positive	Positive	Not included	Unknown	Positive	Not included
QoL	Positive	Positive	Not included	Positive	Not included	Not identified
Safety	Positive	Neutral	Neutral	Positive	Negative	Positive
Recommendation	Recom-mended	ASMR III	Conside-rable AB	STV	Positive	Not recommended
Primary reason negative recommendation						Cost-effectiveness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V); STV= Similar therapeutic value.

Supplementary Table 4. (continued)

13. **Enzalutamide** (+best supportive care) for in men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel chemotherapy

	England/Wales	France	Germany 1[k]	Germany 2[l]	The Netherlands	Poland	Scotland
Comparator	Abiraterone, Placebo + best supportive care (BSC)	Placebo+ BSC	Placebo+ BSC	Placebo+ BSC	Not assessed	Abiraterone, Placebo + BSC	Abiraterone, Placebo + BSC
Impact of endpoint:							
OS	Positive	Positive	Positive	Neutral		Neutral	Positive
PFS	Not identified	Neutral	Not included	Not included		Positive	Positive
QoL	Positive	Unknown	Positive	Positive		Positive	Not identified
Safety	Neutral	Negative	Positive	Positive		Neutral	Neutral
Recommendation	Recommended	ASMR III	Considerable AB	Major AB		Positive	Accepted with restrictions

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V).
[k] patients without visceral metastases
[l] patients with visceral metastases

Supplementary Table 4. (continued)

14. **Axitinib** for advanced renal cell carcinoma after failure of prior systemic treatment

	England/Wales	France	Germany*	The Netherlands	Poland	Scotland
Comparator	Sorafenib, sunitinib, pazopanib, best supportive care (BSC)	Sorafenib, everolimus and placebo	Sorafenib	Not assessed	Sorafenib	Sorafenib, BSC
Impact of endpoint:						
OS	Unknown	Neutral	Neutral		Neutral	Neutral
PFS	Unknown	Positive	Not included		Positive	Positive
QoL	Neutral	Neutral	Neutral		Neutral	Not identified
Safety	Positive	Neutral	Positive		Neutral	Not identified
Recommendation	Optimised	ASMR IV	Considerable AB		Positive (conditional)	Not recommended
Primary reason negative recommendation						Cost-effectiveness

Abbreviations: AB= Added benefit; ASMR= Clinical added value rating (I-V).
* Patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with a cytokine (cytokine population)

chapter 6

THE IMPACT OF OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL GAINS ON HEALTH TECHNOLOGY ASSESSMENT RECOMMENDATIONS FOR NEW ANTICANCER DRUGS

Iga Lipska
Sarah Kleijnen
Teresa Leonardo Alves
Kim Meijboom
Neil McAuslane
Lawrence Liberti
Hubert G.M. Leufkens
Anthonius de Boer
Wim Goettsch
Anke M. Hövels

Prepared for submission

ABSTRACT

Background

Patients' expectations for access to new and potentially valuable anticancer medicines can lead to increased pressure for timely access to these drugs; however, decision makers often struggle to determine the clinical benefit of oncology medicines.

Methods

We compared publicly available HTA reports produced by six European HTA agencies to investigate how the magnitude of overall survival (OS) and progression-free survival (PFS) influenced HTA recommendations for 14 new anticancer medicines. We developed a dichotomous classification of HTA recommendations to allow cross-jurisdiction comparison and compared the data for effect magnitudes of OS and PFS against a threshold of 3 months' incremental gains for OS and PFS and HR = 0·7 (for OS and PFS).

Results

We included 72 HTA recommendations for 14 anticancer drugs. The described OS incremental gains varied from no improvement/OS data not mature to 10·4 months. The PFS incremental gains ranged from 1.4 months to 6·1 months. We noted divergence in HTA recommendations despite the fact that in general, the same effect magnitudes for OS and PFS were referenced by different jurisdictions for the same medicine.

Conclusions

Agencies face difficulties when determining the clinical relevance of new anticancer medicines. HTA guidelines do not contain a clearly defined threshold for clinically relevant improvements of OS or PFS as a prerequisite for positive HTA recommendations. Defining a disease-specific minimum standard for what could be considered a clinically relevant OS and PFS gain could support consistent, transparent, and informed decision making in the rapidly evolving field of oncology.

INTRODUCTION

The burden of cancer on society continues to increase.(1) New cancer drugs pose challenges to health systems not only because of their price, but also because of the varying magnitude of their clinical effect or benefit. Patients' expectations for access to new and potentially valuable anticancer medicines are constantly rising and lead to increased pressure on decision makers to provide timely access for patients facing an unmet medical need. Patients' and healthcare providers' expectations are also being prompted by the use of superlatives descriptors such as "breakthrough" or "miracle" in the media,(2) while most new anticancer drugs present modest or marginal benefit.(2,3) Clinicians(4,5) and decision makers including health technology assessment (HTA) agencies(6) struggle to determine the clinical benefit of anticancer drugs to ensure that patients receive the most effective therapy for their disease.

The aim of anticancer treatment is to extend life, which can be measured by overall survival (OS), and/or to improve quality of life (QoL) or safety. Due to methodological constraints with measuring OS and QoL in controlled studies (such as crossover between study arms or study periods) it is common to use surrogate endpoints such as progression-free survival (PFS), particularly in advanced cancers.(4) The use of PFS as a primary endpoint in clinical trials has increased substantially over the past 20 years;(7) however, the strength of association between PFS and OS in oncology is generally low.(8)

In order to distinguish treatments that are characterised by substantial improvements in clinical efficacy and effectiveness from those whose benefit are modest or even marginal, recent initiatives from clinicians have focused on grading the magnitude of the clinical benefit for anticancer drugs in a standardised manner;(4.9) even suggesting in Poland for example, thresholds for what should be financed from public funds.(10)

Similar discussions are ongoing among European decision makers. In Europe, new prescription drugs must first be approved by the European Medicines Agency (EMA) when a centralised procedure applies and subsequently undergo jurisdiction-specific assessments by HTA agencies. The latter provide recommendations to guide decisions on drug reimbursement and pricing.(11) Even though the approaches used by HTA agencies and EMA differ substantially,(12.13) both play an important role in ensuring access to safe and effective medicines.

In previous research we highlighted that European HTA agencies have difficulties in valuing the clinical relevance of anticancer medicines.(6) OS and QoL are generally considered to be patient-relevant endpoints; however, conclusive data are often unavailable following clinical research. Similarly, jurisdictions differ in their perception of the relevance of PFS data. European Network for HTA (EUnetHTA) guidelines from 2013(14) indicate that PFS may be used as a surrogate endpoint in an advanced setting, but that in metastatic settings, PFS alone is insufficient and should be coupled with QoL assessment and survival data. Therefore, most HTA agencies, with the notable exception of *Germany's Institut für Qualität und Wirtschaftlichkeit im*

Gesundheitswesen (IQWIG) will often evaluate a product based on PFS data, despite weak evidence supporting the use of PFS as a surrogate for OS.

This may also imply that HTA agencies will relate the magnitude of the gain in PFS or OS in patients to a possible clinically relevant benefit. Therefore, the objective of this study is to investigate how the magnitude of OS and PFS impacts on HTA recommendations for new anticancer medicines and whether there are thresholds related to OS and PFS used by HTA agencies.

METHODS

Research design

We conducted a retrospective, comparative, cross-sectional analysis of publicly available assessments produced by HTA agencies in Europe for anticancer medicines. We focused on the magnitude effect of OS and PFS based on data obtained from the clinical sections of HTA reports and the outcome of the respective HTA recommendations.

The methods for selecting the HTA jurisdictions and target medicines along with the evaluation of the HTA reports and the development of the data collection form (DCF) are briefly summarised below and details are published elsewhere.(6)

Selection of HTA jurisdictions and classification of recommendations

We included HTA agencies that conducted formal assessments of medicines to inform pricing/reimbursement decisions and for which HTA reports were publicly available. The list of jurisdictions and their HTA organisations is presented in Figure 1. To enable the comparison of HTA recommendations across jurisdictions, a dichotomous (positive/negative) classification of HTA recommendations was developed. The jurisdiction-specific pricing and reimbursement recommendation systems were analysed and translated into either a positive or negative HTA recommendation (Fig. 1). A distinction was made between jurisdictions that advise whether the new drug has added therapeutic value (France, FR; Germany, GER; The Netherlands, NL) and those that give a positive or negative advice for use (England, EN; Poland, PL; Scotland SCO). While cost effectiveness informs the drug reimbursement process in the latter group, clinical effectiveness is the overarching common criteria for HTA agencies among all jurisdictions.

In particular with regards to jurisdictions which advise on the new drug added therapeutic value (FR, GER, NL) the details of jurisdiction-specific various clinical added benefit scales were analysed, compared and translated into the classification developed.

In case of FR for the new drug evaluation, first SMR (Actual Benefit) scale is used (from major, important, moderate, minor to lesser benefit), then subsequently ASMR

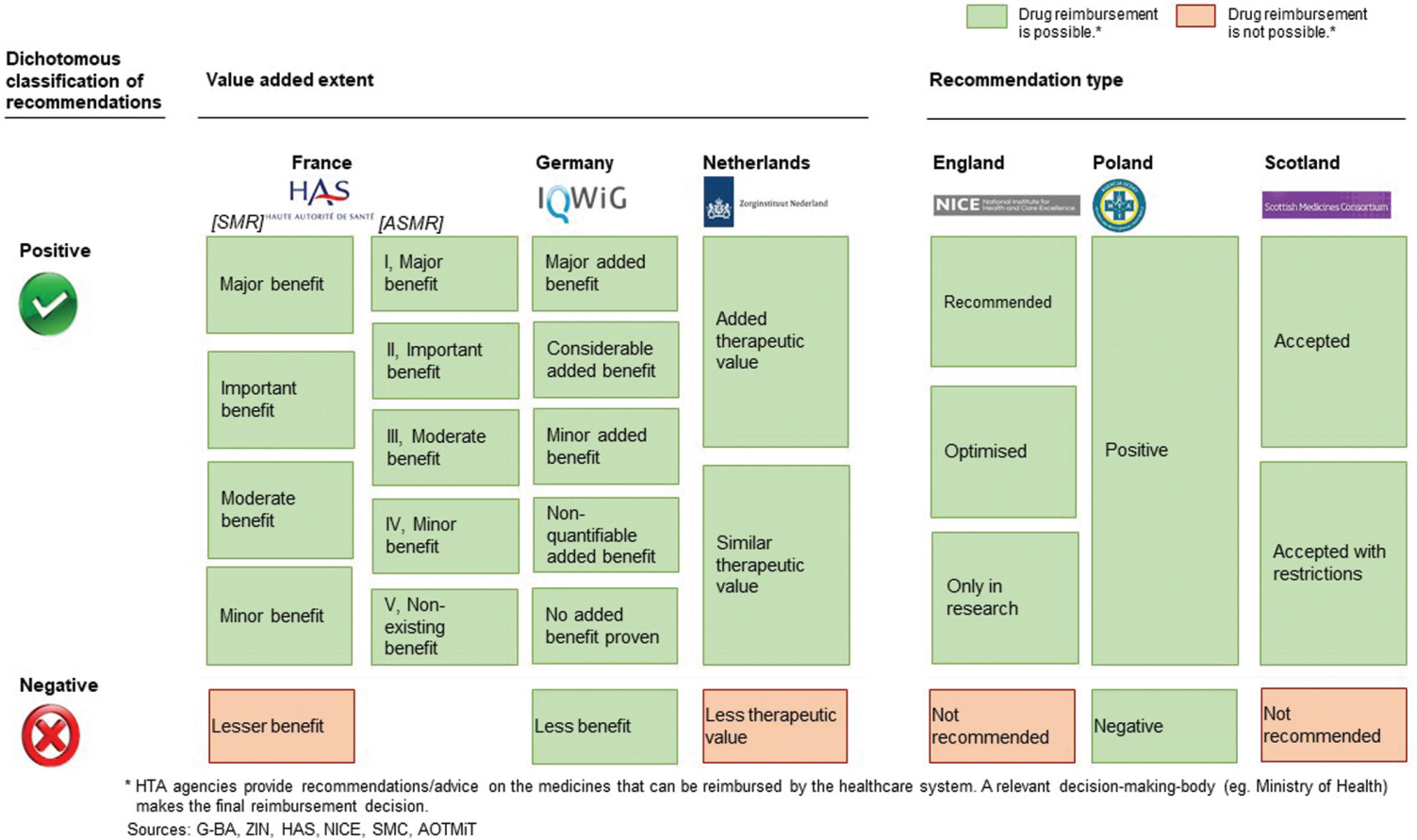


Figure 1. Dichotomous classification of HTA recommendations.

(Clinical Added Benefit I-V) scale is used I meaning major benefit, II – important benefit, III – moderate benefit, IV – minor benefit and V – non-existing benefit. In French system drugs for which SMR scale proved "lesser benefit" are not evaluated further with the use of ASMR scale. Therefore we classified the drugs with SMR "lesser benefit" to the group of negative HTA recommendations. All drugs which were further evaluated based on ASMR scale (from I to V) were classified to the group of positive HTA recommendations (Fig. 1).

Similarly for Germany only the drugs with "less benefit" evaluation were classified to the group of negative HTA recommendations. Drugs with major, considerable, minor and with non-existing added benefit were classified to the group of positiveHTA recommendations (non-existing added benefit in German system thus would be comparable with ASMR V- non-existing benefit in French system) (Fig. 1).

Consistently for the Netherlands drugs with "less therapeutic value" were classified to the group of negative HTA recommendations while drugs with "added therapeutic value" and "similar therapeutic value" were classified to the group of positive HTA recommendations (Fig. 1).

Data collection

All new active substances indicated to treat cancer approved by EMA between 1 January 2011 and 31 December 2013 were included, and for which four or more HTA reports from different jurisdictions were available before April 2015 (n=14). In order to allow consistent comparison across jurisdictions, we analysed only the first HTA reports produced for the first indication in the chosen jurisdictions.

For analysis reported in this paper we included one HTA report for one drug in a given jurisdiction, in case of multiple HTA reports for one drug as in France and Germany we included only one HTA report based on selection criteria listed below (population, comparators and effect magnitude).

Four researchers collected the data from the HTA reports between April–May 2015, using a standardised DCF designed to collect key details about HTA recommendations. The details of the data collection process including validation process, quality check, agreement between researchers, and DCF components are published elsewhere.(6)

This article focuses on the subset of questions in the DCF regarding OS and PFS effect magnitude: median OS and PFS durations for treatment and control arm; hazard ratio (HR), 95% confidence interval (CI), and p-value; statistical significance (statistically significant ($p<0{\cdot}05$), not statistically significant or data not shown) and whether OS and PFS were primary or secondary endpoints.

Data on OS and PFS were abstracted from the clinical sections of the HTA reports. If the information on effect magnitude for either OS or PFS was not specified for a particular medicine in publicly available HTA documents, we considered it to be unavailable. Data used in economic analyses in the reports was considered out of scope for this study.

Selection of (sub)populations, comparators, and effect magnitudes

In order to be able to compare a single OS and PFS effect magnitude across various jurisdictions, we established that:

- If different (sub)populations were assessed in a jurisdiction with separate recommendations we selected the HTA recommendation for the general patient population.
- When multiple comparators were included in the HTA report, we chose the comparator that had greater impact on the recommendation. For example, in a Dutch HTA report, triple therapy was selected as the comparator for tegafur/gimeracil/oteracil indicated for gastric cancer, and this particular comparator was highlighted as most relevant in the recommendation.
- Similarly, when multiple effect magnitudes were included for one comparator in the HTA report, the magnitude considered to have had the most impact on the HTA recommendation was selected.

Data analysis and thresholds used

Descriptive statistics were used to present the percentage of positive and negative HTA recommendations. Data for OS and PFS effect magnitude were analysed for all jurisdictions and compared against a threshold of 3 months' incremental gains for OS and PFS (in accordance with end-of-life criteria implemented by National Institute for Clinical Excellence (NICE) and Scottish Medicines Consortium (SMC). We also used a point estimate for HR (for both OS and PFS) of 0·7 as a threshold.(15) This point estimate for HR is also based on previous research (16) on marketing authorisation approvals by European Medicines Agency for applications indicating a major public health interest which was characterized by pivotal clinical trial HRs below 0.7.

RESULTS

Dichotomous classification of HTA recommendations

Based on our inclusion criteria HTA recommendations for 14 anticancer drugs were analysed. There were 14 HTA recommendations for all anticancer drugs included in FR and PL and for 12, 12, 7, and 13 drugs respectively in EN, GER, NL, and SCO (Figure 2).

Seventy-two HTA recommendations for the 14 anticancer drugs were assigned to dichotomous outcomes. Based on our criteria for dichotomisation, we observed 52 (72%) positive outcomes and 20 (28%) negative outcomes (Figure 3). Of the 14 drugs only three received positive recommendations in all appropriate jurisdictions: afatinib in lung cancer (for a subpopulation in GER), dabrafenib in melanoma (not assessed by NL), enzalutamide in prostate cancer (not assessed by NL). The three jurisdictions (FR, GER, NL) that make recommendations on therapeutic value were positive about all

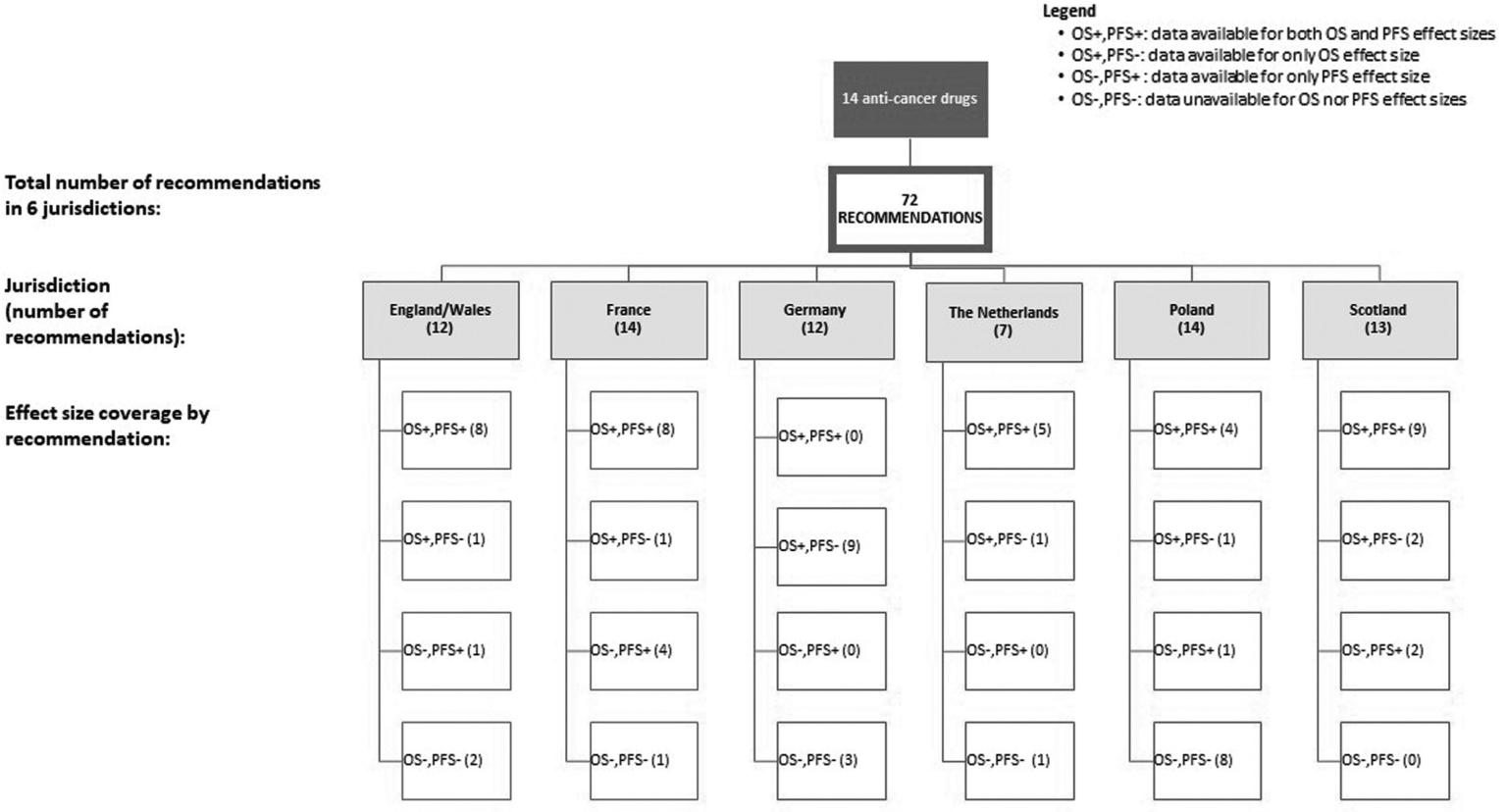


Figure 2. Number of HTA reports included per jurisdiction (with effect size coverage).

		Value added extent			Recommendation type		
Indication	international name (INN)	France/ HAS	Germany/ IQWiG	Netherlands/ ZIN	England/ NICE	Poland/ AOTMiT	Scotland/ SMC
Breast Cancer	Eribulin	(ASMR IV)	(2No AB proven)*	(ATV)	(Not recommended)	(negative)	(Not recommended)
	Pertuzumab	(ASMR III)	(Major AB)	(not assessed)	(not assessed)	(positive)	(Not recommended)
Lung Cancer	Afatinib	(ASMR V)	(Four advice)**	(not assessed)	(Recommended)	(positive)	(Accepted)
	Crizotinib	(ASMR III)	(No AB proven)	(not assessed)	(Not recommended)	(negative)	(Not recommended)
Melanoma	Dabrafenib	(ASMR V)	(No AB proven)	(not assessed)	(Recommended)	(positive)	(Accepted with restrictions)
	Ipilimumab	(ASMR IV)	(Considerable AB)	(ATV)	(Recommended)	(positive)	(Not recommended)
	Vemurafenib	(ASMR III)	(Considerable AB)	(ATV)	(Recommended)	(positive)	(Not recommended)
Others	Denosumab	ASMR IV & V*	(not assessed)	(STV)	Optimised	(negative)	(not assessed)
	Aflibercept	(ASMR V)	(Minor AB)	(not assessed)	(Not recommended)	(positive)	(Not recommended)
	Tegafur/ Gimeracil/ Oteracil	(Lesser benefit)	(not assessed)	(LTV)	(not assessed)	(negative)	(Accepted with restrictions)
	Axitinib	(ASMR IV)	(Considerable AB)	(not assessed)	(Optimised)	(positive)	(Not recommended)
Prostate Cancer	Abiraterone	(ASMR III)	(Considerable AB)	(STV)	(Recommended)	(positive)	(Not recommended)
	Cabazitaxel	(ASMR IV)	(Considerable & Minor AB)*	(ATV)	(Not recommended)	(negative)	(Not recommended)
	Enzalutamide	(ASMR III)	(Considerable & Major AB)*	(not assessed)	(Recommended)	(positive)	(Accepted with restrictions)

* Depending on the indication/ subpopulation. ** Depending on the indication/ subpopulation: Major AB, Minor AB, No AB proven and Lesser benefit

AB – Added Benefit, ATV – Added Therapeutic Value,
ASMR – Improvement of Medical Benefit,
LTV – Less Therapeutic Value, STV – Similar Therapeutic Value

Negative recommendation Positive recommendation

Figure 3. Dichotomous classification of HTA recommendations included in the study.

assessed drugs except one (tegafur/gimeracil/oteracil in gastric cancer; not assessed by GER). The other three jurisdictions (EN, PL, SCO) gave negative advice in 46% of recommendations (18 negative recommendations out of the total 39 recommendations made by these jurisdictions) and unanimously rejected three drugs (cabazitaxel in prostate cancer, crizotininb in lung cancer, eribulin in breast cancer).

Availability and size of OS and PFS effect magnitude in HTA reports

Both OS and PFS effect magnitude were available in 47% of the HTA reports (n=34) while 21% of the HTA reports (n=15) did not report OS or PFS data. The effect sizes reported in the HTA recommendations are presented in Table 1. For PL, a considerable number of the effect sizes are unknown due to partially censored documents. The OS gains reported in the HTA reports varied from no improvement/OS data not mature/median OS not reached (e.g., crizotinib in lung cancer, HR=1·02 or pertuzumab in breast cancer, HR = 0·64) to 10·4 months (afatinib in lung cancer, HR = 0·55, effect size reported only in GER for a subpopulation with epidermal growth factor receptor mutation Del19). The PFS gains ranged from 1·4 months (cabazitaxel in prostate cancer, HR = 0·74) to 6·1 months (pertuzumab in breast cancer, HR = 0·62) (Table 1). In general, the same effect magnitudes were included by different jurisdictions for the same medicine; however, when differences between effect magnitudes were reported, the reasons included: a different comparator (e.g., abiraterone, NL), different time of analysis (e.g., abiraterone, GER) or different (subpopulation (e.g., afatinib, GER). Figures 4 and 5 present respectively the OS and PFS gains and HR for all effect sizes that are reported in the HTA reports.

As the magnitude of clinical benefit should be considered in disease specific context, we analysed OS and PFS effect magnitude per therapeutic area. Figure 6 presents both OS and PFS effect magnitude for three new prostate cancer drugs. Figure 7 presents both OS and PFS effect magnitude three new melanoma drugs. Figure 8 presents both OS and PFS effect magnitude for two new drugs for breast cancer. Figure 9 presents both OS and PFS effect magnitude for two new drugs indicated for non-small cell lung cancer. For all indicated therapeutic areas HTA recommendations were presented for jurisdictions that assessed particular drugs.

In the HTA reports in which both OS gains and HR were available, 19 reports demonstrated an OS gain greater than 3 months (Fig. 4), while 26 reports reported an OS gain less than three months. Meanwhile the value of HR lower than 0·7 was quoted in 17 reports, and 28 reports reported a HR value equal or above 0·7.

Figure 10 and 11 presents OS and PFS effect size (respectively) versus dichotomous classification of HTA recommendations in EN, PL, and SCO. The effect magnitudes for OS/PFS gains are presented against the threshold of 3 months and HR equal to 0·7 (point estimate).

Table 1. Effect sizes reported in HTA recommendations

Indication	Medicine	End-Point	Comparator	Δmonths	Gain	HR	(CI), p-value	Jurisdiction
Breast cancer	Eribulin	OS	TPC	13.1 vs 10.6	2.5	0.809	(0.66-0.99), p=0.041	EN, NL, PL, SCO
				13.1 vs 10.6	2.5	0.809	(0.66-0.99)	FR
			capecitabine / vinorelbine	NA	NA	0.65	(0.46-0.91), p=0.013	GER
		PFS	TPC	3.7 vs 2.2	1.5	0.87	(0.71-1.05), p=0.137	NL
				3.7 vs 2.2	1.5	0.87	(0.71-1.05)	SCO
				3.7 vs 2.2	1.5	NA	p=0.137	EN
				3.7 vs 2.2	1.5	NA	NA	FR
				3.6 vs 2.2	1.4	0.76	(0.64-0.90), p=0,002	PL
	pertuzumab	OS	placebo	NR	NR	0.64	NA, p >0.0012	FR
				NR	NR	0.66	(0.52-0.84), p< 0.001	GER
				NR	NR	0.64	(0.47-0.88), p=0.005	SCO
				NA	NA	NA	NA	PL
		PFS	placebo	18.5 vs 12.4	6.1	0.62	(0.51-0.75), p<0.0001	FR
				18.5 vs 12.4	6.1	0.62	(0.51-0.75)	SCO
				NA	NA	NA	NA	PL
Lung cancer	Afatinib	OS	pemetrexed+ cisplatine [d]	NA	NA	42705,00	(0.73-1.72)	EN
				28.1 vs 28.2	NA	0.91	(0.66 to 1.25), p=0.55	SCO
				28 vs 28	NA	0.907	(0.66 to 1.25), p=0.55	FR
				31.57 vs. 21.13	10.4	0.55	(0.36-0.85),p=0.006	GER
				NA	NA	NA	NA	PL

Table 1. (continued)

Indication	Medicine	End-Point	Comparator	Δmonths	Gain	HR	(CI), p-value	Jurisdiction
		PFS	pemetrexed+ cisplatine	11.14 vs 6.9	4.2	0.58	(0.43-0.78)	EN
				11.1 vs 6.9	4.2	0.58	(0.43-0.78), p=0.0004	FR
				11.1 vs 6.9	4.2	0.58	(0.43-0.78), p=0.0001	SCO
				NA	NA	NA	NA	PL
	Crizotinib	OS	docetaxel or pemetrexed	20.3 vs 22.8	0	1.02	(0.68-1.54), p=0.54	EN, GER, PL
				NA	NA	1.02	(0.68-1.54), p=0.54	FR
				20.3 vs 22.8	0	1.02	(0.68-1.54)	SCO
		PFS	docetaxel or pemetrexed	7.7 vs. 3.0	4.7	0.49	(0.37 – 0.64), p<0.0001	EN, FR
				7.7 vs 3.0	4.7	0.49	(0.37 – 0.64)	SCO
				7.7 vs 3.0	4.7	0.49	(0.37 – 0.64), p<0.001	PL
Melanoma	dabrefenib	OS	vemurafenib[b]	NA	NA	1	(0.62-1.62)	EN
				NA	NA	NA	NA	PL
			dacarbazine	NR	NR	0.61	(0.25 – 1.48), NA	FR, GER
				18.2 vs. 15.6	2.6	0.76	(0.48-1.21)	SCO
		PFS	vemurafenib[b]	NA	NA	0.97	(0.59-1.60)	EN
				NA	NA	NA	NA	PL
			dacarbazine	5.1 vs 2.7	2.4	0.3	(0.18 – 0.51), p < 0.0001	FR
				6.9 vs. 2.7	4.2	0.37	(0.24-0.58), p<0.0001	SCO
	ipilimumab	OS	placebo	9.95 vs 6.44	3.5	0.68	(0.55-0.85), p<0.001	NL
				Δ3.5	3.5	0.68	(0.55-0.85), p=0.0004	EN
				10.0 vs. 6.4	3.6	0.68	(0.55-0.85), p<0.001	GER,SCO
				10.1 vs. 6.4	3.7	0.66	(0.51-0.87),NA	FR,PL

Table 1. (continued)

Indication	Medicine	End-Point	Comparator	Δmonths	Gain	HR	(CI), p-value	Jurisdiction
		PFS	placebo	NA	NA	NA	NA	EN, FR,SCO
				2.76 vs 2.76	0	0.81	(0.66-1.00), p=0.0464	NL
				NA	NA	0.64	NA	PL
	vemurafenib	OS	dacarbazine[c]	13.6 vs 10.3	3.3	0.76	(0.63-0.93), (p<0.01)	EN
				13.2 vs 9.6	3.6	0.62	(0.49-0.77), NA	FR, NL, SCO
				9.23 vs. 7.75	1.5	0.37	(0.26-0.55), p<0.001	GER
				NA	NA	0.37	(0.26-0.55),p<0.001	PL
		PFS	dacarbazine	5.32 vs 1.61	3.7	0.26	(0.20-0.33), p<0.0001	EN
				5.32 vs 1.61	3.7	0.26	(0.20-0.33)	NL, SCO
				5.3 vs 1.6	3.7	NA	NA	FR, PL
Others (Bone metastases from solid tumours)	denosumab	OS, PFS	zoledronic acid	NA	NA	NA	NA	EN, FR, NL, PL
Others (Colo-rectal cancer)	aflibercept	OS	placebo	13.5 vs 12.1	1.4	0.82	(0.71-0.93), p=0.0032	EN, FR, GER, SCO
				NA	NA	NA	NA	PL
		PFS	placebo	6.9 vs 4.67	2.2	0.758	(0.66-0.87), p<0.0001	SCO
				6.9 vs 4.67	2.2	0.758	(0.66-0.87)	EN
				6.9 vs 4.67	2.2	0.758	(0.57-0.99), p=0.00007	FR
				NA	NA	NA	NA	PL
Others (Gastric cancer)	tegafur/gime-racil/oteracil	OS	5-fluorouracil	8.6 vs 7.9	0.7	0.92	(0.80-1.05), NA	FR, SCO
				NA	NA	0.92	(0.80-1.05), NA	PL

Table 1. (continued)

Indication	Medicine	End-Point	Comparator	Δmonths	Gain	HR	(CI), p-value	Jurisdiction
			triplet therapy[b]	8.6 vs 9.9	0	NA	NA	NL
		PFS	5-fluor	4.8 vs 5.5	0	0.99	(0.86-1.14),	FR
				4.8 vs 5.5	0	NA	NA	SCO
				NA	NA	0.99	(0.86-1.14),	PL
			triplet therapy[b]	NA	NA	NA	NA	NL
Others (Renal cell carcinoma)	Axitinib	OS	sorafenib	20.1 vs 19.2	0.9	0.97	(0.800-1.174), p=0,374	EN, PL
				20.1 vs 19.2	0.9	0.97	(0.800-1.174)	FR, SCO
				15.9 vs. 12.2	3.7	0.744	(0.423-1.307), p=0.304	GER
		PFS	sorafenib	6.7 vs 4.7	2	0.67	(0.54-0.81), p<0.0001	EN, FR, PL
				6.7 vs 5	1.7	0.66	(0.54-0.81), p<0.0001	SCO
Prostate cancer	abiraterone[a]	OS	placebo	14.8 vs 10.9	3.9	0.65	(0.54-0.77), p<0.001	SCO
				14.8 vs 10.9	3.9	0.65	(0.54-0.77)	EN
				14.8 vs 10.9	3.9	NA	NA	FR
				15.8 vs 11.2[a]	4.6	0,74	(0.64-0.86), p< 0.001	GER
				NA	NA	NA	NA	PL
			cabazitaxel[b]	15.8 vs 15.1	0.7	NA	NA	NL
		PFS	placebo	5.62 vs 3.62	2	0.67	(0.59 to 0.78), p<0.0001	EN
				5.6 vs 3.6	2	NA	NA	FR
				NA	NA	NA	NA	PL
			cabazitaxel[b]	NA	NA	NA	NA	NL
	cabazitaxel	OS	mitoxantron	15.1 vs 12.7	2.4	0.7	(0.59-0.83), p<0.0001	EN, GER, NL
				15.1 vs 12.7	2.4	0.7	(0.59-0.83)	FR, SCO

Table 1. (continued)

Indication	Medicine	End-Point	Comparator	Δmonths	Gain	HR	(CI), p-value	Jurisdiction
				15.1 vs 12.7	2.4	NA	NA	PL
		PFS	mitoxantron	2.8 vs 1.4	1.4	0.74	(0.64 – 0.86), p<0.0001	EN, NL
				2.8 vs 1.4	1.4	0.74	(0.64 – 0.86)	FR, SCO
				2.8 vs 1.4	1.4	NA	NA	PL
	enzalutamide	OS	placebo	18.4 vs 13.6	4.8	0.631	(0.531-0.754) p<0.001	EN, GER
				18.4 vs 13.6	4.8	0.631	(0.531-0.754) p<0.0001	FR
				18.4 vs 13.6	4.8	0.63	(0.531-0.75)	SCO
			abiraterone	NA	NA	0.91	(0.73-1.13), NA	PL
		PFS	placebo	8.3 vs 2.9	5.4	0.404	(0.35 to 0.47), p<0.001	EN, SCO
				8.3 vs 3	5.3	NA	p<0.0001	FR
			abraiterone	NA	NA	NA	NA	PL

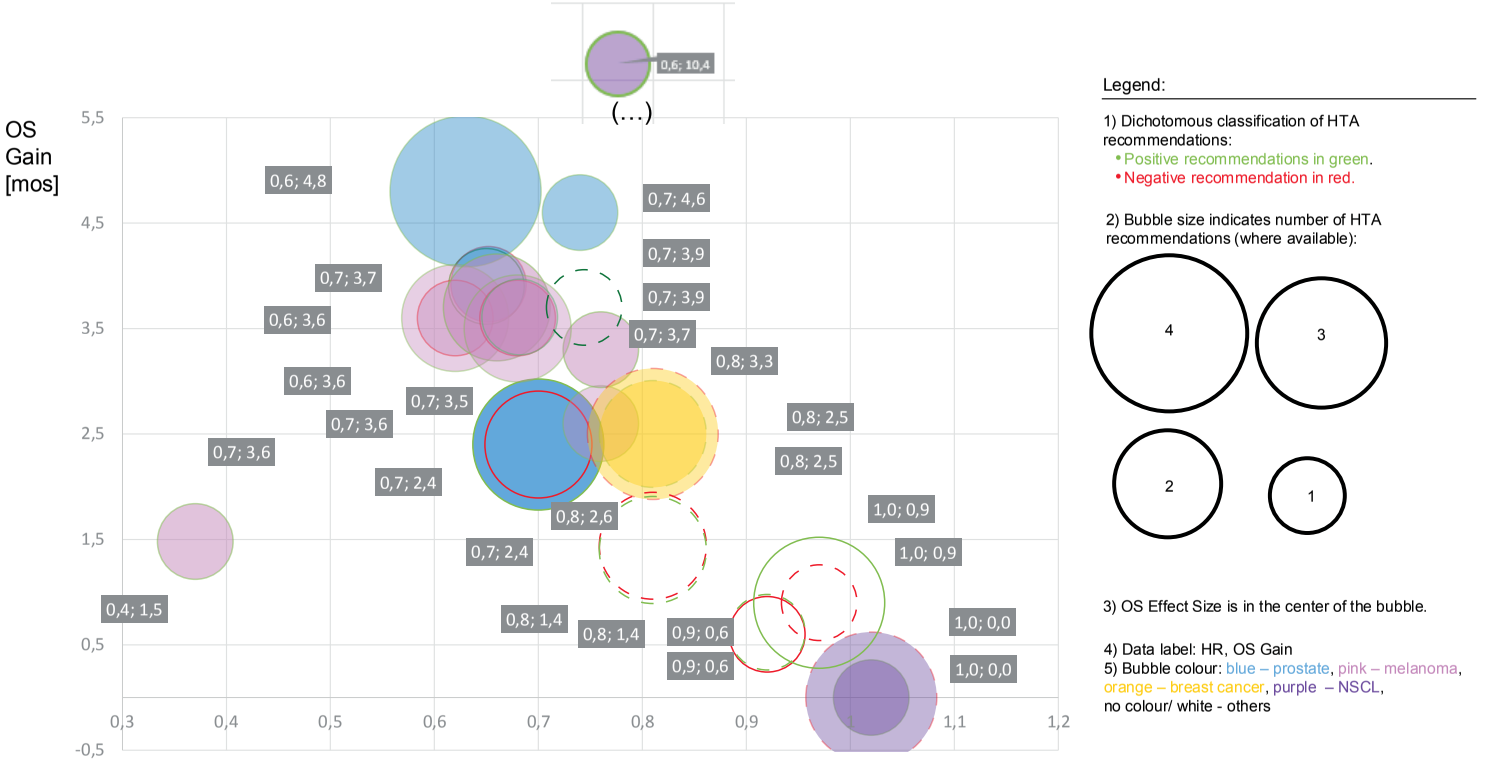
Abbreviations: NA=not available; NR=not reached; TPC= treatment of physician's choice; EN=England/Wales; GER=Germany; FR=France; NL=Netherlands; PL=Poland; SCO=Scotland.

[a] For Poland the comparator was placebo + prednis(ol)on but the effect size is unknown due to partially blinded document. For Germany the data is based on an updated analysis (cut-off of 20 September 2010).

[b] indirect comparison

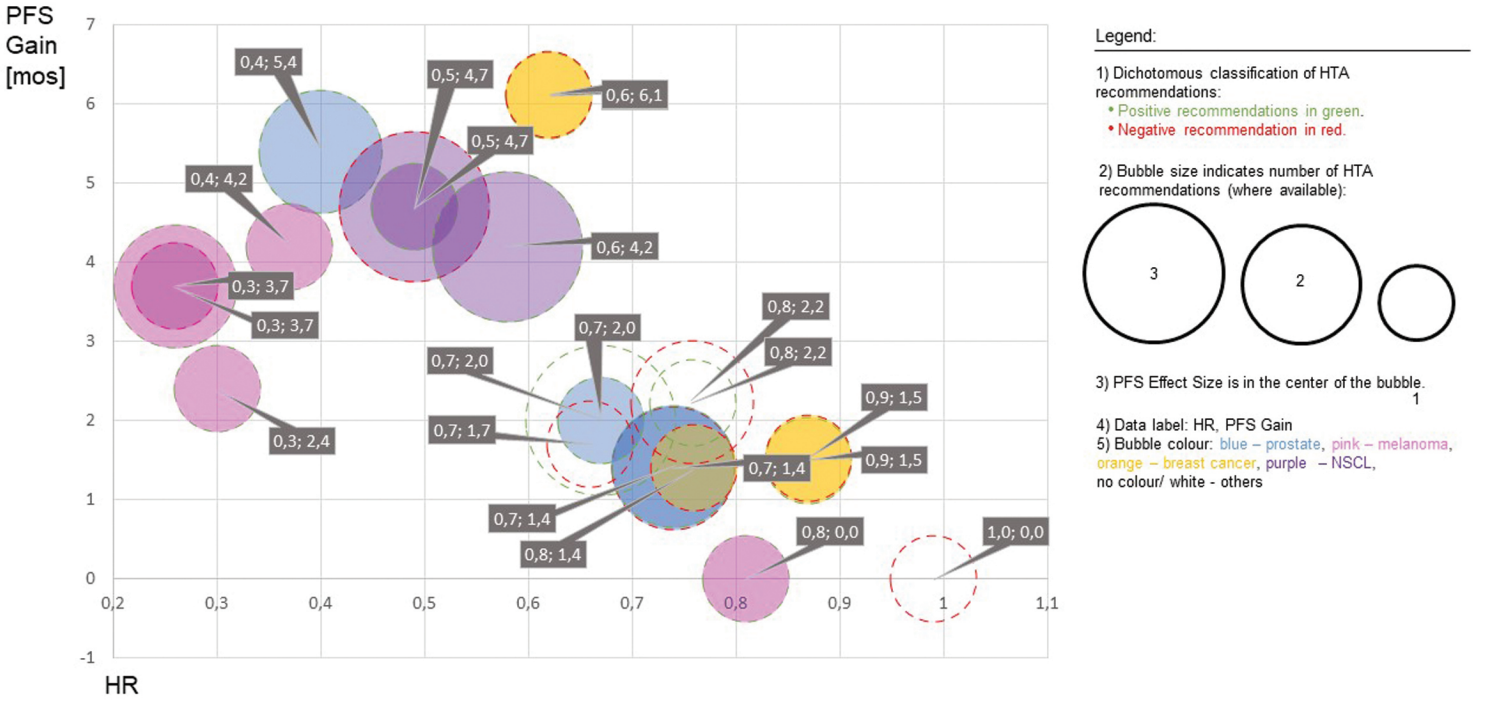
[c] 4 data cut offs are part of this study (BRIM3): the first data cut-off (30 December 2010), the second data cut-off (31 March 2011), third data cut-off (03 October 2011) and the fourth data cut-off, post-hoc (1 February 2012). For England/ Wales the OS data refer to the latter. For France, Netherlands and Scotland reference is made to the October 2011 cut-off (with censoring of cross-over patients, which was permitted after the first data cut-off), while for Germany the December 2010 cut-off (without censoring of patients who switched treatment).

[d] there were 3 data cut offs for this study (LUX-Lung 3): the first data cut-off (9 February 2012), the second data cut-off (21 January 2013) and the third data cut-off (14 November 2013). The results refer to the second cut-off. For France and Scotland OS measures the general population (Eastern Co-operative Oncology Group Performance Status ECOG PS 0 to 1) while for Germany the subpopulation ECOG PS 0 to 1 with the Epidermal Growth Factor Receptor (EGFR) mutation Del19. IQWIG provided four recommendations for afatinib. We selected the recommendation for non-pretreated patients with (ECOG PS) 0 to 1 and Epidermal Growth Factor Receptor (EGFR) mutation Del19 as the other 3 recommendations applied to narrower patient populations: 1.non-pretreated patients with ECOG PS 0 to 1 and EGFR mutation L858R below 65 years old and 2. over 65 years old and 3.non-pretreated patients with ECOG PS 0 to 1 and other EGFR mutations.



[Eribulin, Pertuzumab, Afatinib, Crizotinib, Dabrafenib, Ipilimumab, Vemurafenib, Denosumab, Aflibercept, Tegafur/ Gimeracil/ Oteracil, Axitinib, Abiraterone, Cabazitaxel, Enzalutamide]

Figure 4. Overall survival gain and hazard ratio included in HTA recommendations in six European jurisdictions.



[Eribulin, Pertuzumab, Afatinib, Crizotinib, Dabrafenib, Ipilimumab, Vemurafenib, Denosumab, Aflibercept, Tegafur/ Gimeracil/ Oteracil, Axitinib, Abiraterone, Cabazitaxel, Enzalutamide]

Figure 5. Progression-free survival gain and hazard ratio included in HTA recommendations in six European jurisdictions.

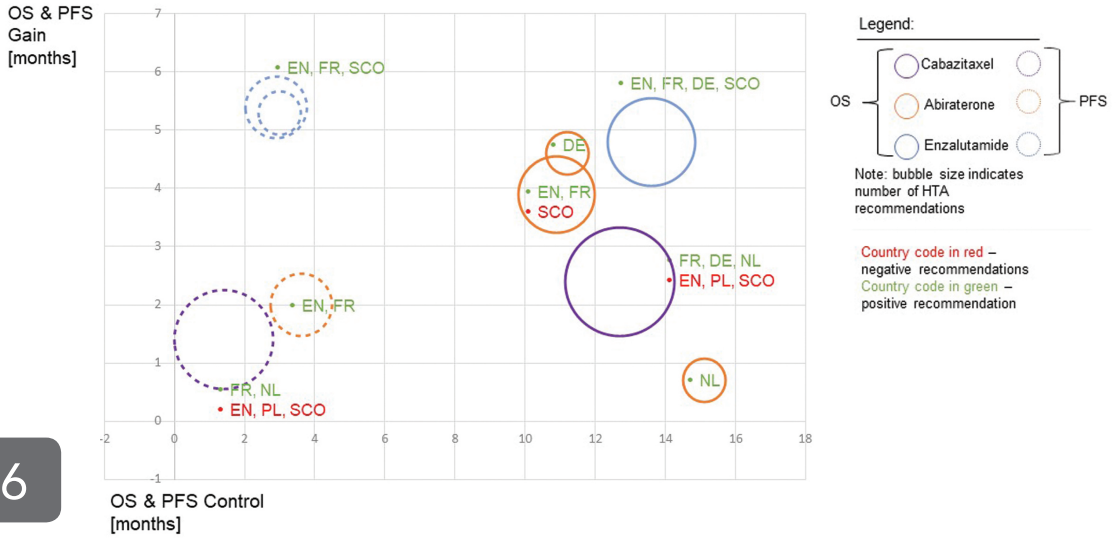


Figure 6. Effect Size vs. Dichotomous Classification of HTA Recommendations in 6 EU jurisdictions (3 prostate drugs).

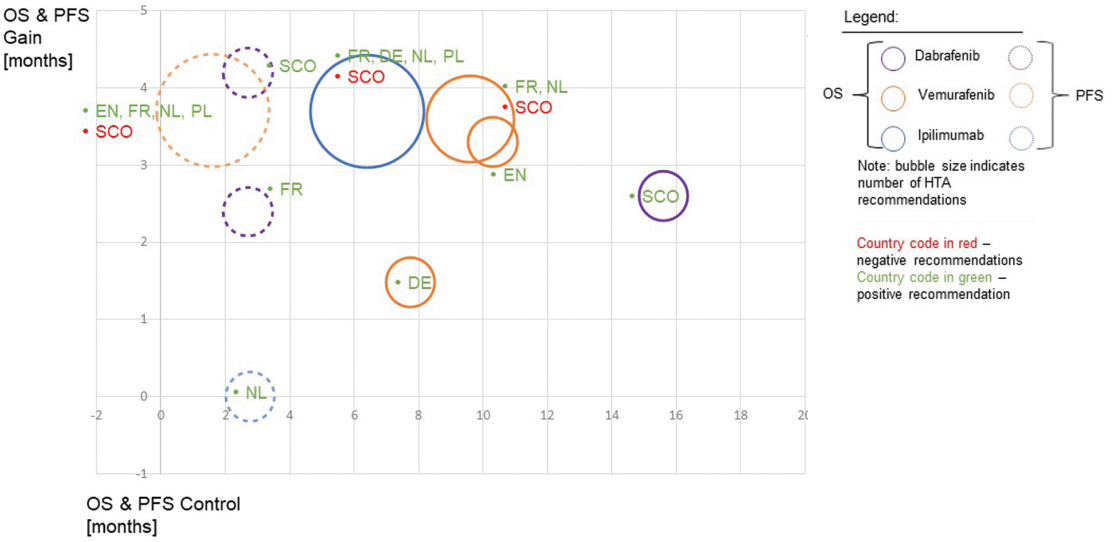


Figure 7. Effect Size vs. Dichotomous Classification of HTA Recommendations in 6 EU jurisdictions (3 melanoma drugs).

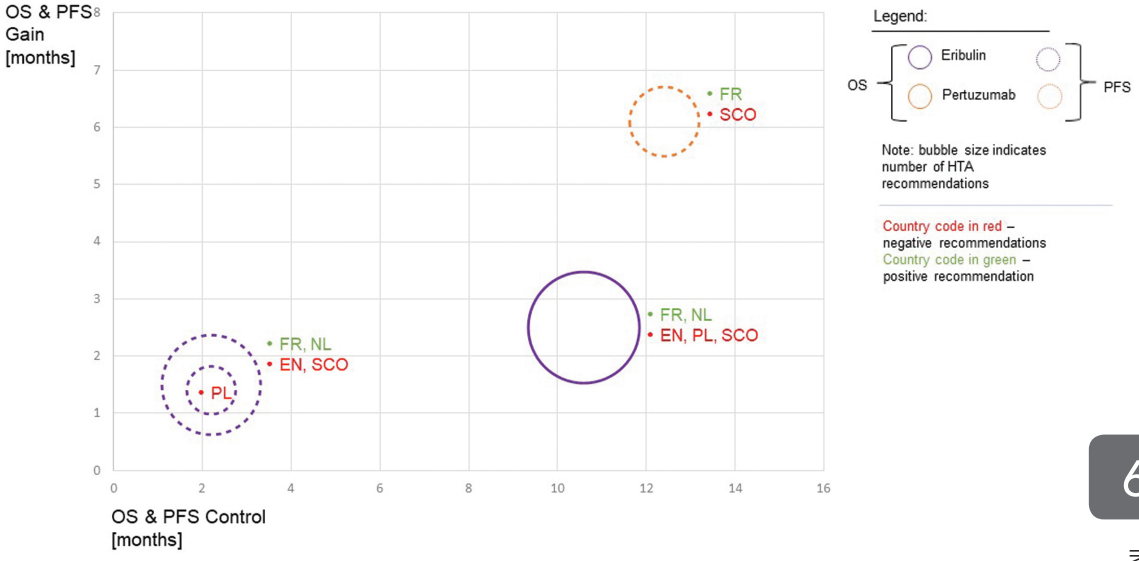


Figure 8. Effect Size vs. Dichotomous Classification of HTA Recommendations in 6 EU jurisdictions (2 breast cancer drugs).

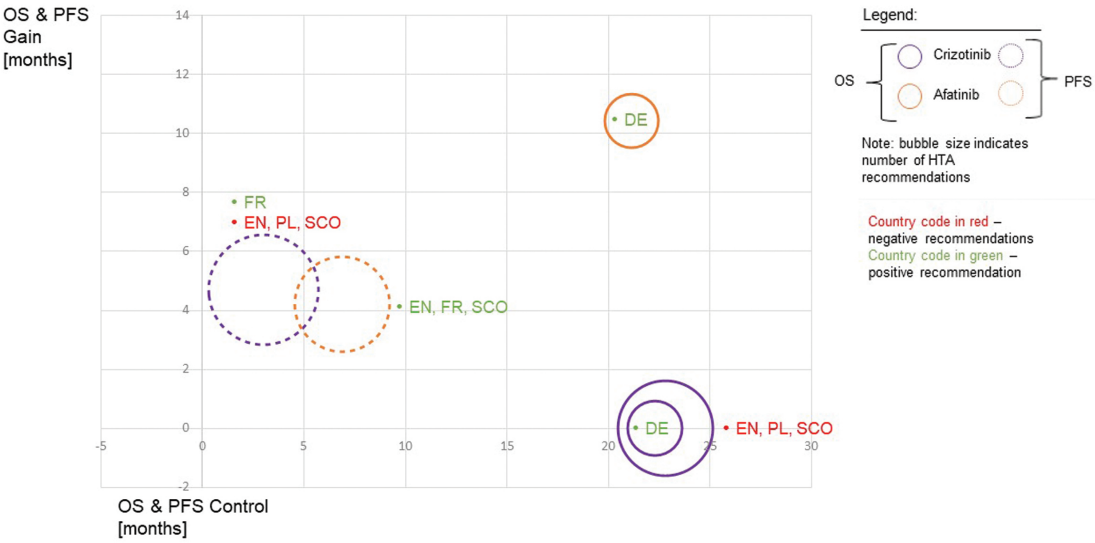
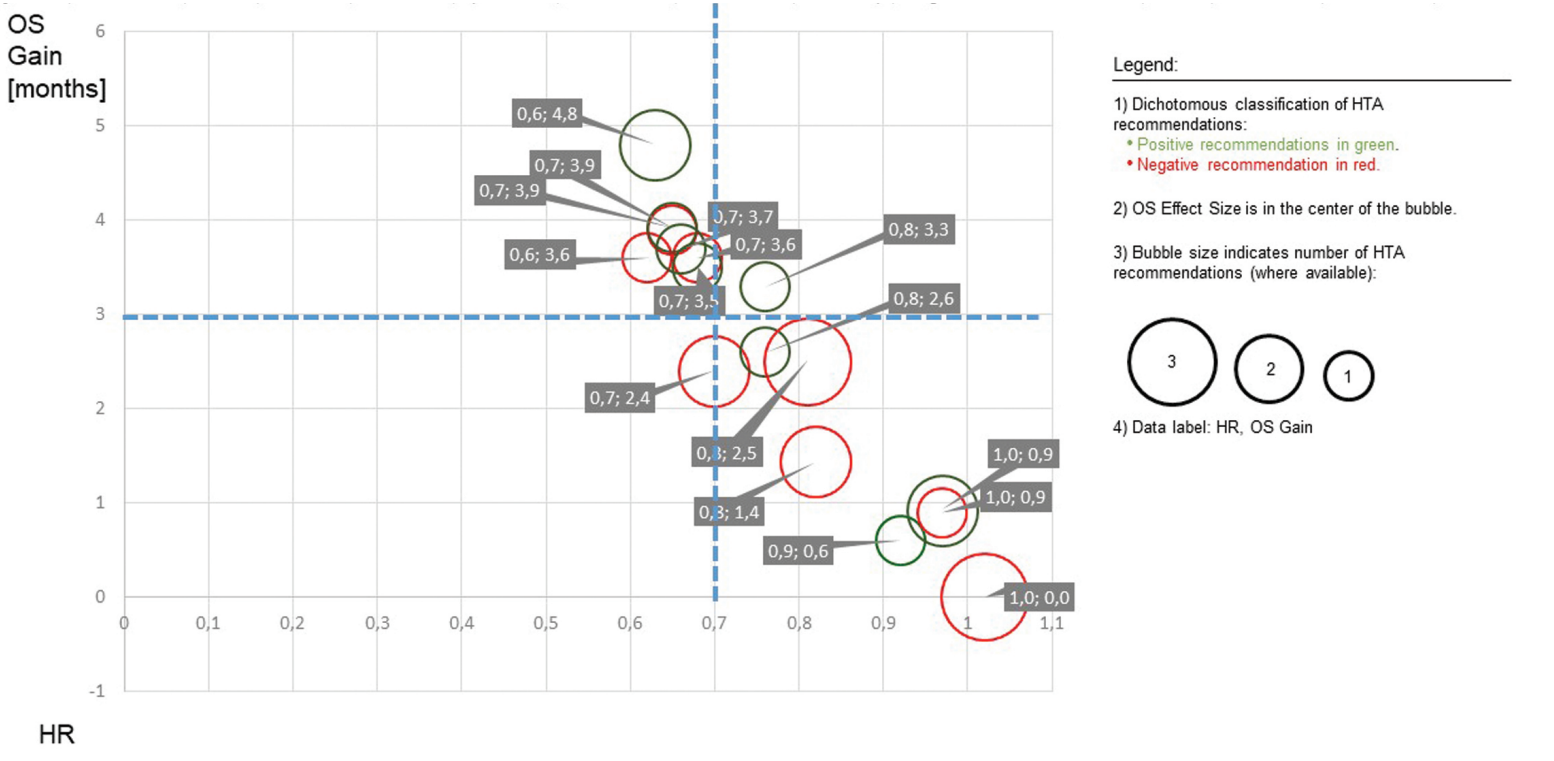
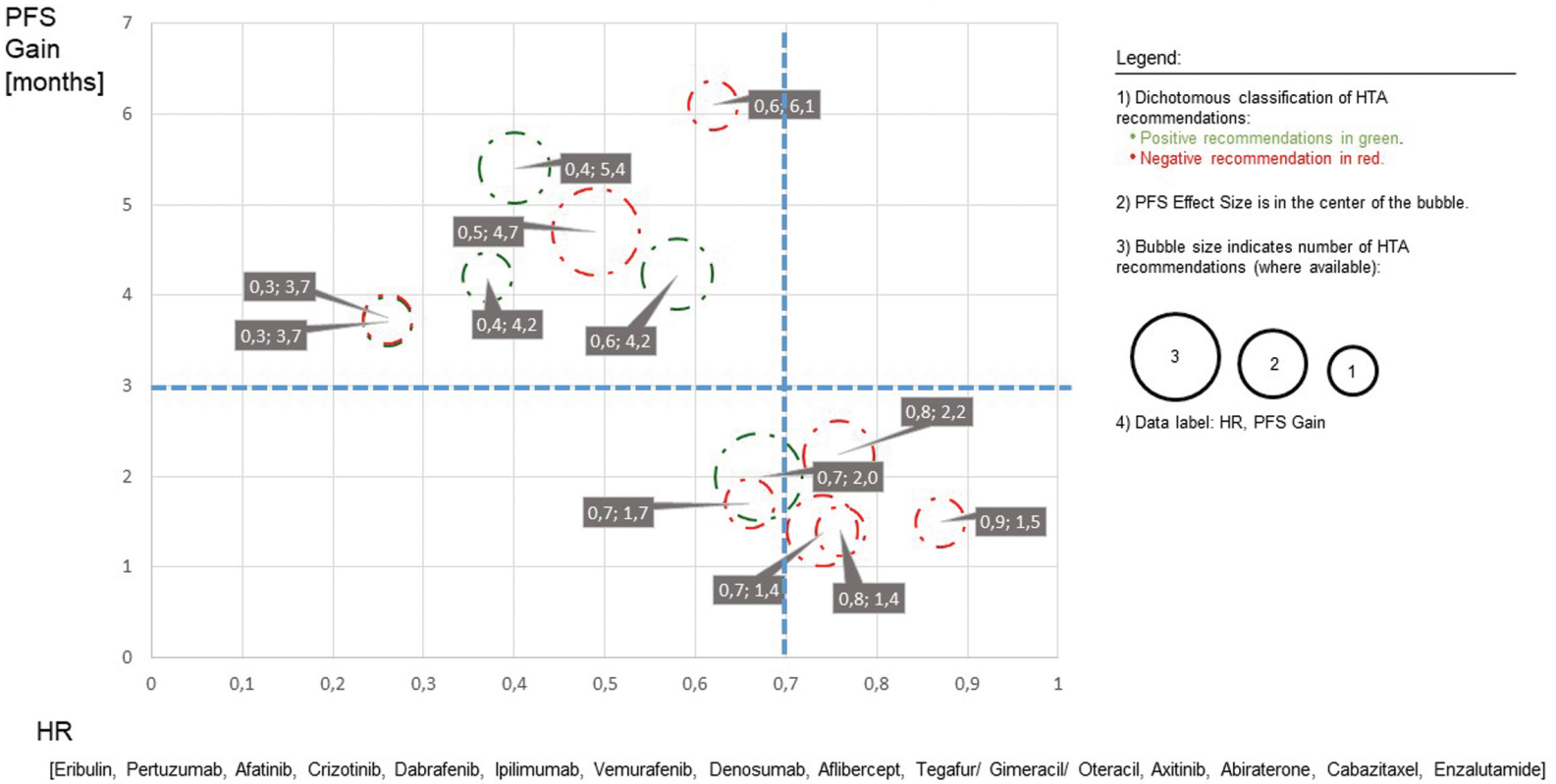


Figure 9. Effect Size vs. Dichotomous Classification of HTA Recommendations in 6 EU jurisdictions (2 non-small cell lung cancer drugs).



[Eribulin, Pertuzumab, Afatinib, Crizotinib, Dabrafenib, Ipilimumab, Vemurafenib, Denosumab, Aflibercept, Tegafur/ Gimeracil/ Oteracil, Axitinib, Abiraterone, Cabazitaxel, Enzalutamide]

Figure 10. Overall survival effect size versus dichotomous classification of HTA recommendations in England, Poland & Scotland- all drugs.



[Eribulin, Pertuzumab, Afatinib, Crizotinib, Dabrafenib, Ipilimumab, Vemurafenib, Denosumab, Aflibercept, Tegafur/ Gimeracil/ Oteracil, Axitinib, Abiraterone, Cabazitaxel, Enzalutamide]

Figure 11. Progression-free survival effect size versus dichotomous classification of HTA recommendations in England, Poland & Scotland- all drugs.

DISCUSSION

Our results suggest that HTA agencies vary in their approach in assessing the clinical value of new anticancer drugs. For two out of the three jurisdictions that provide recommendations based on therapeutic value, only one drug received a negative recommendation.

One of our findings is the limited availability of the data on OS and PFS effect magnitude in public HTA reports. The need for increased transparency of decision-making processes for drug reimbursement has been the topic of many discussions(11,17) the increased availability of the data on OS/PFS effect magnitude in the public HTA reports could provide better understanding of these processes.

The lack of the quality of life data for a substantial proportion of new drugs could potentially also impact the differences in HTA recommendations. However the national HTA guidelines recognize the importance of health-related quality of life in determining the value of new drugs, in fact it is not well reflected in current assessments (18).

Our results also show that some medicines with similar magnitude of OS and/or PFS effect have different HTA recommendations across the various jurisdictions. In some cases, this was related to the cost-effectiveness of the drugs. However, for eribulin in breast cancer, crizotinib in lung cancer or cabazitaxel in prostate cancer, the effect magnitude (clinical relevance) was rated differently between countries.

The HTA guidelines from the jurisdictions in our study indicate a general preference for clinically relevant endpoints and related to morbidity, mortality, and QoL. There is limited information as to what is considered a relevant effect gain for OS and PFS. Only NICE and SMC state that in order for a medicine to qualify as "life-extending treatment at the end of life" it should offer an OS gain of at least 3 months, compared with current National Health Service treatment. Hartmann and colleagues have proven the existence of an implicit threshold for HR equal to 0·7 and also OS gain of 3 months for recommendations on considerable added benefit for new anticancer drugs in Germany.(15) Based on our results, a positive recommendation seems more likely when the effect magnitude is above 3 months and HR is less than 0·7. But as explained above, other factors such as cost effectiveness may play a role.

In their proposed ESMO-Magnitude of Clinical Benefit Scale, Cherny and associates recommend the use of the lower end of 95% CI at the level of 0·65 (or below) for HR as the threshold for meaningful efficacy.(4) This approach has been methodologically challenged by some researchers, as the CI depends on the number of endpoints observed and can narrow as the trial data mature.(19) In addition, using the lower end of CI as the threshold can be an optimistic evaluation.(20)

Previous research indicates regulatory agencies use efficacy thresholds. (21) However, because of the procedures used by Committee for Human Medicinal Products (CHMP) at EMA even if there is divergence between members indicating a lack of clear threshold CHMP reaches consensus in its opinions by voting which is obviously not the

case in the context of HTA. However, some researchers argue that anticancer drugs are too easily approved by regulators,(22) especially if they present minor incremental advances.(23) Therefore, clinical oncologists have opted to raise the bar for new anticancer medicines and assess their value.(9) Even thresholds for superiority trials in advanced solid tumours have been suggested and defined as minimum clinically meaningful outcome.(24) The latter concept was built upon OS as the primary indicator of patient benefit (four OS-related parameters are used: HR, gains in median OS, proportional and absolute increases at long-term OS), and therefore required mature OS data, which was not the case for all drugs included in our study.

LIMITATIONS

In order to allow comparison across jurisdictions we have simplified the complexities of HTA processes in the selected jurisdictions. Most importantly, we simplified HTA recommendations into a dichotomous classification of HTA recommendations. Different dichotomisation may lead to a different outcome in this assessment. Patients' access depends on details of the pricing negotiations and the national settings for funding of medicines that are used in hospitals, which are not within the scope of this study.

In order to allow clear comparisons between the countries only one (sub)population, one comparator and one effect magnitude were selected per HTA recommendation, whereas in some instances the decision-making process was more complex.

We have looked at the effect magnitudes presented in the clinical sections of the HTA reports; however, different effect magnitudes may have been included in the cost-effectiveness analysis for EN, SCO, and PL. Further research would help to understand the impact of effect magnitudes on cost-effectiveness analysis. Clinical considerations are generally granted priority over cost effectiveness across jurisdictions as well as when joint relative assessments for pharmaceuticals are proposed at the European level: EUnetHTA joint assessments of pharmaceuticals currently only consider the clinical value of medicines.(25,26)

FUNDING

This work was supported by the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands and the Centre for Innovation in Regulatory Science, London, UK.

CONFLICT OF INTEREST STATEMENT

Prof Anthonius de Boer is the Chairman of the Drug Committee of the National Health Care Institute (ZIN) in the Netherlands. Several assessment reports evaluated in this manuscript were handled by this committee.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
2. Abola MV, Prasad V. The use of superlatives in cancer research. JAMA Oncol. 2016;2:139–41.
3. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics-the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. JAMA Otolaryngol Head Neck Surg. 2014;140:1225–36.
4. Cherny NI, Sullivan R, Dafni U et al. 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. 2015;26:1547–73.
5. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology Statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol. 2015;33:2563–77.
6. Kleijnen S, Lipska I, Leonardo Alves Tet al. Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries. Ann Oncol. 2016;27:1768–75.
7. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol. 2012;30:1030–33.
8. Prasad V, Kim C, Burotto M, Vandross A. The strength of association between surrogate end points and survival in oncology: A systematic review of trial-level meta-analyses. JAMA Intern Med. 2015;175:1389–98.
9. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32:1277–80.
10. Krzakowski M, Wysocki P, Jassem J, Krzemieniecki K, Potemski P, Zyśk R. The algorithm assessing the value of new anticancer drugs — the proposal of the Polish Society of Clinical Oncology and Polish Oncological Society. Oncol Clin Prac.2015;11:9 –15 .
11. Cleemput I, Franken M, Koopmanschap M, le Polain M. European drug reimbursement systems' legitimacy: five-country comparison and policy tool. Int J Technol Assess Health Care. 2012;28:358–66.
12. Henshall C, Mardhani-Bayne L, Frønsdal KB, Klemp M. Interactions between health technology assessment, coverage, and regulatory processes: Emerging issues, goals, and opportunities. Int J Technol Assess Health Care. 2011;27:253–60.
13. Lipska I, Hoekman J, McAuslane N, Leufkens H, Hovels AM. Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? Clin Pharmacol Ther. 2015;98:489–91.
14. EUnetHTA. Guidelines on Surrogate endpoints. 2013. Available at http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Surrogate%20Endpoints.pdf Accessed Septebmer 15,2016.
15. Hartmann M. The ESMO magnitude of clinical benefit scaling tool: from theory to practice. Ann Oncol. 2015;26:2357–8.
16. Hartmann M, Mayer-Nicolai C, Pfaff O. Approval probabilities and regulatory review patterns for anticancer drugs in the European Union. Crit Rev Oncol Hematol. 2013;87(2):112-21.
17. Fojo T, Lo AW. Price, value, and the cost of cancer drugs. Lancet Oncol. 2016;17:3–5.
18. Kleijnen S, Leonardo Alves T, Meijboom K, Lipska I, De Boer A, Leufkens HG, et al. The impact of quality-of-life data in relative effectiveness assessments of new anti-cancer drugs in European countries. Qual Life Res. 2017.
19. Muhonen T, Joensuu H, Pfeiffer P. Comment on ESMO Magnitude of Clinical Benefit Scale. Ann Oncol. 2015;26:2504.

20. Cherny NI, Sullivan R, Dafni U, et al. Reply to the letter to the editor 'The ESMO Magnitude of Clinical Benefit Scaling Tool: from theory to practice' by Hartmann and the letter 'Comment on ESMO Magnitude of Clinical Benefit Scale' by Muhonen et al. Ann Oncol. 2016;27:203–5.
21. Hartmann M, Mayer-Nicolai C, Pfaff O. Approval probabilities and regulatory review patterns for anticancer drugs in the European Union. Crit Rev Oncol Hematol. 2013;87:112–21.
22. Light DW, Lexchin J. Why do cancer drugs get such an easy ride? BMJ. 2015;350:h2068.
23. Sobrero A, Bruzzi P. Incremental advance or seismic shift? The need to raise the bar of efficacy for drug approval. J Clin Oncol. 2009;27:5868–73.
24. Sobrero AF, Pastorino A, Sargent DJ, Bruzzi P. Raising the bar for antineoplastic agents: how to choose threshold values for superiority trials in advanced solid tumors. Clin Cancer Res. 2015;21:1036–43.
25. Kleijnen S, George E, Goulden S, et al. Relative effectiveness assessment of pharmaceuticals: similarities and differences in 29 jurisdictions. Value Health. 2012;15:954–60.
26. Kleijnen S, Toenders W, de Groot F, et al. European collaboration on relative effectiveness assessments: What is needed to be successful? Health Policy. 2015;119:569–76.

part C

FOCUS ON POLAND

chapter 7

A DECADE OF HEALTH TECHNOLOGY ASSESSMENT IN POLAND

Iga Lipska
Neil McAuslane
Hubert G.M. Leufkens
Anke M. Hövels

Published in: Int J Technol Assess Health Care. 2017;33(3):1-8

ABSTRACT

Objectives

The objective is to illustrate and provide a better understanding of the role of HTA processes in decision making for drug reimbursement in Poland and how this approach could be considered by other countries of limited resources.

Methods

We analyzed the evolution of the HTA system and processes in Poland over the last decade and current developments based on publicly available information.

Results

The role of HTA in drug-reimbursement process in Poland has increased substantially over the recent decade, starting in 2005 with the formation the Agency for Health Technology Assessment and Tariff System (AOTMiT). The key success factors in this development were effective capacity building based on the use of international expertise, the implementation of transparent criteria into the drug reimbursement processes and the selective approach to the adoption of innovative medicines based on the cost-effectiveness threshold among other criteria.

Conclusions

While Poland is regarded as a leader in Central and Eastern Europe, there is room for improvement, especially with regard to the quality of HTA processes and the consistency of HTA guidelines with reimbursement law. In the "pragmatic" HTA model use by AOTMiT, the pharmaceutical company is responsible for the preparation of a reimbursement dossier of good quality in line with HTA guidelines while the assessment team in AOTMiT is responsible for critical review of that dossier. Adoption of this model may be considered by other countries with limited resources to balance differing priorities and ensure transparent and objective access to medicines for patients who need them.

BACKGROUND

The importance of health technology assessment (HTA) in the decision-making processes for publicly financed health services has increased in recent years (1). A substantial number of jurisdictions worldwide have implemented HTA, especially as it applies to transparent processes for drug reimbursement (2). There is an impressive tradition of HTA in Europe, starting with HTA activities in Sweden in the 1970s and quickly followed by the development of formal and informal programs in other European countries (3).

Central and Eastern European countries have followed a similar route of implementing HTA processes into decision making (4) especially when they accessed into the EU and were obliged to implement Council Directive 89/105/EEC of 1988 otherwise known as "Transparency Directive" which relates to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems. Poland belonged to this group of countries that implemented HTA in its healthcare system and has been even perceived as a leader among new member states in the field (5). The remaining CEE countries are much smaller and face more limitations in full HTA implementation because of correspondingly fewer resources and larger difficulties in building large capacities for HTA (6).

As the largest country in the region of Central and Eastern Europe with 38.5 million inhabitants as compared to the second largest country in the region which is the Czech Republic with the population of 10.5 million people (7), Poland has a unique role among Western and Eastern European countries. On the one hand, the Polish government is dedicated to making transparent decisions that result in the best allocation of financial resources and to allowing timely patient access to innovative medicines, on the other hand, the country's financial resources are very limited, its pharmaceutical market is mainly generic driven, and there is not always transparent pressure on decision makers from an innovative pharmaceutical industry (8). As a result, Poland has evolved a balanced, data driven system that could be utilized as an example for countries looking to establish HTA within their country.

From an absolute lack of the utilization of and reimbursement for innovative medicines (6) Poland has evolved into a late adopter of potentially valuable therapies through the implementation of an HTA process that employs a selective approach based on the clinical value of medicines as well as on cost-effectiveness criteria. A cost to quality-adjusted life year (QALY) threshold has been embedded in Polish legislation that is equal to the tripled gross domestic product (GDP) value per capita or approximately 130,002 zloty (30,500 Euros) (9). In addition, HTA evaluations have steadily increased since the inception of the Polish HTA agency in 2005 and its formal implementation in 2006. Figure 1 shows this progression over the decade 2006-2016.

The objective of this paper is to illustrate and provide a better understanding of the role of HTA processes in decision making for drug reimbursement in Poland

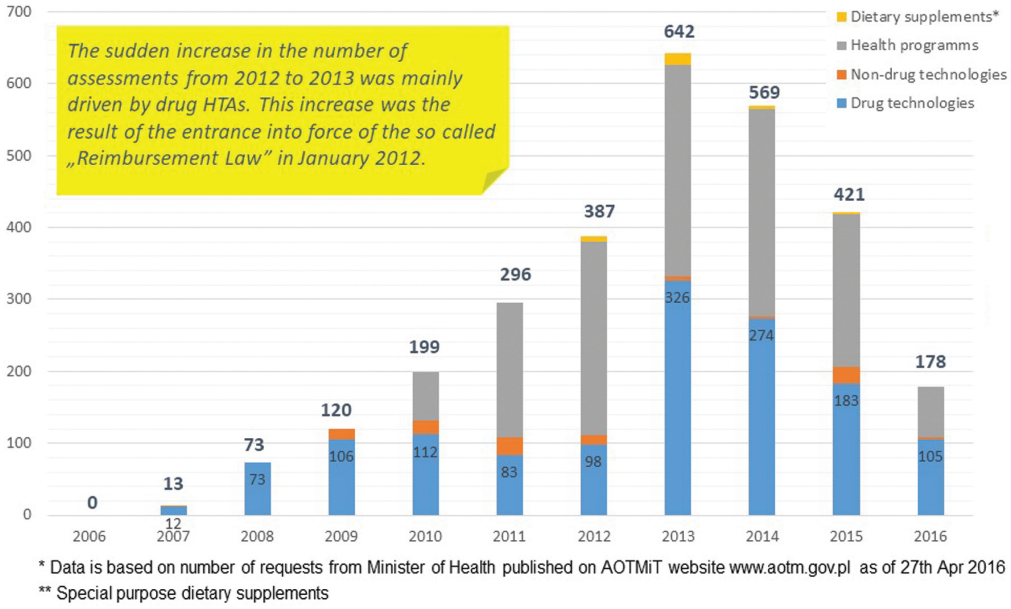


Figure 1. Assessments by AOTMiT, 2006-2016: Drug technologies, non-drug technologies, health programs and dietary supplements.

and how this approach could be considered by other countries of limited resources taking into account the historical perspective and the evolution of the HTA system and processes in Poland over the last decade and current developments.

The rationale for the establishment of an HTA agency in Poland

In the first decade of the twenty-first century, pricing and reimbursement decisions for new medicines were issued in an untimely manner in Poland, resulting in a delay of several years for listing decisions for some drugs. In addition, there was no homogeneity in the rationale for negative ministerial decisions and no appeal mechanisms were in place. Therefore, when Poland accessed into the EU in 2004, there was substantial political pressure from the EU Commission to implement a transparent criteria for drug reimbursement and to allow timely patient access to innovative medicines. After becoming an EU member, Poland adopted the EU *acquis communautaire*, or the accumulated body of European law, as part of the Polish legal order, including the previously cited "Transparency Directive." The three main guarantees of the Directive regarding individual pricing and reimbursement decisions are that:

- *decisions must be made within a specific timeframe (90/180 days);*
- *decisions must be communicated to the applicant and contain a statement of reasons based on objective and verifiable criteria; and*
- *decisions must be open to judicial appeal at national level (10) .*

The Polish HTA Agency, Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT; the Agency for Health Technology Assessment and Tariff System), was created formally in 2005 and in operation by 2006. The need to implement Council Directive 89/105/EEC of 1988 otherwise known as "Transparency Directive" played an important role in decision to establish the agency (11). AOTMiT, first known as the Agency for Health Technology Assessment (AOTM), was established through an Ordinance of the Minister of Health in 2005 and began to function in 2006 as an advisory body to the Minister of Health.

In 2009, the AOTMiT position was reinforced with the revision of the "Basket Law" regarding healthcare services financed from public funds, and HTA was officially anchored in the Polish pricing and reimbursement process. The pragmatic HTA model was affirmed in which AOTMiT is mainly the assessor of reports for innovative drugs however may also serve as a producer of reports for medical procedures. In parallel, agency funding increased with the introduction of fees for the assessment and appraisal of HTA dossiers submitted by pharmaceutical companies for innovative drugs.

Over the past decade, AOTMiT has mainly assessed drug technologies and several non-drug technologies. Since 2009, the evaluation of health programs developed by regional governments has become a separate, substantial task performed by a dedicated team of internal and external analysts. The next milestone for the HTA process in Poland was the entrance of the Reimbursement Law in 2012 on the reimbursement of medicinal products, special purpose dietary supplements and medical devices (12). At this time, Poland had managed to fully implement the Transparency Directive to its legal system. In 2015, the agency competencies were broadened, adding the valuation of health services, otherwise known as the "tariff system" (taryfikacja) and the agency changed its name from AOTM to AOTMiT. Key milestones in the evolution of AOTMiT are illustrated in Figure 2.

Capacity building in the field of HTA

One of the critical activities to increase the transparency and competence of the Polish pricing and reimbursement system was the twinning project between Poland's AOTMiT and Ministry of Health and France's Haute Autorité de Santé (HAS) and Ministry of Health, which included substantial participation from international experts. This project, took place from October 2006 through April 2008 (13). The aim of the project was to enhance the transparency and competence of the Polish drug reimbursement decision-making process (14).

The twinning project produced workshops and conferences. Specific proposals were put forth for a transparent and clear pricing and reimbursement process in Poland including a set of recommendations regarding the role of AOTMiT and MoH, separate tracks for generic and innovative drugs as well as guidance for the applicants based on HTA guidelines. These proposals were implemented to the Polish legal system by means of amending the Basket Law regarding healthcare services financed from public funds in June 2009 (13) and later on the implementation of Reimbursement Law in 2012.

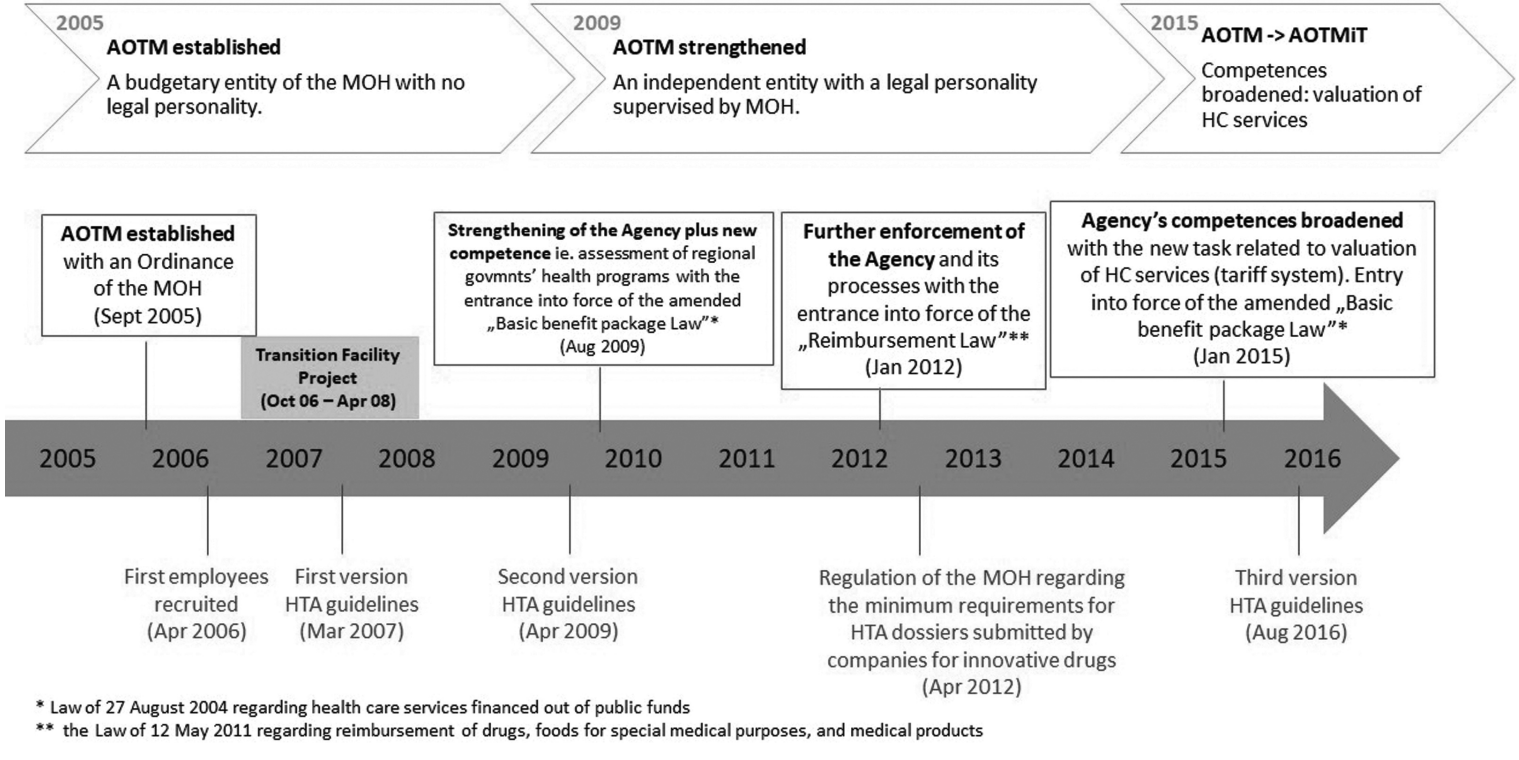


Figure 2. Key milestones in AOTMiT evolution.

The drug reimbursement process in Poland

The Reimbursement Law that entered into force in 2012 regulates drug reimbursement in Poland and asserts leadership of the Ministry of Health in the process. The Reimbursement Law introduced some order and transparency to the system; however, it is not free from defect, and in 2015, the newly elected Polish government began an investigation into potential modifications of this law, although it is currently too early to specify the ultimate legal ramifications of these modifications.

As the principal owner of the pricing and reimbursement process in Poland, the Ministry of Health has the responsibility to coordinate all of its elements, starting with the receipt of pricing and reimbursement applications from marketing authorization holders and ending in the formulation of pricing and reimbursement decisions. These decisions must be made within a specific timeframe set out in the Transparency Directive; that is, 90 days from receipt of application for decisions on prices; 90 days for decisions on reimbursement; and 180 days for both pricing and reimbursement decisions.

The process for innovative drugs begins with the sponsor submitting a pricing and reimbursement application to the Ministry of Health (Figure 3). The elements of the application dossier are precisely listed in the Reimbursement Law and these include: general data regarding the applicant; a commitment to ensure continuity of supply in case the drug is reimbursed; marketing authorization data; a proposal of reimbursed indication(s), price, reimbursement limit, a risk-sharing scheme (the Reimbursement Law specifically points towards outcome based schemes and financially based schemes mainly discounts or price volume arrangements), a proposal of drug program if relevant, international price comparisons and proof of payment for the application procedure with the Ministry of Health and AOTMiT (9).

The Ministry of Health first examines the application from a formal perspective and if necessary informs the applicant on the need to complete or modify any of its elements. The applicant then has 7 days to update the dossier, and this delay stops the 90/180-day clock. Once the application is complete, the Ministry of Health refers it to AOTMiT for a recommendation as to whether the drug meets the criteria specified in the Polish HTA guidelines and should be financed from public funds.

The President of AOTMiT has 60 days to present its recommendation to the Minister. The internal process at AOTMiT begins with an assessment by an analytical team that results in an evaluation report called a verification analysis (*analiza weryfikacyjna*). Both an application dossier and a verification analysis are based on Polish HTA guidelines (15) (which are described in Supplementary Material 2). The evaluation report compiles the reimbursement decisions and conditions from other countries. It also includes an assessment and critical review of the pharmacoeconomic dossier submitted by the applicant; that is the clinical, economic, budget impact and rationalization analyses, which are submitted if the budget impact analysis demonstrates an increase of reimbursement costs and show scenario(s) for releasing public funds in the amount

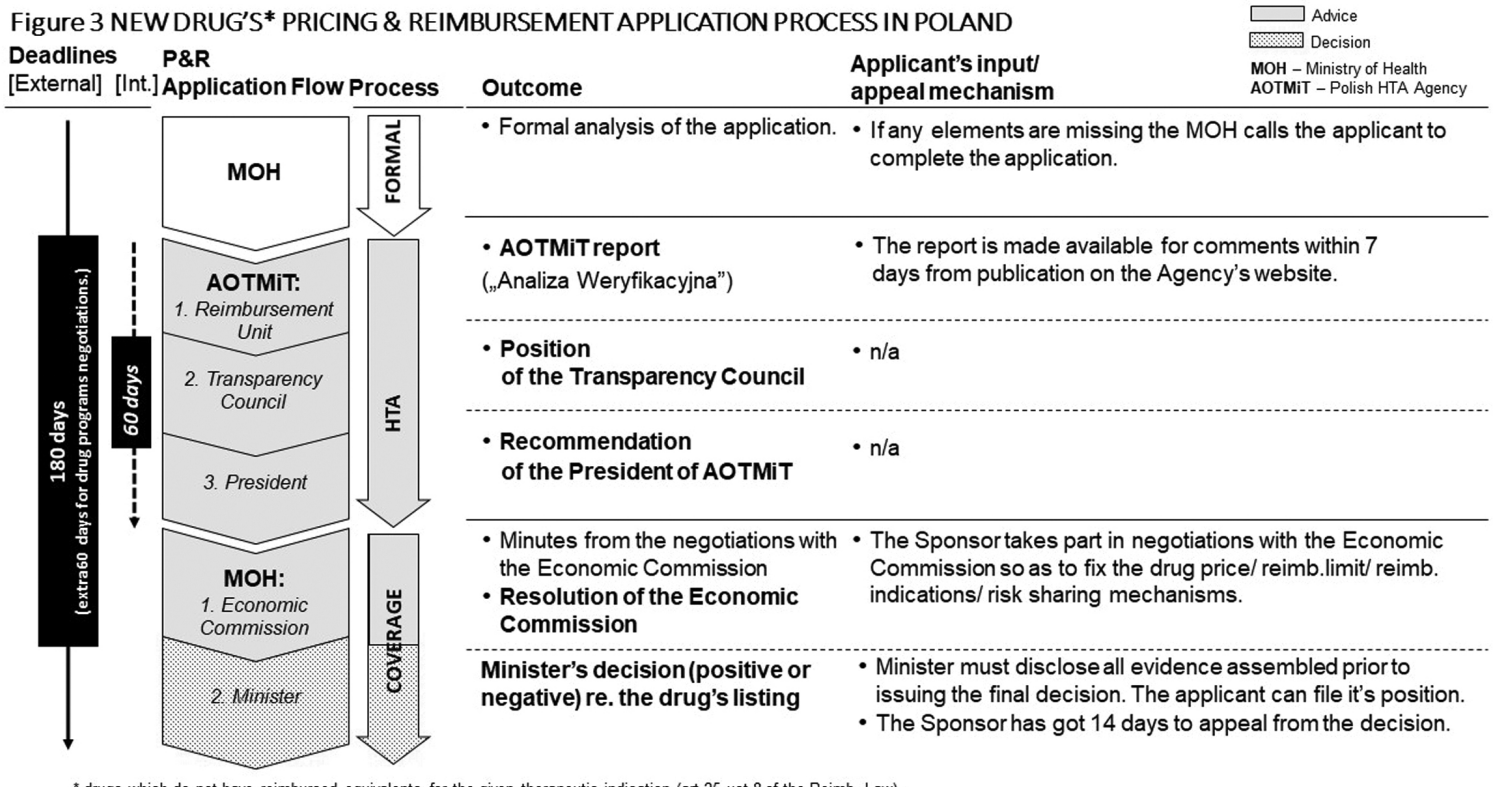


Figure 3. The pricing and reimbursement application process for new drugs in Poland.

corresponding to the increase in budget impact. The evaluation report, which is available for comments 7 days from its publication online, is then presented to the Transparency Council for appraisal, which issues its opinion in the form of a position (the composition and tasks of the Transparency Council in comparison to previous Consultative Council are described in Supplementary Material 1). The recommendation of the Agency is issued by its President based on the position of the Transparency Council and the formal assessment criteria; it comprises the rationale for the recommendation including conditions for drug reimbursement such as possible restrictions and/ or risk-sharing schemes.

The current strong position of the Transparency Council in the HTA decision process is unquestionable and according to Instytut Arcana, the concordance between the Council's and the Agency President's recommendation is high. Indeed, from January 1, 2012 through December 13, 2014, the President's recommendation differed from the Council's position for 7% of cases (16). However, more recent research indicates a growing divergence between the Council's and Agency President's judgments in the last three years (17).

The recommendation of the President together with the Position of the Transparency Council and the verification analysis are referred by the Minister to the Economic Commission affiliated with the Ministry of Health for pricing and listing negotiations with the sponsor. The Commission is made up of 12 representatives of the Minister of Health and 5 representatives of the public payer (National Health Fund). The output of the negotiations is two-fold: resolution of the Economic Commission and the minutes from the negotiations.

The process may be affected by unanticipated interventions from individuals in particular government officials. The most illustrious case is that of the 2015 intervention by the Deputy Health Minister in the form of a letter where the Agency is urged not to value the clinical efficacy over cost effectiveness (18).This intervention led to an increase in negative recommendations from approximately 20% in the end of 2014 to more than 70% the beginning of 2015 (19).

Having received the Agency's and Commission's output, the Minister of Health makes an independent reimbursement decision. The Minister's decision is discretionary and is based on legal reimbursement criteria. The Minister must disclose all evidence assembled prior to issuing the final decision, and the applicant has the right to file its position. The decision is subject to appeal within 14 days by the Sponsor. It is worth noting that research suggests the concordance between the ministerial decision on reimbursement of innovative medicines and AOTMiT recommendations is low, and only one third of positive HTA recommendations result in positive reimbursement decisions from the Ministry of Health (16). However the MOH can also decide that a medicine given a negative opinion is reimbursed as seen recently (September 2016) with a Chronic Obstructive Pulmonary Disease medicine which received a positive reimbursement decision by the Minister of Health despite a prior negative recommendation by the President of AOTMiT (20).

The Minister publishes the reimbursement list once every two months in the Official Journal of the Minister of Health. The list contains information such as the medicine's category and level of reimbursement, its price, and patient co-payment level as well as the date of entry into force of the reimbursement decision and its validity.

Drug reimbursement criteria

The current (since 1st January 2012) and previous drug' reimbursement criteria (binding up to 31st December 2011) are described in Table 1.

Previously, the law stated that the Minister of Health should take the above mentioned criteria into account after receiving the recommendation of the AOTMiT

Table 1. A comparison of current (since 1st January 2012) and previous drug reimbursement criteria in Poland (binding up to 31st December 2011)

Current Drug Reimbursement Criteria (since 1st January 2012)	Previous Drug Reimbursement Criteria (up to 31st December 2011)
1) the position of the Economic Commission; 2) the recommendation of the President of the Agency; 3) the significance of the clinical condition for which the reimbursement application is made; 4) clinical and practical effectiveness; 5) safety; 6) the ratio of health benefits to the risk of use; 7) medical cost benefit ratio of the drug applying for reimbursement in comparison with already reimbursed medicines; 8) price competitiveness; 9) budget impact; 10) the existence of alternative medical technologies with their clinical effectiveness and safety, as specified in the Act on health care services financed out of public funds; 11) the reliability and accuracy of estimates provided in the criteria 3 to 10 above; 12) health priorities set out in the Act on health care services financed out of public funds; 13) the threshold of quality-adjusted life year (QALY) at the level of three times the gross domestic product per capita. In the case the latter cannot be determined, the cost of obtaining an additional year of life – while taking into account other possible medical procedures that may substitute for the drug in question.	1) the impact on public health by taking in to account: a. health priorities b. indicators of prevalence and mortality 2) the effects of a disease or health condition especially with regards to: a. premature death, b. inability to lead an independent life, c. inability to work, d. chronic suffering or illness, e. reducing the quality of life; 3) the significance for the health of citizens while taking into account the necessity: a. to save lives and obtaining full recovery, b. to save lives and achieving health improvement, c. to prevent premature death, d. improving the quality of life without significant impact on its length; 4) clinical effectiveness and safety; 5) the health benefit risk ratio; 6) medical cost benefit ratio; 7) budget impact.

President. Currently, agency recommendations reflect an improvement in the order and transparency of the drug pricing and reimbursement decision process in Poland. Moreover, reimbursement verdicts are now published in the form of "administrative decisions" and enable an appeal mechanism for the applicant. Formerly, reimbursement decisions were issued in bulk and there were years where no one single reimbursement decision was published by the Minister. Today's reimbursement decisions are drug related and are disseminated in the form of the Minister's Communique in bimonthly intervals.

Drug decisions include formal information regarding the applicant and the drug as well as the classification into a reimbursement category or drug program. In parallel, they include data on the relevant level of funding, price, reference group and risk-sharing schemes.

DISCUSSION

Prior to the establishment of AOTMiT, new innovative drugs were not even considered for reimbursement from public funds in Poland due to budgetary constraints, and even more importantly, there was a lack of objective criteria. In fact, there were several corruption scandals around reimbursement processes in Poland, based on very subjective criteria for drug reimbursement in the late 1990s. At that time, regularly submitted reimbursement applications were not evaluated at the Ministry of Health, due to the lack of appropriate procedures, objective criteria, and defined timelines.

Successful implementation of HTA in Poland

The evolution started in 2005 from an unquestionable lack of objective reimbursement criteria and progressed via a capacity and institutional building exercise with the French institutions HAS and Ministry of Health and international experts between 2006-2008 up to the full implementation of the EU Transparency Directive into the Polish legal system through the Reimbursement Law in January 2012.

The twinning project between AOTMiT, Polish MoH and French partners HAS and MoH played a key role in HTA capacity building and the implementation of evidence based criteria into drug reimbursement decision making in Poland.

Today, HTA has been successfully implemented into the decision-making processes for drug reimbursement in Poland, and is based on a solid legal foundation that includes the Reimbursement Law. However, there are some current political tensions regarding the scope of activities performed by AOTMiT, which has been recently expanded to include new tasks dedicated to tariffs. Although these tasks have been defined as a political priority by the Polish government, there is a concern that this work may devalue the importance of HTA activities and processes developed by AOTMiT. Capacity and expertise in HTA has been steadily increasing for stakeholders at AOTMiT and among those producing HTA reports and working in academic centers

and industry, especially during the EU-funded twinning project between Poland and France. AOTMiT management teams should be aware of the potential risk of the loss of highly trained staff, who may feel that the HTA functions have been devalued, to higher paying positions within the pharmaceutical industry, and look to mitigate against potential loss of expertise and experience. The issue of experts' movements between private and public institutions in the Polish reimbursement system, known as "institutional nomads," has been investigated by Ozierański and King (21).

Room for improvement

Because transparent HTA processes have been implemented by AOTMiT in recent years and efficacy and safety profile seem to contribute most to final Agency's recommendations (22), drug reimbursement decision making based on objective verifiable criteria will likely continue regardless of political pressures. However, attention must continue to be paid to the quality of the HTA processes in place at the agency and to continuous capacity building to avoid potential compromise.

It is worthwhile to note that the transparent well designed HTA system in Poland has got several gaps which enable mostly political not evidence based interventions from individuals at different stages of reimbursement processes (21) notably from the AOTMiT's President (7% recommendations are not coherent with TC positions) and the Minister of Health (only one third of positive HTA recommendations result in positive reimbursement decisions) (16).

Previous research indicates that the concordance/agreement between AOTMiT President and TC measured by V-Cramer equals 0,549 where 0 corresponds to no association and 1 to complete association (23). The association between AOTMiT President recommendations and MoH reimbursement decisions is even much lower amounting to 0,314 measured by V-Cramer association (24).

External factors can also influence the work of the Agency. The above mentioned 2015 intervention by the deputy minister of health (18) led to a surge in negative recommendations issued by the AOTMiT (19). The discretionary power of the Minister of Health affects the outcome of reimbursement decisions. The stated above case of the COPD medicine receiving a positive reimbursement decision despite negative AOTMiT recommendation is emblematic (20). Similar situations may result in substantial unpredictability of final reimbursement decisions.

"Pragmatic" model

The HTA model that has been implemented in Poland can be called "pragmatic" because the pharmaceutical company is fully responsible for the preparation of a reimbursement dossier of good quality in line with HTA Guidelines and the assessment team in AOTMiT is responsible for critical review of that dossier (*"analiza weryfikacyjna"*). This is a similar approach to that implemented in Scotland by the Scottish Medicine Consortium (SMC) in which through the use of very limited

but extremely competent resources, all new active substances can be fully assessed based on the dossier submitted by the industry.

This is in comparison to the so called "full model" HTA agency, such as that of the National Institute for Health and Care Excellence (NICE) in England, in which the report on a new health technology is prepared by the HTA agency either internally or through external resources such as academic centers. A full model HTA agency requires substantial financial and human resources as a precondition that are not feasible for the Polish healthcare system.

Consideration of Polish HTA model by new and evolving countries

The development of HTA activities in Poland can be perceived as a unique intermediate model of late adoption of innovative technologies, given the limited financial resources of the Polish healthcare system. The key success factors in this development were effective capacity building based on the use of international expertise, the implementation of transparent criteria into the drug reimbursement processes and the selective approach to the adoption of innovative medicines based on the cost-effectiveness threshold among a variety of other criteria.

The Polish experience in the implementation of HTA into the health care system could be utilized by countries which have limited resources seeking for potential solutions to implement HTA based on international models. There are three key aspects which underpin the process in Poland and would need to be considered by countries looking to adopt the Polish model: a policy framework, methodological developments and capacity building. Firstly the creation of a policy framework with corresponding legal acts is recommended to be considered as the foundation of HTA implementation (eg. "Basket Law", "Reimbursement Law" in Poland). Secondly, this policy framework needs to be directly linked with methodological developments in the field of HTA, eg. HTA guidelines development and implementation (first HTA guidelines developed in Poland in 2007 with the update in 2009 and 2016). Thirdly, capacity building in the field of HTA in a given jurisdiction with regards to both internal (HTA agency) and external resources (academia, pharmaceutical industry, patients organizations) based on international expertise needs to be considered as a key long term perspective success factor (in Poland both HTA agency employees and external institutions eg. academia have been trained by international experts within EU Transition Facility project). The way Poland approached these three key aspects of HTA implementation create potential value for international utilization in particular in countries with limited financial resources.

The Polish experience is an example of pragmatic approach to implementation of an HTA model which could be considered by other countries looking to establish HTA systems. It is unique both in terms of potential learnings from the country with very limited resources in health care system and also the adoption of methodological challenges related to HTA implemented into health care system, in particular into drug reimbursement system.

CONCLUSION

The role of HTA in the drug reimbursement process in Poland has increased substantially over the recent decade leading to a sensible and balanced system which has enabled the implementation of objective data driven criteria.

However, while Poland is regarded as a leader in Central and Eastern Europe, there is room for improvement, especially with regard to the quality of HTA processes, especially the consistency of HTA guidelines with Reimbursement Law, staff competence and turnover. Moreover, the gap between Poland and the rest of Europe should be narrowed in terms of making innovative drugs accessible to patients as Poland lags behind other countries in reimbursing innovative oncology drugs (25).

As countries around the world look to establish their own HTA process and procedures the evolution of the HTA process in Poland may give some direction on how to balance differing priorities and ensure transparent and objective access to medicines for patients who need them.

REFERENCES

1. Garrido MV, Kristensen FB, Nielsen CP, Busse R. Health technology assessment and health policy-making in Europe. European Observatory of Health Systems and Policies 2008. Available from http://www.euro.who.int/__data/assets/pdf_file/0003/90426/E91922.pdf?ua=1 [Accessed 9 Nov 2016].
2. Cleemput I, Franken M, Koopmanschap M, le Polain M. European drug reimbursement systems' legitimacy: five-country comparison and policy tool. Int J Technol Assess Health Care. 2012;28(4):358-66.
3. Banta D, Kristensen FB, Jonsson E. A history of health technology assessment at the European level. Int J Technol Assess Health Care. 2009;25 Suppl 1:68-73.
4. Gulacsi L, Rotar AM, Niewada M, et al. Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria. The European journal of health economics : HEPAC : health economics in prevention and care. 2014;15 Suppl 1:S13-25.
5. Nizankowski R, Wilk N. From idealistic rookies to a regional leader: the history of health technology assessment in Poland. Int J Technol Assess Health Care. 2009;25 Suppl 1:156-62.
6. Kaló Z, Gheorghe A, Huic M, Csanádi M, Kristensen FB. HTA Implementation Roadmap in Central and Eastern European Countries. Health Econ. 2016;25(S1):179-92.
7. OECD Statistics: http://stats.oecd.org/ [Accessed 13 September 2016].
8. Ozieranski P, McKee M, King L. Pharmaceutical lobbying under postcommunism: universal or country-specific methods of securing state drug reimbursement in Poland? Health economics, policy, and law. 2012;7(2):175-95.
9. The Law on the reimbursement of medicinal products, special purpose dietary supplements and medical devices. Available from http://isap.sejm.gov.pl/DetailsServlet?id=WDU20111220696 [Accessed 9 Nov 2016]
10. European Commission. Transparency Directive. Available from http://ec.europa.eu/growth/sectors/healthcare/competitiveness/products-pricing-reimbursement/transparency-directive/index_en.htm [Accessed 9 Nov 2016.]
11. Sagan A, Panteli D, Borkowski W, Dmowski M, Domanski F, Czyzewski M, et al. Poland health system review. Health systems in transition. 2011;13(8):1-193.
12. Kawalec P, Sagan A, Stawowczyk E, Kowalska-Bobko I, Mokrzycka A. Implementation of the 2011 Reimbursement Act in Poland: Desired and undesired effects of the changes in reimbursement policy. Health Policy. 2016;120(4):356-61.
13. Zagorska A, Krol Z, Lipska I, et al. Case 1 Implementation of transparent process of drug reimbursement decisions in Poland. Value Health. 2008;11(6):A348-A9.
14. Lipska I. HTA capacity building using international experience and know how. Presentation at TAIEX workshop, Croatia, Zagreb Dec 2010. Available from http://ec.europa.eu/enlargement/taiex/dyn/taiex-events/library/detail_en.jsp?EventID=43260 [Accessed 2 June 2016].
15. AOTMiT. Wytyczne oceny technologii medicznych (HTA). Available from http://www.aotm.gov.pl/www/hta/wytyczne-hta/ [Accessed 9 Nov 2016].
16. Skóra K, Wilk N. Rada swoje, urzędnicy swoje. Menedżer Zdrowia. 2014;9.
17. Getmedi analysis from http://getmedi.pl/static/grafika/articles/0052/wykres2.png [Accessed 9 Nov 2016].
18. http://www.zdrowie.abc.com.pl/artykuly/infarma-protestuje-przeciwko-naciskom-wywieranym-na-aotmit-przez-ministra-zdrowia,2859.html [Accessed 9 Nov 2016].
19. Getmedi analysis from http://getmedi.pl/static/grafika/articles/0027/wykres1a.png [Accessed 9 Nov 2016].
20. Ministry of Health information from http://www.mz.gov.pl/aktualnosci/refundacja-leku-incruse/ [Accessed 9 Nov 2016].
21. Ozierański P, King L. The persistence of cliques in the post-communist state. The case of deniability in drug reimbursement policy in Poland. Brit J Sociol 2016:n/a-n/a.

22. Niewada, M., Polkowska, M., Jakubczyk, M., & Golicki, D. (2013). What Influences Recommendations Issued by the Agency for Health Technology Assessment in Poland? A Glimpse Into Decision Makers' Preferences. Value in Health Regional Issues, 2(2), 267-272. doi:10.1016/j.vhri.2013.05.002
23. Getmedi analysis from http://getmedi.pl/static/grafika/articles/0065/wykres4.png [Accessed 9 Nov 2016].
24. Getmedi analysis from http://getmedi.pl/static/grafika/articles/0065/wykres9.png [Accessed 9 Nov 2016]
25. 2015 EY Report "The availability of innovative oncology drugs in Poland and in European Union countries and Switzerland" for Alivia Oncology Fundation from https://www.alivia.org.pl/raport2015/15_04_2015_Raport_innowacyjne_leki.pdf [Accessed 9 Nov 2016].

SUPPLEMENTARY MATERIALS

Annex 1: The comparison between current (from 2012) and previous (2007-2012) appraisal council at AOTMiT: Transparency Council and Consultative Council

Area	Current Transparency Council	Previous Consultative Council
Brief description	Advisory appraisal committees affiliated with the President of AOTMiT.	
Timespan	2012 – today	2007 – 2012
Main tasks	» Classifying or not a given healthcare service as guaranteed or financed from public funds together with a proposal regarding the mechanism and level of reimbursement. » Removing a given healthcare service from the basket of guaranteed services. » Issuing opinions on health programs. » Carrying out other tasks at the request of the President of the Agency. » Issuing opinions regarding group limits and withdrawal of reimbursement decision. » Issuing opinions regarding the reimbursement in off-label use.	» Classifying or not a given healthcare service as guaranteed or financed from public funds together with a proposal regarding the mechanism and level of reimbursement. » Removing a given healthcare service from the basket of guaranteed services. » Issuing opinions on health programs. » Carrying out other tasks at the request of the President of the Agency.
Composition (members)	20 members in total: » 10 recognized experts in the field of medical sciences or alike alternatively in the field of health care services evaluation, including ethics (phD at minimum); » 4 representatives of the Minister of Health; » 2 representatives of the National Health Fund;2 representatives of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products;2 representatives of the Commissioner for Patients' Rights.	12 members in total: » 7 representatives of the Minister of Health; » 1 representative appointed by the rectors of medical schools; » 1 representative designated by the Supreme Medical Council; » 1 representative appointed by the Supreme Council of Pharmaceutical; » 1 representative designated by the Supreme Council of Nurses and Midwives; » 1 representative designated by the National Health Fund.
Legal basis	Reimbursement Law and also Law on health care services financed out of public funds	Law on health care services financed out of public funds

The Transparency Council (TC) is an advisory appraisal committee affiliated with the President of the Polish HTA Agency. With the entrance of the Reimbursement Law in 2012, the TC replaced the Consultative Council. The strictly defined by law TC composition is supposed to reflect the balance of different stakeholders in Polish health care system.

The chairman and two vice-chairmen manage the Council's work and are elected by members during the first TC meeting. Ten members are appointed by sortition prior to every Council meeting in such a manner that each authority has its representative. The ten member teams adopt resolutions in the form of the Council's positions. The resolutions require a simple majority to pass in the presence of at least 2/3 of its members. The chairman decides in case of a tie vote.

The position of the TC with regards to medicinal products includes:

- the Council's opinion on whether the drug should be financed from public funds;
- conditions under which a drug may be listed ie. proposed reimbursed indications and reference groups limits;
- if relevant, comments on drug program proposal;
- comments on risk sharing mechanisms if applicable.

As in the case of the TC today, the outcome of the Consultative Council's work regarding medicinal products was its Position. The latter classified or not a given healthcare service (drug) as guaranteed or financed from public funds together with a proposal regarding the mechanism and level of reimbursement. An important difference between CC and TC positions is that previously CC positions were considered as final AOTM recommendations while currently this role plays recommendation issued by AOTMiT President who takes into account TC position.

With the entrance of the Reimbursement Law, the TC received additional task such as issuing opinions regarding group limits, the withdrawal of reimbursement decisions and issuing opinions regarding the reimbursement in off-label use.

Annex 2: HTA Guidelines in Poland

The first set of HTA Guidelines were introduced in March 2007 and updated in April 2009 and in August 2016. HTA Guidelines are structured in a form of an official AOTMiT document that presents an analytical approach for technology assessment and appraisal in Poland. According to this document, "the purpose of the guidelines is to indicate the principles and acceptable methods of performing Health Technology Assessment to ensure high quality of analyses and reliable results". As stated on the AOTMiT website: "The agency bases its work on scientific evidence that determine whether the drug is safe and effective for the patient. This information is crucial for making decisions that shape the national health policy. Three elements make up a full assessment: clinical effectiveness analysis, economic analysis and the budget impact analysis".

The current HTA Guidelines are structured in the following manner:

- Decision problem analysis following the PICO scheme ie. Population, Intervention, Comparators, Health Outcomes
- Clinical analysis: data (sources, search strategy, information selection and quality assessment, presentation of included trials and data extraction); data synthesis for effectiveness (qualitative synthesis, meta-analysis, simple and network indirect comparison); safety assessment (purpose, scope of safety analysis); presentation of results; limitations; discussion and final conclusions.
- Economic analysis: analytical strategy; perspective; time horizon; analytical technique (cost-utility analysis, cost-effectiveness analysis; cost-minimisation analysis; cost-consequences analysis); modelling; health outcomes assessment; cost assessment (cost categories, identification and measurement of used resources, determination of unit costs); discounting; data presentation; presentation of results; sensitivity analysis and result uncertainty assessment; limitations and discussions; final conclusions.
- Analysis of impact on health care system: budget impact analysis (perspective, time horizon, elements of analysis, data sources, population, compared scenarios, cost analysis, sensitivity analysis, presentation of results, limitations and discussion); ethical, social, legal aspects, impact on the organization of service providing.

In parallel to the guidelines, a 2012 regulation by the Minister of Health determines the manufacturer's submission template. It specifies the components and data framework of the application within the three main categories: clinical analysis, economic analysis, and budget impact analysis. It also includes guidance for preparing a rationalization analysis if the budget impact analysis demonstrates an increase of reimbursement costs. The rationalization analysis shows scenario(s) for releasing public funds in the amount corresponding to the increase in budget impact.

The clinical analysis builds on the following:

» A description of health problem with epidemiology;
» An overview of existing reimbursed treatments;
» The position of the new drug with regards to existing treatments;
» A systematic review of primary trials and their selection criteria;
» An overview of published systematic reviews.

The economic analysis includes:

» A basic analysis;
» A sensitivity analysis;
» A systematic review of the published economic analyses with regards to comparator technologies for relevant populations.

The budget impact analysis estimates:

» The population size;
» Annual expenditures for the payer, broken down in various categories;
» Additional costs.

It has been noted that HTA Guidelines developed by AOTMiT in 2007 and updated in 2009 and further in 2016 represent significant step toward improved transparency, and even more importantly, toward consistency between the Reimbursement Law of 2011 and HTA Guidelines.

chapter 8

COMPARISON OF HTA AGENCY RECOMMENDATIONS FOR NEW ONCOLOGY DRUGS WITH NON-ONCOLOGY DRUGS IN THE CHANGING HTA ENVIRONMENT IN POLAND

Iga Lipska
Neil McAuslane
Hubert G.M. Leufkens
Anke M. Hövels

Submitted

ABSTRACT

Objective

To compare AOTMiT outcomes, determinants of outcomes and timelines of decision making between 2012 and 2015 for new oncology drugs with non-oncology drugs.

Methods

Lists of new drugs authorised by the European Medicines Agency from 2012- 2015 and those also assessed by Poland's AOTMiT were retrieved from the agencies' websites. Timing and timing gaps from regulatory approval through AOTMiT recommendation were calculated. AOTMiT recommendations were classified as positive, positive with restrictions and negative and defined reasons for restrictions as well as for negative recommendations as clinical, economic, both clinical and economic, and organisational. Results for oncology and non-oncology products were differentiated.

Results

AOTMiT assessed only 39% of all NASs approved by EMA from 2012-2015. Most (57%) received a negative recommendation (48%, oncology; 64%, non-oncology). Only 4% received a purely positive recommendation; the main rationale for restricted recommendations was economic (50%, oncology, 75%, non-oncology). A mixture of economic and clinical reasons was the most common rationale for rejection (85%) for all drugs and the only rationale for rejection in oncology drugs.

Conclusions

Despite improved processes and transparency at AOTMiT, timely patient access to medicines is threatened as only the minority of NASs are assessed and the majority assessed are evaluated negatively, although oncology drugs are evaluated slightly less negatively. AOTMiT must now consider reimbursement criteria explicitly listed in the Reimbursement Law and restriction reasons have become a combination of clinical and economic or purely economic. Median timing for reviews exceeds legal requirements, slightly less so for oncology medicines.

INTRODUCTION

Across the globe, health technology assessment (HTA) plays an increasingly important role in informing decision makers about the value and application of novel drugs (1). However, the way HTA is implemented greatly depends upon the national setting (2).

The Agency for Health Technology Assessment in Poland (AOTMiT) has been in operation since 2005 and has evaluated medical technologies with a main focus on pharmaceuticals since 2007. The role and authority of AOTMiT have expanded over the last decade, but even at an early stage of development, the Polish agency was often looked to as a role model and the HTA leader in Central and Eastern Europe (3). Previous research indicates that an HTA appraisal process has been successfully implemented in Poland although there is room for improvement with regard to international standards of transparency and quality (4). Several countries from Central and Eastern Europe have followed and implemented HTA processes; however, given the differences in the national contexts, the extent of the implementation has varied (5), including the use and understanding of cost-effectiveness criteria (6).

Over the recent 10 years, the entire drug pricing and reimbursement process in Poland has become increasingly transparent and evidence driven. New drugs have systematically been made accessible to Polish patients, although it should be noted that not all new drugs approved by the European Medicines Agency (EMA) via the centralised procedure are destined for Poland and thus assessed by AOTMiT. Furthermore, if these drugs are assessed, there may be a substantial delay. The time from regulatory approval to HTA recommendation is longer in Poland in comparison with other European Union (EU) member states and in fact, increased substantially between 2011 and 2013 (7). This raises questions regarding equity of access, which is one of the EU values for health (8), as a substantial proportion of new drugs approved by EMA will not be available or will not be available in a timely manner for patients in Poland. This is despite the commitment of the Stakeholders of the High-Level Pharmaceutical Forum in 2008 to "... ensuring sustainable availability and delivery of medicines to all EU Member States ... This should be done in parallel and in collaboration with regulatory efforts, taking into account the work of the Heads of Medicines Agencies" (9). The lack of equity in access to medicines can have various reasons in addition to delays in assessment and appraisal at AOTMiT, such as the lack of industry submission in Poland due to company pricing strategies based on the international reference pricing system.

The entrance into force of the so-called "Reimbursement Law" in 2012, deeply re-organised the pricing and reimbursement system in Poland and undoubtedly affected the HTA process. As a result of this legislation, new reimbursement criteria have been introduced, including a cost-effectiveness threshold (10) and the Transparency Directive was fully implemented (11) into the Polish legal system. Pricing and reimbursement decisions are now based on objective and verifiable criteria, an appeal mechanism has been instituted and HTA decisions must to be issued within a 90-/180-day timeframe.

This timeframe was subsequently further reduced by Polish legislation to a 60-days deadline for the HTA process within AOTMiT.

However, some researchers still point toward a vast need for improvement with regard to the transparency of the HTA process and the accountability of its procedures (12) and also indicate that the cliques in Poland that still have impact on the drug reimbursement process remain a legacy of the communism (13). Some researchers even indicate the influence of pharmaceutical companies over the system (14).

Prior to the entrance into force of the Reimbursement Law in 2012, researchers measured the Polish HTA outcomes and analysed the reasons for restrictions and rejections (15). However, there is no research available so far as to how the implementation of the Reimbursement Law have impacted HTA outcomes; in particular, the reasons for restrictions and rejections and the timelines of HTA processes.

We compare oncology drugs with non-oncology drugs because oncology is defined as a health policy priority in Poland and there is high unmet medical need in this field, in addition there is also high proportion of oncology drugs among drugs being authorised by EMA and assessed by AOTMiT.

Objective

The objective of this study was to compare HTA agency recommendations in Poland between 2012 and 2015 for new oncology drugs with those for non-oncology drugs with regard to assessment outcome, determinants of outcome and timelines of decision making.

METHODS

We systematically reviewed HTA recommendations from AOTMiT for all new drugs approved by the EMA between 2012 and 2015. First, we retrieved the list of all new active substances (NASs) that were authorised for use by EMA from 1 January 2012 until 31 December 2015 from the EMA website. This timeframe was chosen deliberately, as the Reimbursement Law in Poland came into force in January 2012. Then we excluded drugs that were withdrawn from marketing authorisation by the time of data collection (April 2016). We also excluded drugs that were considered out of the scope of AOTMiT.

As a second step, we verified which of the latter NASs were assessed by AOTMiT regardless of the assessment years, by collecting data from publicly available reports as those published by AOTMiT on their website.

Data collection

The cohort of drugs assessed by AOTMiT from the list of NASs granted marketing authorisation by EMA from 1 January 2012 until 31 December 2015 were further analysed using both regulatory data (EMA) and HTA data. The regulatory data were obtained from the EMA website and included generic and brand names, company

name, compound and review type, the Anatomical Therapeutic Chemical (ATC) classification, marketing authorisation date and detailed clinical indication.

The data were collected in April 2016 from HTA reports publicly available on the AOTMiT website using a standardised report form. Only final recommendations issued by the President of AOTMiT were considered. When two or more recommendations were issued for the same NAS, only the first recommendation was analysed. The following information on HTA recommendations was collected for each drug: the recommendation type; that is, classified as positive, positive with restrictions, negative, reasons for restrictions and negative decisions, information as to whether reimbursement is through drug programmes, the submission date to AOTMiT, the date of the AOTMiT President's recommendation, comments, and website address.

HTA recommendations

We classified HTA recommendations into a trichotomous system: positive, positive with restrictions and negative (16). We also defined reasons for restrictions as well as for negative HTA recommendations and classified them into four groups: 1) clinical, that is, inappropriate comparator used, study design, poor efficacy/effectiveness, safety issues, treatment line, subpopulation; 2) economic, that is, poor economic data, issues regarding modelling method used, issues regarding lowering the price, unjustified price, budget impact considerations such as unacceptable budget impact; 3) both clinical and economic, that is, reasons for restrictions or negative recommendations were a mixture of both clinical and economic arguments), 4) organisational, that is, whether the drug was indicated to be reimbursed under a drug programme. The organisational group refers to products categorised into drug programmes when the reasons for restrictions could not be accurately classified as economic or clinical. Drug programmes are health services financed entirely from public funds, designed specifically for innovative and expensive pharmaceuticals in a selected indication and for a strictly defined population of patients.

The classification into the "positive with restrictions" category required more information, as the restrictions had to be identified in the other sections of recommendation text. We indicated whether the restrictions were of clinical, economic, both clinical and economic reasons or organisational. We also indicated the reasons for negative decisions. The classification was made into clinical, economic or both clinical and economic.

Timelines

We analysed the time gap between marketing authorisation approval by EMA and HTA recommendation by the AOTMiT President. This time interval or "access gap" is very important from a patient perspective, as it indicates how much time that patients need to wait for a drug to be recommended for reimbursement in Poland after it is approved by the EMA. However reimbursement decisions in Poland are often delayed and are not always consistent with HTA recommendation (12).

To analyse timelines from HTA submission to HTA recommendation, we considered the pharmaceutical company submission date to the HTA agency; that is the date the company submission was referred to AOTMiT by the Ministry of Health and the HTA recommendation date; that is, the date of the recommendation from the AOTMiT President. Therefore an analysis of the timeframes for each drug was performed with regards to the marketing authorisation dates, submission dates and recommendation dates.

Data analysis

Descriptive statistics were used to present the percentage of positive, positive with restrictions and negative HTA recommendations. We specifically looked at how the proportions changed depending on the medicine type; that is, oncology versus non-oncology drugs. We analysed detailed and predefined reasons for restricted and negative HTA recommendations and analysed timelines from EMA regulatory approval to HTA recommendation (access gap) and from pharmaceutical company submission to HTA recommendation (HTA process).

RESULTS

We retrieved the list of 122 NASs approved by EMA between 2012 and 2015 of which five NASs were excluded: two withdrawn from marketing authorisation and three considered out of the scope of AOTMiT. Thus, we included 117 NASs that were authorised for use by EMA from 1 January 2012 until 31 December 2015 and which were in the scope of AOTMiT for further analysis (Figure 1).

In total, AOTMiT assessed 46 (39%) out of the 117 NASs that met our study inclusion criteria; that is, that were approved by EMA between 2012-2015, still authorised for use at the point of data collection and were within the scope of AOTMiT. Almost half of the drugs were oncology drugs (n=21, 46%; Figure 1).

A total of 10 (48%) recommendations for oncology medicines were negative; whereas 16 (64%) recommendations for non-oncology drugs were negative. The restricted recommendations applied to 10 (48%) of oncology and 8 (32%) non-oncology drugs. For both groups, 1 recommendation was qualified as positive (Figure 1). In total, AOTMiT recommended 2 drugs positively (4%) while 18 drugs (39%) received restricted recommendations. The majority (26; 57%) of drugs received negative recommendations from the AOTMiT President (Figure 2).

HTA recommendations for new drugs: reasons for rejections and restrictions

The rationale for rejections and restrictions for all NASs differed (Figure 2). The restrictions concerned 18 (39%) drugs. We identified purely economic reasons

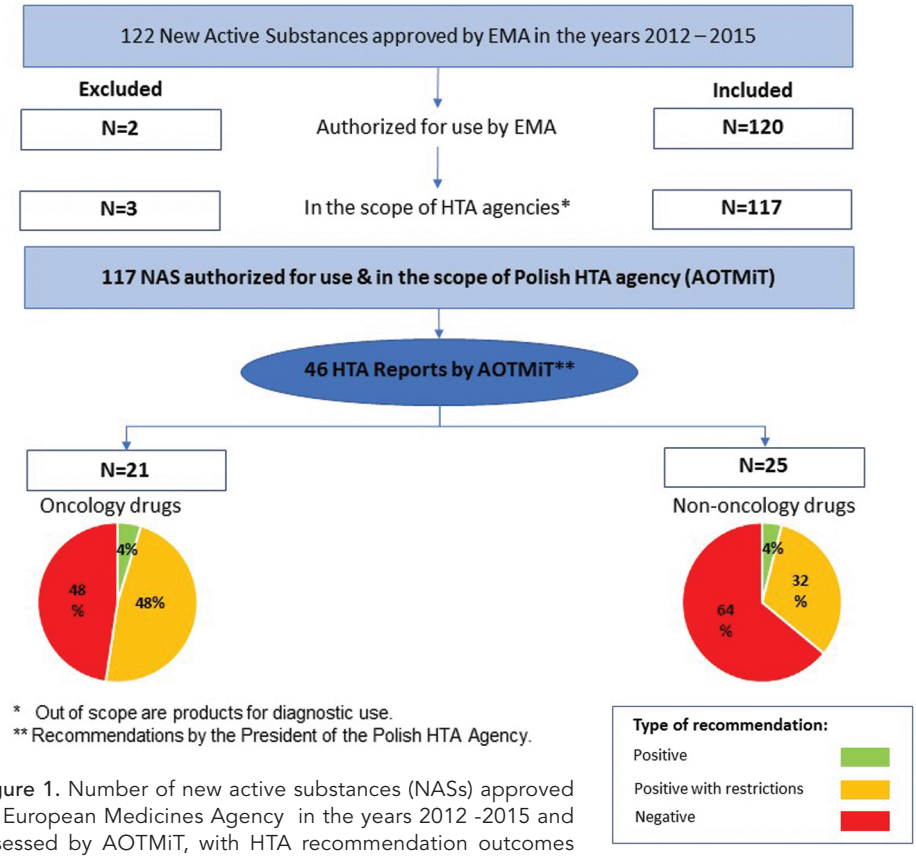


Figure 1. Number of new active substances (NASs) approved by European Medicines Agency in the years 2012 -2015 and assessed by AOTMiT, with HTA recommendation outcomes for oncology vs. non-oncology drugs.

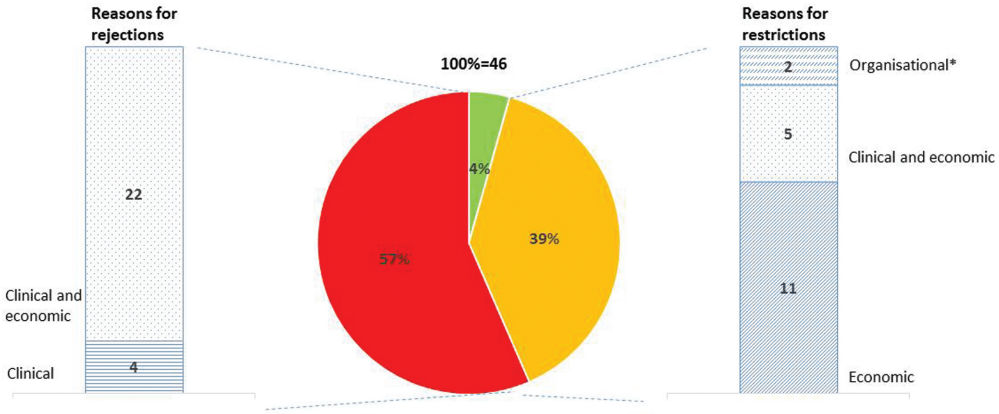


Figure 2. HTA recommendations for new drugs: reasons for rejections and restrictions.

for restrictions for 11 drugs (61% of restricted recommendations), a mixture of both clinical and economic reasons for 5 drugs (28%) and organisational reasons for 2 drugs (11%). There were no purely clinical reasons for restrictions. No negative HTA recommendations were based on only economic reasons, whereas 22 drugs (85%) received negative recommendation because of both clinical and economic reasons and another 4 drugs (15%) were not recommended based on only clinical reasons (Figure 2).

The reasons for restrictions in the group of oncology drugs were only economic for 5 drugs (50% of restricted drugs), a mixture of clinical and economic reasons for 3 drugs (30%) and organisational for 2 drugs (20%; Figure 3). In parallel, the reasons for negative recommendations in the group of oncology drugs were a mixture of clinical and economic nature.

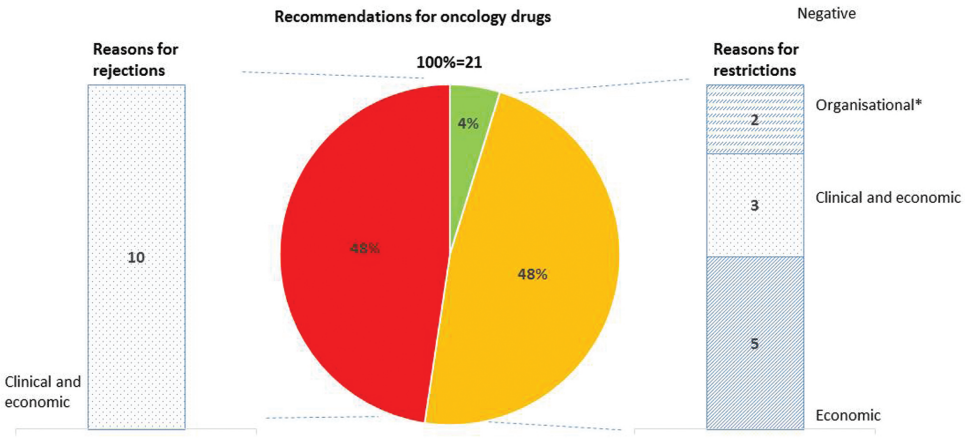
For non-oncology drugs the reasons for restrictions were economic for 6 drugs (75%) and a mixture of clinical and economic nature for two drugs (25%; Figure 4). Reasons for negative recommendations were clinical as well as both clinical and economic for 4 drugs (25%) and 12 drugs (75%) respectively (Figure 4).

Access gap – time between regulatory approval and HTA recommendation

We analysed the access gap, defined as the time between regulatory approval by EMA and HTA recommendation by AOTMiT (Figure 5). The median access gap for all assessed drugs was 421 days, varying from 112 days for 2 drugs indicated for chronic hepatitis C (ombitasvir/paritaprevir/ritonavir and dasabuvir) to 1064 days (over 3 years) for 1 drug indicated for cystic fibrosis (ivacaftor; Figure 5). In the case of oncology drugs, the access gap was a minimum of 174 days for pembrolizumab (indicated for advanced melanoma) and a maximum of 886 days for vismodegib (indicated for basal cell carcinoma). The median access gap was 348 days for oncology drugs while for non-oncology drugs it was over 100 days longer (453 days).

Timelines from HTA submission to HTA recommendation

The timing from HTA submission to HTA recommendation was a minimum of 60 days (pasireotide diaspartate indicated for Cushing's disease) and a maximum of 172 days (fluticasone furoate/vilanterol indicated for asthma), with the median being 74 days (Figure 6). For oncology drugs, the minimum was 63 days (radium Ra223 dichloride indicated for castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases), the maximum was 135 days (regorafenib for metastatic colorectal cancer), with the median being 81 days; while for non-oncology drugs, the median was 70 days (Figure 6).



* For drugs categorised into drug programmes when the reasons for restrictions cannot be accurately classified as economicor clinical.

Figure 3. HTA recommendations for new oncology drugs: reasons for rejections and restrictions.

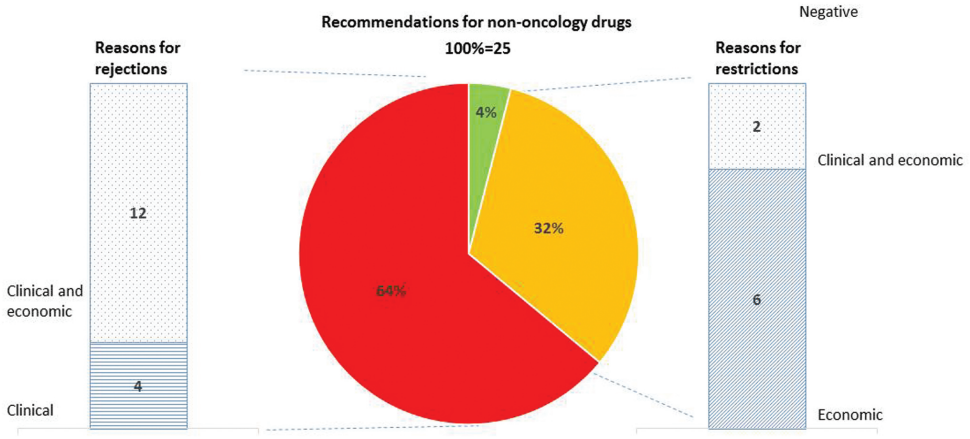
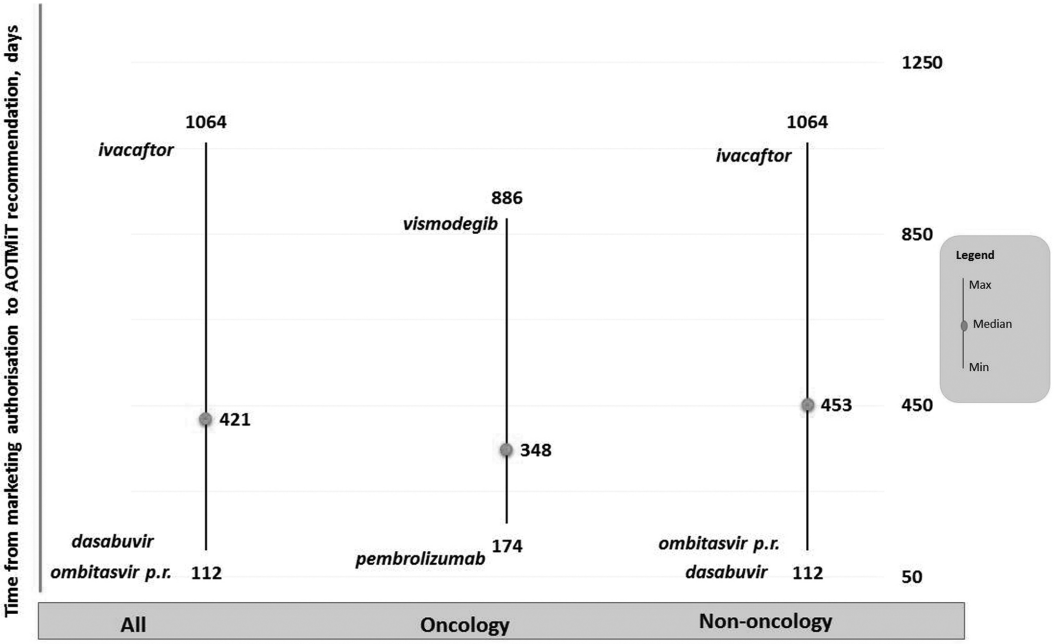


Figure 4. HTA recommendations for new non-oncology drugs: reasons for rejections and restrictions.



8

Figure 5. "Access gap" – timespan from regulatory aproval by European Medicines Agency to HTA recommendation by AOTMiT.

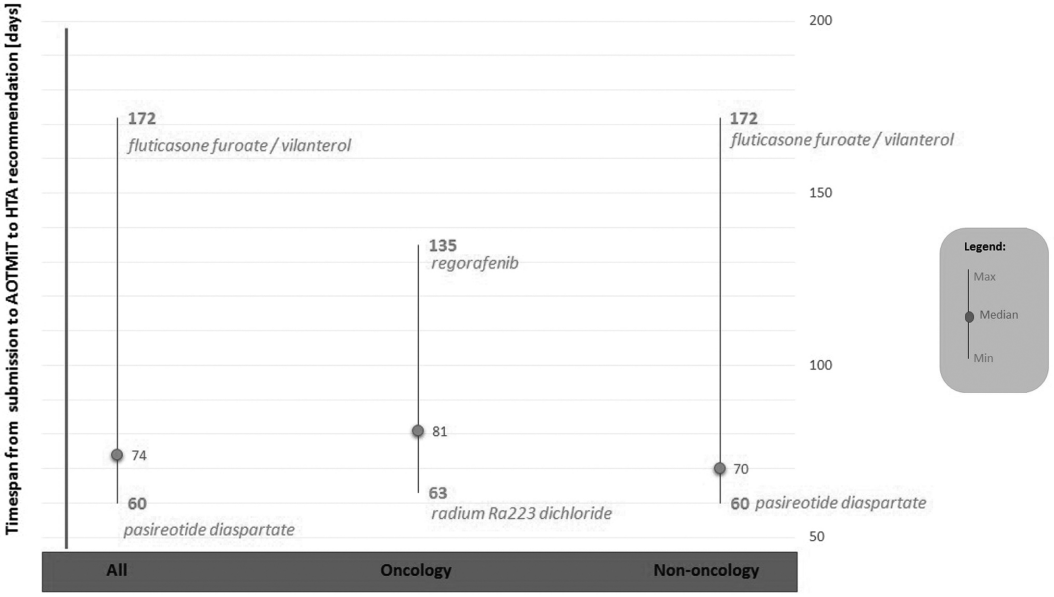


Figure 6. Timelines from HTA submission date* to HTA recommendation.

DISCUSSION

Our study indicates that timely accessibility to innovative pharmaceuticals for patients in Poland may be threatened due to a low assessment rate and a high proportion of negative recommendations and restrictions for NASs that are assessed. We found that AOTMiT assessed only 39% of all NASs approved by EMA between 2012 and 2015. Furthermore, the majority of new drugs assessed by AOTMIT received a negative HTA recommendation from the agency (57%). However when we compared oncology and non-oncology drugs, the AOTMiT attitude toward oncology drugs appeared less strict than that toward non-oncology drugs (48% negative recommendations for oncology drugs compared with 64% for non-oncology drugs. Previous research (15) that analysed all HTA recommendations in Poland for drugs issued between 2007 and 2009, described a less negative AOTMiT approach to drugs, as only 43% of all drugs received negative HTA recommendations.

A minimal proportion of new drugs received purely positive HTA recommendation (4%) while other drugs received a restricted HTA recommendations with the main reasons for restrictions being economic (50% and 75% for oncology and non-oncology drugs, accordingly). Furthermore, it is worth noting that even though there were no purely economic reasons for rejections, economic reasons were a popular rationale for products receiving restrictions. Our study indicates that the mixture of economic and clinical reasons was the most common rationale for rejection (85%) for all NASs; it was the only rationale for rejection in oncology drugs. In non-oncology, group purely clinical reasons for rejections were also possible but not common, as they constituted the rationale for approximately 25% of rejections.

Previous research (15) regarding Polish HTA recommendations for drugs issued from 2007 to 2009 indicated the reasons for rejection were mainly clinical (80% insufficient clinical data and poor efficacy and safety) and it also indicated that clinical arguments were the most prevalent rationale for restrictions. The prevalence of safety issues as rationale was surprising in that it is typically considered being within the scope of regulatory review. This finding was also supported by another study on Polish HTA recommendations issued in 2008, which also indicated that clinical reasons were the dominant rationale for rejections (18).

One of the most important reasons for this dramatic change indicated by our study results as compared with previous research (15,18) could be the implementation of cost-effectiveness criteria into the drug reimbursement system in Poland from 1January 2012 (the cost-effectiveness threshold for drugs being reimbursed from public funds defined as triple the gross domestic product per capita). Equally important is the fact that HTA recommendations from AOTMiT are used as the basis for pricing negotiations by the Economic Commission at the Ministry of Health. Therefore, such an economic restriction in HTA recommendation could create a solid argument for subsequent pricing negotiations and could facilitate the process of lowering the prices for new drugs.

The outcomes of HTA recommendations are the most important aspect in determining patient access to new drugs, however the access gap is also an important factor, as substantial delays impact patient access. The Polish Reimbursement Law implemented all measures from the EU Transparency Directive into the Polish legislative system including timelines of a maximum of 90 and 180 days for pricing and reimbursement decisions accordingly. Polish Reimbursement Law also defined a maximum 60 days for both assessment and appraisal time at the Polish HTA agency (from HTA submission to HTA recommendation). In our research we found out that AOTMiT does not fulfil this formal requirement for the majority of new drugs, with the median being 74 days for all drugs (81 and 70 days for oncology and non-oncology drugs accordingly). The maximum time in both groups was far beyond legally binding deadlines (135 days and 172 days for oncology and non-oncology drugs accordingly). These delays in the HTA processes inside Polish HTA agency have obvious consequences for patient access to new drugs.

The whole process from EMA marketing authorisation approval to Polish HTA recommendation (access gap) takes up to almost three years for all drugs, with a median time of 421 days. The reasons for this timing can be diverse including the delay in the HTA submission from pharmaceutical companies due to company marketing or pricing strategy.

Our study has some limitations. First, we collected the data from public domain only (EMA, AOTMiT websites). Second, in the case of multiple assessments, we considered only first HTA recommendations and the outcome of subsequent HTA recommendations could differ with divergent reasons for restrictions and rejections being considered. Third, we analysed only HTA recommendations from the AOTMiT President as we deliberately did not consider positions from the Polish appraisal body, the Transparency Council, as these are not the final HTA outcomes issued by the Polish HTA agency. Previous research indicates there could be discrepancies between the Transparency Council positions and those of the AOTMiT President (17). As we focused only on HTA processes and outcomes, we reviewed and analysed Polish HTA recommendations, which are subsequently used by the Ministry of Health for final reimbursement decisions. However previous research indicates there is inconsistency between HTA recommendations and Ministry of Health reimbursement decisions in about one out of three drugs (17). Furthermore we used a trichotomous classification of HTA recommendations with detailed reasons for rejections and restrictions. However, in a previous study on Polish HTA recommendations for drugs (15) a different classification of HTA recommendations was used, as researchers followed the one developed and implemented by Raftery (19).

CONCLUSIONS

Currently, accessibility to innovative pharmaceuticals for patients in Poland is threatened. We concluded that only the minority of NASs approved by EMA have been assessed by AOTMiT. In general, the majority of new drugs which actually undergo an assessment at AOTMiT are assessed negatively; however, the attitude toward oncology drugs is less strict than that toward non-oncology drugs. Due to the implementation of a cost-effectiveness threshold into the Polish drug reimbursement system economics have been playing a more important role in the decision-making processes. Over the recent years, the AOTMiT approach has become more negative, as it takes into consideration the reimbursement criteria explicitly listed in the Reimbursement Law. The reasons for restrictions have also evolved over time from mainly clinical to a combination of clinical and economic or even purely economic, which can potentially facilitate pricing negotiations at the Ministry of Health. The rationale for negative recommendations was found to be mainly a combination of both clinical and economic reasons. Based on our study findings we concluded that meeting the Reimbursement Law timelines still remains an issue for Polish HTA agency and such delays can impact patients' access to new innovative drugs.

REFERENCES

1. Oortwijn W, Broos P, Vondeling H, Banta D, Todorova L. Mapping of health technology assessment in selected countries. Int J Technol Assess Health Care. 2013;29(4):424-34.
2. Garrido MV, Kristensen FB, Nielsen CP, Busse R. Health technology assessment and health policy-making in Europe. European Observatory of Health Systems and Policies, 2008. Available at http://www.euro.who.int/__data/assets/pdf_file/0003/90426/E91922.pdf (Accessed 5 February 2017).
3. Nizankowski R, Wilk N. From idealistic rookies to a regional leader: the history of health technology assessment in Poland. Int J Technol Assess Health Care. 2009;25 (Suppl 1):156-62.
4. Kolasa K, Dziomdziora M, Fajutrao L. What aspects of the health technology assessment process recommended by international health technology assessment agencies received the most attention in Poland in 2008? Int J Technol Assess Health Care. 2011;27:84-94.
5. Gulacsi L, Rotar AM, Niewada M et al. Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria. Eur J Health Econ. 2014;15 (Suppl 1):S13-25.
6. Gulacsi L, Orlewska E, Pentek M. Health economics and health technology assessment in Central and Eastern Europe: a dose of reality. Eur J Health Econ.. 2012;13:525-31.
7. Wilsdon T, Fiz E, Haderi A. A comparative analysis of the role and impact of health technology assessment. Available at http://www.efpia.eu/uploads/documents/cra-comparative-analysis.pdf (Accessed February 5 2017.)
8. The Council of the European Union. Conclusions on Common values and principles in European Union Health Systems. 2006;C146:1-3.Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2006:146:0001:0003:EN:PDF (Accessed 5 Febr 2017).
9. High- Level Pharmaceutical Forum. Conclusions and recommendations: recommendation 7.2. Available at http://bookshop.europa.eu/en/high-level-pharmaceutical-forum-2005-2008-pbND3008692/ (Accessed 5 February 2017)
10. Internetowy System Aktów Prawnych (Polish online legal database). The Reimbursement Law on the reimbursement of medicinal products, special purpose dietary supplements and medical devices. Available at http://isap.sejm.gov.pl/DetailsServlet?id=WDU20111220696 (Accessed 5 February 2017).
11. The Council of the European Communities.Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems. Available at http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_1989_105/dir_1989_105_en.pdf. (Accessed 5 February 2017).
12. Ozieranski P, McKee M, King L. The politics of health technology assessment in Poland. Health Policy. 2012;108(2-3):178-93.
13. Ozierański P, King L. The persistence of cliques in the post-communist state. The case of deniability in drug reimbursement policy in Poland. Br J Sociol. 2016.
14. Ozieranski P, McKee M, King L. Pharmaceutical lobbying under postcommunism: universal or country-specific methods of securing state drug reimbursement in Poland? Health Econo Pol Law. 2012;7:175-95.
15. Kolasa K, Schubert S, Manca A, Hermanowski T. A review of health technology assessment (HTA) recommendations for drug therapies issued between 2007 and 2009 and their impact on policymaking processes in Poland. Health Pol. 2011;102(2-3):145-51.
16. Lipska I, Hoekman J, McAuslane N, Leufkens H, Hovels AM. Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? Clin Pharmacol Ther. 2015;98:489-91.
17. Skóra K, Wilk N. Rada swoje, urzędnicy swoje. Menedżer Zdrowia. 2014;9.
18. Kolasa K, Wasiak R. Health technology assessment in Poland and Scotland: comparison of process and decisions. Int J Technol Assess Health Care. 2012;28:70-6.
19. Raftery J. Review of NICE's recommendations, 1999-2005. BMJ. 2006;327:1266-8.

chapter 9

GENERAL DISCUSSION

GENERAL DISCUSSION

In this thesis we studied the cross-jurisdictional variations in the health technology assessment (HTA) of new medicines and attempted to disentangle these variations by exploring some of their possible determinants. We looked at HTA processes, outcomes and timelines for new drugs across jurisdictions included in our research, as well as differences between HTA for oncology and non-oncology drugs, and the impact of regulatory outcomes on HTA and access, finally focussing on HTA in Poland in the context of a changing HTA environment in a country with limited resources. This final section summarises our main findings and discusses the challenges and opportunities that cross-jurisdictional HTA variations constitute for the evidence-based decision-making process for the reimbursement of new drugs.

Main findings

HTA has become an important policy tool for its ability to inform policy makers regarding the optimal allocation of increasingly limited resources and to ensure evidence-based decision processes. Existing definitions of HTA emphasise its multidisciplinary character, its required robustness as a scientific process and its link with health policy (1).

We concluded that EU jurisdictions vary substantially in their approach to oncology and non-oncology drugs, with Germany issuing more positive recommendations for oncology drugs and England issuing more positive recommendations for non-oncology drugs. The Netherlands was the only studied jurisdiction with recommendations that were consistent across oncology and non-oncology drugs.

In this study we also explored the access gap, or the time between regulatory approvals and HTA recommendations for oncology and non-oncology drugs and concluded that timelines for these processes vary considerably across jurisdictions. We further concluded that both HTA outcomes and timelines can only be interpreted with in-depth understanding of jurisdiction-specific HTA processes.

A trichotomous classification of HTA recommendations based on publicly available information was developed and presented in this thesis to enable international comparison of HTA recommendations across jurisdictions. To facilitate additional comparisons of HTA recommendations and timelines between jurisdictions as well as beyond Europe, a survey of HTA agencies yielded agency-provided data and an agreement on common HTA milestones to develop a benchmarking methodology. This methodology is presented and discussed in this thesis with a focus on methodological challenges and recommendations (chapter 2). This methodology allowed the investigation of HTA timelines in greater detail, including the HTA review process and the time dedicated to interactions between HTA agencies and pharmaceutical companies during the assessment and appraisal components of the HTA review process. This study shows that it is feasible to find consensus among HTA agencies regarding the common milestones of the HTA review process. Whilst HTA agency benchmarking across jurisdictions has promising potential, timelines

alone cannot be used as a single measure to compare or measure performance of HTA agencies; and an in-depth understanding of jurisdiction- specific HTA processes is required.

As oncology is defined as a public health priority across jurisdictions (including Poland) and there are substantial differences in cancer care in Europe and globally including patients' access to new oncology drugs (2) another focus of this research was the comparison of HTA recommendations between oncology and non-oncology drugs. In the study, in which we investigated whether conditional versus standard regulatory pathways lead to differences in HTA outcomes, similar variability between two groups was found. This implies that improved alignment between regulatory and HTA agencies is important, especially for drugs with post-launch evidence generation requirements because of less than complete data on benefits and risks. In chapter 5 we investigated how the relevance of commonly used endpoints in clinical trials, overall survival (OS), progression-free survival (PFS), quality of life (QoL) is valued by European HTA agencies and we found that this value is affected by a gap in requested versus available evidence, mainly because regulators vary in their willingness to accept some degree of clinical uncertainty. Further, for new oncology drugs we investigated the impact of OS and PFS gains on HTA recommendations, concluding that HTA agencies face difficulties when determining the clinical relevance of new anticancer medicines (chapter 6).

Poland is a country of limited resources with successful implementation of HTA. Chapter 7 provides a better understanding of the role of HTA processes in decision making for new drugs in Poland and how this approach could be considered by other countries of limited resources. In the pragmatic HTA model use by Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), the pharmaceutical company is responsible for the preparation of a reimbursement dossier of good quality in line with HTA guidelines, while the assessment team in AOTMiT is responsible for the critical review of that dossier. Adoption of this model may be considered by other countries with limited resources to balance differing priorities and to ensure transparent and objective access to medicines. Despite the development of this pragmatic HTA model, however, additional progress in Poland is required. Chapter 8 compares HTA recommendations for new oncology and non-oncology drugs in the changing environment in Poland, concluding that timely patient access to medicines is threatened, as only a minority of drugs approved by EMA are assessed by the Polish agency and the majority assessed are evaluated negatively, although oncology drugs are evaluated slightly less negatively.

Classifications used to enable international comparison of HTA recommendations

Substantial differences exist in healthcare systems and thus HTA systems and processes across European jurisdictions (3). In previous research, a dichotomous classification of HTA recommendations, in which a distinction is made only between positive and

negative HTA outcomes, was used for both cross-country comparison (4) (5) as well as for description of one jurisdiction such as Poland (6) (7) or Scotland (8). We used a dichotomous classification of HTA recommendations, exploring the impact of OS and PFS gains on HTA recommendations for new oncology drugs (chapter 6). In France only drugs that were evaluated as having a "lesser medical benefit" using the Service Médical Rendu (SMR) scale were classified as having received a negative recommendation as were drugs in Germany that received a "less benefit" evaluation and drugs in the Netherlands that received a "less therapeutic value" assessment. In all three systems, other classifications received positive HTA recommendations. Such an approach is practical, but simplistic.

In our research, HTA processes were mapped and based on in-depth understanding of each jurisdiction's characteristics and a trichotomous classification of HTA recommendations, *positive*, *positive with restrictions* and *negative* was also developed (chapter 2). Agencies that offer advice on added clinical value were the most challenging to classify into such a trichotomous system. The assumption was made that drugs with a benefit score "important, major" (FR), "considerable, major" (GER) or "added therapeutic value" (NL) were classified as having received positive recommendations. Whereas those with "moderate, minor "(FR), "non-quantifiable, minor" (GER) and "similar therapeutic value" (NL) were classified as having received positive recommendations with restrictions. Lastly, the categories "lesser" (FR, SMR scale), "non-existing" (FR, Amélioration du Service Médical Rendu, [ASMR] scale V)," less, no added benefit" (GER) and "less therapeutic value" (NL) were grouped as negative recommendations.

The trichotomous classification was also used to compare HTA recommendations in the HTA agencies benchmarking study (chapter 3) and to explore the details of Polish HTA recommendations and develop a rationale for restrictions and negative recommendations there (chapter 8). We also used this classification to investigate how conditional versus standard regulatory pathways impact HTA recommendations (chapter 4).

Both the dichotomous and trichotomous classifications enable recommendations to be compared across divergent jurisdictions. However, this is a simplification of HTA recommendations that are far more complex. The biggest challenge in using both these classifications is for those agencies in France, Germany and the Netherlands, which undertake a clinical value-added scale to their assessment, as this affects a new drug's reimbursement status more than its listing. However the trichotomous classification allows researchers to capture more jurisdiction-specific details and indeed, the majority of classifications published in the literature could easily be translated into our trichotomous classification (9).

Can HTA agencies be benchmarked?

The variation in HTA processes and outcomes raises the question as to whether HTA agencies can be benchmarked across jurisdictions. Our research (chapter 3) shows

that benchmarking HTA agencies is a feasible and useful but challenging method to compare HTA agencies and should be encouraged systematically. The key challenge is to identify and agree on common milestones during HTA review process and to define the type of information required to enable comparative analysis. Importantly, the type of information required to benchmark HTA agencies is not always available in the public domain and thus needs to be provided by HTA agencies, which may be complicated by the necessary time and resources as well as the sensitive nature of the data.

The specific focus of our research was to develop a robust methodology to enable comparative benchmarking across HTA agencies. The resulting approach was developed and tested in cooperation with the agencies. In using this methodology we found no substantial differences across jurisdictions in HTA practices such as the review sequence, which consisted of an assessment phase followed by an appraisal phase. However, HTA agencies do differ in their processes and thus in their timelines. Whilst these timelines can be easily measured, they cannot be used as a single measure to compare HTA agencies' performance but rather can be interpreted only with an in-depth understanding of jurisdiction-specific HTA processes and practices.

There is a common understanding that HTA agencies should adhere to key principles such as those outlined by Drummond and colleagues (10), which could be organised into the four domains of: 1) the structure of HTA programs; 2) the methods of HTA; 3) the processes for conduct of HTA; and 4) the use of HTAs in decision making.

One of the challenges identified in this study is that information needed for HTA agency benchmarking is not available in the public domain. Therefore, we call for more transparency, at least regarding agreed common milestones in HTA processes to be available in the public domain. Importantly, to enable increased collaboration in HTA, transparently available quantitative and qualitative comparative information about HTA agencies is needed as a platform on which to build trust in and across agencies. In addition, process maps, together with agreed milestones can support the design of procedures in newly established HTA agencies and the improvement of processes in the existing HTA bodies. It is key, however, to consider context when evaluating the processes, procedures and performance of existing HTA agencies (11).

Divergent HTA outcomes may potentially create a barrier for joint EU assessments of relative effectiveness (12) which may be overcome by an in-depth understanding of these differences and why they exist. We investigated variations in HTA recommendations for new oncology versus non-oncology drugs across European jurisdictions (chapter 2).

Our research shows that even in a country like Poland with defined cost-effectiveness thresholds economic reasons may not be the rationale for negative HTA recommendations (chapter 8). However economic causes did emerge as important reasons for restrictions for both oncology and non-oncology drugs that may be used as a basis for pricing and reimbursement negotiations by the Economic Commission

at the Ministry of Health (chapter 7). Our research indicated that the identification of detailed reasoning for recommendations based on the information available in the public domain can be challenging (chapters 5, 8).

HTA agencies face difficulties while assessing the value of oncology medicines. We investigated how European decision makers value the relevance of clinical trial endpoints (OS, PFS and QoL) for oncology medicines (chapter 5), concluding that variations in HTA agency approaches lead to variations in the valuation of available evidence. HTA guidelines indicate a preference for clinically and patient-relevant endpoints such as OS and QoL over surrogate endpoints (most guidelines do not specify whether PFS is considered a surrogate or patient-relevant endpoint). Whilst OS and QoL data are relevant for patients, conclusive data for these endpoints are not always available. The magnitude of effect size of OS and PFS can also impact HTA recommendations (chapter 6), which is of particular importance in the context of the most recent initiatives from European Society for Medical Oncology (13) and American Society of Clinical Oncology (14) on the clinicians' approach to the value of the clinical benefit of oncology drugs. Our research (chapter 6) showed that HTA guidelines do not contain a clearly defined threshold for clinically relevant improvements of OS or PFS as a prerequisite for positive HTA recommendations. Therefore we concluded that defining a disease-specific minimum standard for what could be considered a clinically relevant OS and PFS gain could support consistent, transparent and informed decision making in oncology.

Previous research showed that HTA bodies vary considerably in their approach to new drugs (3) raising the question as to whether the approach of these agencies differs across therapeutic areas. As oncology is a public health priority across EU jurisdictions and as there are differences in cancer care among EU countries, we investigated and compared HTA approach to oncology versus non-oncology drugs and also the access gap for these drugs. Oncology drugs constitute a high proportion of all new drugs approved by licencing bodies and in our research the proportion of oncology drugs approved by EMA was almost 40% (chapter 2). Some oncology drugs are indicated for treatment of cancers with significant unmet medical need (chapter 4), but high and continuously increasing costs are associated with the use of anticancer drugs (15) and patient access to new oncology products varies considerably across jurisdictions (16). Previous research indicates for example, that there are tremendous differences in access to anticancer drugs between European countries (2). Austria, Spain and Switzerland are the most progressive countries regarding the adoption and access to new drugs while the UK, the Czech Republic, Norway and Poland lag far behind.

Cost-effectiveness and budget impact (affordability) considerations

Although not explored in our research, cost-effectiveness and budget impact considerations are perceived to be the main area of HTA agencies' activities and in many cases the main driver for HTA recommendations (17). In several jurisdictions

cost-effectiveness criteria play a considerable role in the decision making process for the reimbursement of new drugs, with the most prominent examples being England and Scotland (18).

We investigated the reasons for positive, restricted and negative HTA recommendations across jurisdictions (chapters 2, 6 and 8). Overall, almost 40% of all HTA recommendations were negative, while over 60% were positive and positive with restrictions across jurisdictions included in our study (chapter 2). However, when this is viewed at a jurisdictional level, about half of HTA recommendations in Scotland, Germany and France were negative. These differences can be explained by variations in healthcare systems and thus HTA processes in selected jurisdictions. Based on our study results, the Scottish Medicines Consortium (SMC) would appear as the most restrictive, with more than half of HTA recommendations being negative. The proportion of negative recommendations issued by the French Haute Autorité de Santé (HAS) and German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) was extremely close to that by SMC. However, HAS and IQWIQ typically base their recommendations on the therapeutic value of new drugs and do not consider cost-effectiveness criteria. Our results indicated that cost-effectiveness is not the main reason for negative recommendations or restrictions across jurisdictions.

Cost-effectiveness is also not the main rationale for the overwhelming majority (85%) of negative HTA recommendations in Poland, but rather both clinical and economic reasons (chapter 8). Poland has a cost-effectiveness threshold embedded in a legal framework (19), defined as triple the gross domestic product per capita (chapter 7). However, even though there were no purely economic reasons for HTA rejections in Poland, we identified purely economic reasons for restrictions in more than half of restricted HTA recommendations (chapter 8). Importantly, HTA recommendations from AOTMiT are used as the basis for pricing negotiations by the Economic Commission at the Ministry of Health. Therefore, such an economic restriction in HTA recommendation could create a solid argument for subsequent pricing negotiations and could facilitate the process of lowering the prices for new drugs.

Eichler and colleagues predicted that cost-effectiveness thresholds were expected to emerge as one of the criteria important for a transparent decision- making process, especially in high-income countries (20). By definition, the affordability issue is beyond the scope of regulatory agency activities; yet regulators are in a position to influence affordability by their behaviour and regulatory processes. Raising regulatory evidence requirements could, for example, increase drug prices (21). Conversely, better alignment between regulators and HTA bodies with regard to pre- and post-launch evidence requirements could reduce R&D costs although it is uncertain if this could reduce drug prices. The incremental cost-effectiveness ratio (ICER) for multi-indication drugs can change considerably over the product life cycle and should be taken into account in any transparent decision-making process for resource allocation. For example, the projected whole-cycle ICER for trastuzumab, indicated for early

or late-stage (metastatic) breast cancer is reduced by half as compared with cost-effectiveness for the initial indication (22).

Alignment between regulatory and HTA agencies

Regulatory bodies such as EMA in Europe and HTA agencies have different remits and thus differing scopes of activities and requirements. The main difference between the two groups lies in the regulator's focus on quality, efficacy and safety of new medicines and HTA bodies' concentration on the cost-effectiveness aspects of therapies (23). By definition, HTA bodies assess the clinical value of a health technology in comparison with currently available treatment alternatives and therefore focus on providing the best value for money. It is of crucial importance to understand HTA evidence requirements and how they differ from regulatory needs (24). Importantly, safety is considered by HTA agencies and has a negative impact on HTA recommendations for new oncology drugs that varies between 21% and 56%, according to European jurisdiction (25). Although this suggests some overlap between regulatory and HTA bodies (26), there is still room for improvement in the development of closer collaboration between EMA and HTA bodies. There are numerous ongoing initiatives for better alignment of regulatory and HTA activities for the development of potential synergies between the two groups, with the collaboration between EMA and the European Network for HTA (EUnetHTA) being probably the most influential in Europe (27).

To enable earlier patients' access to potentially beneficial drugs that have accrued less than complete data for benefits and risks but that address unmet medical needs, EMA implemented a special regulatory pathway for conditional approval (28). However, regulatory approval alone is no longer sufficient for true patient access and HTA recommendations for reimbursement are now also required. This raises the question as to how HTA recommendations are affected by uncertainties related to conditional regulatory approval. Although new drugs conditionally approved by EMA might be expected to result in a higher proportion of positive HTA recommendations because they typically address high unmet medical need, the degree of uncertainty around the benefits and risks of these drugs might also be expected to lead to a lower proportion of positive HTA recommendations. Our research in fact, showed little to no difference in HTA recommendations for new oncology drugs approved through conditional versus standard regulatory pathways (29). Whilst special regulatory pathways were developed and introduced to increase the early uptake of potentially beneficial medicines in clinical practice, this study suggests that the use of this conditional regulatory pathway does not increase the likelihood of positive HTA recommendation.

Differing evidentiary requirements by regulatory bodies and HTA bodies are well reported (3) although some overlap has been identified (30) and better alignment should be considered and implemented through the whole product life cycle. Current interactions among regulators, the pharmaceutical industry and HTA bodies mainly

consist of early scientific advice provided in early drug development; however, future trends may potentially reflect the product life cycle approach (31). Indeed the most recent initiative of further collaboration between EMA and EUnetHTA goes in the direction of the alignment of pre- and post-launch data requirements (32). Post-launch evidence generation for conditionally approved drugs would be an ideal opportunity for close collaboration between regulators and HTA agencies and the whole product life cycle approach may potentially result in closing the gap between efficacy and effectiveness (33). It is expected that patients will ultimately benefit from life cycle collaboration as it enables timely access to new drugs and will also help to achieve the sustainability of healthcare systems.

In other progress needed for collaboration, previous research showed that the minimum set of evidence requirements across HTA bodies could be defined (34) and steps have already been undertaken to improve the use of regulators' reports such as European Public Assessments Reports by HTA bodies (35). It is critical for the role of payers to be increased in this collaboration, in particular with regards to real world evidence (RWE) and post-launch evidence generation, which is frequently discussed in the context of registries and their standards and is one of scheduled EUnetHTA JA3 core activities (36). It may be possible to use electronic health record data already being regularly collected by payers as RWE with minor modifications.

Access gap (timelines from regulatory approval to HTA recommendation)

Because marketing authorisation is no longer sufficient and HTA recommendations are now a crucial component of the availability of new therapies, HTA agencies are often blamed for delaying patients' access to new drugs (37) (38). The time from regulatory approval by EMA to HTA recommendation is often called the access gap and two main components of this gap have been identified as the time from regulatory approval to HTA agency submission and the time from HTA agency submission to HTA recommendation. In general, the former component is dependent on pharmaceutical company initiative to submit its reimbursement application to the HTA agency and the latter component is mainly HTA agency-dependent. However, interactions between an HTA agency and a pharmaceutical company in the HTA process also impact timelines. In fact, time- and resource-consuming involvement of stakeholders including patients, clinicians and payers can take place throughout the HTA procedure, depending on jurisdiction-specific processes. Therefore, mapping HTA processes is of crucial importance to enable understanding and interpretation of the timelines, as jurisdictions vary considerably in their approach to stakeholder involvement (11).

This research shows that access gap differs considerably across European jurisdictions, with a median time of less than four months in Germany and over 1.5 years in Poland (chapter 2). This variability in timing could be a potential barrier for joint EU assessments. The access gap could be reduced by closer collaboration

between regulators and HTA bodies. In Europe, the time interval between Committee for Medicinal Products for Human Use (CHMP) opinion and European Commission (EC) decision on marketing authorisation approval usually takes around 60 days (39) and may represent the ideal time to initiate an earlier HTA review process. This time interval is already being considered by EUnetHTA to start joint assessments and future developments will show whether this approach is efficient and practical and results in an increase in national uptake (40). However the risk of starting the HTA review before formal MA approval should also be considered, in particular with regard to limitations in HTA resources.

Regulatory concerns have arisen that are specific to products granted earlier access including efficacy issues such as experienced with gefitinib for non-small cell lung cancer and safety issues such as experienced with the nonsteroidal anti-inflammatory drug rofecoxib, which reportedly increased cardiovascular risk. Also, post-marketing evidence requirements have not been met by marketing authorisation holders for a variety of reasons (41). Despite these challenges, there are potential mechanisms to accelerate reimbursement decisions along with early regulatory approval through cooperation between regulators and HTA bodies (42).

HTA review timelines (from HTA submission to HTA recommendation)

In this thesis we investigated a methodology to examine HTA review timelines based on the information provided by HTA agencies (chapter 3) since crucial information on HTA submission dates are frequently not available in the public domain. For the five HTA agencies analysed in our study HTA review timelines differed, from a median of approximately three months up to over two years. Interestingly, our study results indicated that the shortest median HTA review time was achieved by the smallest agency; however, HTA constitutes the core function of this agency and more than 75% of its human resources are dedicated to HTA-related activities. We have explored timelines from regulatory approvals to HTA recommendations based on publicly available information (chapter 2) and also timelines from HTA submission to HTA recommendations based on the information provided by HTA agencies (chapter 3). Timelines are important only as they determine patient access to new drugs and timely access can have an impact on the effectiveness of treatment. Speeding up the decision-making process could lead to earlier patient access to new drugs and provide better value for money by providing treatment at the earlier stage of a disease (34). Based on the HTA agency benchmarking study, the time from regulatory approval to HTA submission is approximately 70 days. Assuming that the HTA process could start as soon as the CHMP opinion is issued, timelines could be reduced by four months without any additional changes in the HTA review processes. Hence it seems that current initiatives on the alignment between the EMA and HTA bodies may potentially reduce timelines (32).

Marketing authorisation holder activities can also significantly impact timelines. For example, pharmaceutical companies can delay patients' access to new drugs in particular markets due to the company pricing strategy based on international reference pricing systems. However, it is not feasible to extract pharmaceutical company time based on the information available in the public domain (chapter 2). Previous research has indicated that in the 11 EU countries in which for the new promising drug for hepatitis C (sofosbuvir) the drug has not yet been assessed, 5 Eastern European countries reported that the marketing authorisation holder has not submitted the application for reimbursement (43).

As the level of HTA expertise varies considerably across EU jurisdictions (44) the importance of capacity building should not be underestimated. Capacity building in HTA based on the use of international expertise was identified as one of three main success factors in the successful implementation of HTA in Poland (chapter 7). Importantly, an equal level of expertise across EU jurisdictions is also seen as a prerequisite for joint EU production (45). The Polish example could be used by jurisdictions that intend to implement HTA in their decision-making processes for resource allocation decisions. It may be particularly useful for countries with limited resources, as local capacity is seen as one the drivers or facilitators for HTA implementation in real local settings (46).

Future developments

Towse and associates identified the most influential factors for the production of evidence of relative effectiveness for new drugs as 1) the extent to which the regulator uses adaptive licensing and post-launch evidence; 2) the degree of European HTA agency coordination in reviewing pre-launch evidence and developing post-launch evidence requirements and 3)the nature of the regulator-HTA interaction (47). The most recent initiative for further EMA and EUnetHTA collaboration explores these precise factors (32). Based on previous research, more interactions between regulators and HTA bodies could increase the efficiency of health systems, in particular with regard to market access processes (48). Defining minimal common evidence requirements between regulators and HTA bodies as well as across HTA bodies could increase the efficiency of both regulatory and HTA processes. Currently, there are also inefficiencies in reimbursement submissions by pharmaceutical companies across EU jurisdictions, which differ in their requirements; however Drummond predicted that one pricing and reimbursement EU agency will probably exist in the near future (49).

Much effort remains to be expended to affect the considerable differences in HTA processes and outcomes across EU jurisdictions, including work on the clinical assessment component of HTA review process both across HTA agencies and in close collaboration with the EMA. This work can comprise an important current and future role for EUnetHTA with political support from the European Commission (50).

The clinical component of HTA should be closely linked to the regulatory process with regards to life cycle evidence requirements and timelines, increasing the efficiency of HTA processes across jurisdictions and likely reducing the access gap and expediting patients' access to beneficial drugs.

Cooperation across EU jurisdictions can also be the basis for joint EU REAs. In the context of the European Commission proposal on strengthening cooperation in HTA (50) and based on the most recent study from the pharmaceutical industry perspective (51), joint EU REAs, especially those with early dialogue, would also be beneficial as they would improve predictability and consistency without creating challenges to national autonomy.

From an industry perspective, joint EU full HTA would not bring any benefits and could potentially even bring delays and present challenges national autonomy, in particular with regard to assessment of economic considerations (51). European HTA collaboration has become a reality in recent decades, but key barriers have been identified regarding issues such as the relevance of specific assessment topics for individual institutions or jurisdictions and the timing of EU joint assessments (52). While limited, the initial experience regarding joint assessments has been positive (52). Based on EUnetHTA website information, 12 joint assessments have been conducted in European national settings, including four joint assessments on drugs and eight on non-drug technologies (40). The forms of adaptation used in these joint assessments varied across jurisdictions from cross-checking evidence to the updating of existing local or national HTA reports.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) commissioned an independent analysis of the EUnetHTA pilot of five rapid REAs (53), evaluating their consistency regarding process, methods and outcomes and their uptake or re-use in the national and regional systems. Four domains of the REA methods were explored: 1) health problem and current use of technology; 2) description and technical characteristics of technology; 3) clinical effectiveness and 4) safety. No issues were reported regarding the first two domains while there were issues with clinical effectiveness; namely the selection of comparators and endpoints, indirect comparisons and the quality of evidence. These issues were considered minor; however safety issues included the need for clarification on the type of data for relative safety assessment and were considered as leaving substantial room for improvement. The report also concluded that there was limited evidence as to why the re-use of REAs is so constrained, although the length of time required to perform a review was suggested as one the most important barriers. Future efforts will need to focus on overcoming existing barriers.

Limitations of our research

Our study has some limitations. First, HTA recommendations do not mean automatic reimbursement and final reimbursement decisions can sometimes differ from HTA

recommendations, in countries such as Poland (54). Second, we included a limited number of jurisdictions for our international comparison.

The focus of this thesis is on new medicines but HTA is by no means limited to drugs (3) (55). It should be noted that there are promising developments that can potentially bring full HTA assessment of medical devices into decision-making systems for countries such as Poland (56). However, when countries consider implementing HTA in decision-making processes, they most often begin with the evaluation of new and often very expensive drugs. In this thesis we investigated initial HTA recommendations, however it should be recognised that re-assessments can be undertaken for drugs and initial HTA recommendations can change over time.

Further research

Based on our research findings and considering persisting inequalities between EU countries and predictions about future epidemiological trends, oncology should be a priority field for further research regarding patients' access to treatments options. Further research is also required for regulatory HTA interactions including the alignment of evidence requirements, the potential for closer cooperation and even the incorporation of HTA functions within regulatory remits to avoid the duplication of work and to increase the efficiency of public organisations (47). Previous research showed that conditional regulatory pathways can result in longer regulatory review times (28) and further study should determine if conditional marketing approval also prolongs HTA review times.

Additional research is also needed as to how new drugs that have been judged to have major added therapeutic value by agencies that use clinical effectiveness criteria such as those in Germany and France are assessed by agencies that use cost-effectiveness criteria in their evaluations such as England and Scotland. Finally, based on our research and the uncovered challenges posed by the variation in HTA outcomes, international comparisons based on an in-depth understanding of jurisdiction-specific processes should be recommended for further study. Such research can provide evidence for joint EU assessments and increase national uptake of those decisions.

Conclusions

The objective of this thesis was to investigate the variations in HTA processes and outcomes across jurisdictions, with a focus on oncology versus non-oncology medicines and on Poland, a country with limited resources.

HTA processes and outcomes vary across jurisdictions, impacting the timely access to new medicines for patients. There are many possible determinants for these variations. The recommendations are made in a complicated multi-stakeholder field and many factors must be taken into account. Variations in HTA processes and outcomes can be explained by jurisdiction- and agency-specific determinants such as health priorities in a given jurisdiction, a legal framework, the engagement of stakeholders, the use of

cost-effectiveness criteria, the assessment of added clinical value, HTA guidelines and evidence required from a pharmaceutical company. Variations can also be explained by drug- and disease-specific determinants such as therapeutic field, available versus required evidence and the magnitude of effect size). Regardless of the explanation, however, these variations in HTA processes and outcomes could create a potential barrier for joint EU assessments.

Collaboration between regulators and HTA bodies throughout the product life cycle may improve the evidence generation required at different stages and may reduce overlap between regulators and HTA bodies as well as the medicine access gap. We recommend that current and future cooperation between regulators and HTA bodies should progress in the direction of continuous close collaboration throughout the whole product life cycle. Closer true collaboration such as that being promulgated by EUnetHTA is needed also across HTA bodies, however this collaboration is still challenging as considerable differences in the level of expertise across European countries exist. Therefore, continued capacity building based on international expertise, in which countries with less experience in the implementation of HTA and lower levels of expertise learn from countries with greater experience and expertise is important to build trust between HTA agencies, enabling joint HTA production. Among countries with limited resources, the Polish experience in successful implementation of the pragmatic model for HTA in decision-making processes on drug reimbursement could be utilised as a model. Closer collaboration, joint HTA production and use of joint assessments in national decision making would potentially mitigate the risk of unnecessary delays across jurisdictions.

Activities should be undertaken by HTA agencies to provide timely assessments and thus support timely patients' access to needed drugs. Systematic benchmarking of HTA activities based on agreed common milestones across HTA agencies and in-depth understanding of jurisdiction-specific processes will enable the objective measurement and improvement of HTA processes. The increase in efficiency of HTA processes will be of particular value for jurisdictions with limited experience in HTA and with limited resources. Such benchmarking studies should be performed systematically and be based on the data provided directly by HTA agencies; however, data on common milestones should be available in the public domain to make HTA processes more transparent.

REFERENCES

1. Kristensen FB, Nielsen C, Chase B, Lampe K, Lee-Robin SH, Makela M. Health technology assessment and health policy-making in Europe. Current status, challenges and potential. European Observatory of Health Systems and Policies 2008.
2. Wilking N. Comparator report on patient access to cancer drugs in Europe. 2009.
3. Kanavos P. The impact of heath technology assessment: an international comparison. EuroObserver. 2010.
4. Context Matters Global Variability in HTA Decisions Poses Challenges for Innovative Biopharmaceutical Research and Development. 2014.
5. Chabot I, Rocchi A. Oncology drug health technology assessment recommendations: Canadian versus UK experiences. Clinicoecon Outcomes Res. 2014;6:357-67.
6. Niewada M, Polkowska M, Jakubczyk M, Golicki D. What Influences Recommendations Issued by the Agency for Health Technology Assessment in Poland? A Glimpse Into Decision Makers' Preferences. Value in Health Regional Issues. 2013;2(2):267-72.
7. Kolasa K, Schubert S, Manca A, Hermanowski T. A review of Health Technology Assessment (HTA) recommendations for drug therapies issued between 2007 and 2009 and their impact on policymaking processes in Poland. Health Policy. 2011;102(2-3):145-51.
8. Charokopou M, Majer IM, Raad Jd, Broekhuizen S, Postma M, Heeg B. Which Factors Enhance Positive Drug Reimbursement Recommendation in Scotland? A Retrospective Analysis 2006–2013. Value Health. 2015;18(2):284-91.
9. Nicod E, Kanavos P. Developing an evidence-based methodological framework to systematically compare HTA coverage decisions: A mixed methods study. Health Policy. 2016;120(1):35-45.
10. Drummond M. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care. 2008;24:3:244-58.
11. Sampietro-Colom L. Consider context and stakeholders. Int J Technol Assess Health Care. 2012;28(2):166-7.
12. Kleijnen S, George E, Goulden S, d'Andon A, Vitre P, Osinska B, et al. Relative effectiveness assessment of pharmaceuticals: similarities and differences in 29 jurisdictions. Value Health. 2012;15(6):954-60.
13. Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. 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. 2015;26(8):1547-73.
14. Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, et al. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. J Clin Oncol. 2015;33(23):2563-77.
15. Drummond MF, Mason AR. European Perspective on the Costs and Cost-Effectiveness of Cancer Therapies. J Clin Oncol. 2007;25(2):191-5.
16. McCabe C, Bergmann L, Bosanquet N, Ellis M, Enzmann H, von Euler M, et al. Market and patient access to new oncology products in Europe: a current, multidisciplinary perspective. Ann Oncol. 2009;20(3):403-12.
17. Nicod E. 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. The European journal of health economics : HEPAC : health economics in prevention and care. 2016.
18. Sarah KS, Jon S, Nancy D, Andrew W. Searching for Cost-effectiveness Thresholds in NHS Scotland. Office for Health Economics; 2013.
19. Lipska I, McAuslane JN, Leufkens H, Hovels AM. A decade of health technology assessment in Poland accepted for publication. Int J Technol Assess Health Care. 2017.

20. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health. 2004;7(5):518-28.
21. Eichler H-G, Hurts H, Broich K, Rasi G. Drug Regulation and Pricing — Can Regulators Influence Affordability? N Engl J Med. 2016;374(19):1807-9.
22. Garrison LP, Jr., Veenstra DL. The economic value of innovative treatments over the product life cycle: the case of targeted trastuzumab therapy for breast cancer. Value Health. 2009;12(8):1118-23.
23. Eichler H-G, Bloechl-Daum B, Abadie E, Barnett D, König F, Pearson S. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nature Reviews Drug Discovery. 2010;9(4):277-91.
24. Henshall C, Sansom L, Eichler HG, Lemgruber A, Longson C, O'Rourke B, et al. Understanding the Role and Evidence Expectations of Health Technology Assessment and Coverage/Payer Bodies: What Are They Looking for, and How and Why Does This Differ From What Regulators Require? Therapeutic Innovation & Regulatory Science. 2013;48(3):341-6.
25. Kleijnen S, Lipska I, Leonardo Alves T, Meijboom K, Elsada A, Vervolgyi V, et al. Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries. Ann Oncol. 2016.
26. Breckenridge A, Woods K, Walley T. Medicines regulation and health technology assessment. Clin Pharmacol Ther. 2010;87(2):152-4.
27. Cooperation between regulators and HTA bodies creates synergies [press release]. 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2016/04/WC500204827.pdf (available 07th July 2017)
28. Hoekman J, Boon W, Bouvy JC, Ebbers HC, de Jong JP, De Bruin ML. Use of the conditional marketing authorization pathway for oncology medicines in Europe. Clin Pharmacol Ther. 2015.
29. Lipska I, Hoekman J, McAuslane N, Leufkens H, Hovels AM. Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? Clin Pharmacol Ther. 2015;98(5):489-91.
30. Tsoi B, Masucci L, Campbell K, Drummond M, O'Reilly D, Goeree R. Harmonization of reimbursement and regulatory approval processes: a systematic review of international experiences. Expert Rev Pharmacoecon Outcomes Res. 2013;13(4):497-511.
31. Henshall C, Mardhani-Bayne L, Frønsdal KB, Klemp M. Interactions between health technology assessment, coverage, and regulatory processes: Emerging issues, goals, and opportunities. Int J Technol Assess Health Care. 2011;27(03):253-60.
32. EMA and EUnetHTA step up interaction to align data requirements [press release]. 2017 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002771.jsp&mid=WC0b01ac058004d5c1 (available 04th July 2017).
33. Nordon C, Karcher H, Groenwold RHH, Ankarfeldt MZ, Pichler F, Chevrou-Severac H, et al. The "Efficacy-Effectiveness Gap": Historical Background and Current Conceptualization. Value Health. 2016;19(1):75-81.
34. Oyebode O, Garrett Z, George E, Cangini A, Muscolo LAA, Warren S, et al. Evidence requirements for Reimbursement of Pharmaceuticals across Europe. Int J Technol Assess Health Care. 2015;31(1-2):59-67.
35. Berntgen M, Gourvil A, Pavlovic M, Goettsch W, Eichler H-G, Kristensen FB. Improving the Contribution of Regulatory Assessment Reports to Health Technology Assessments—A Collaboration between the European Medicines Agency and the European network for Health Technology Assessment. Value Health. 2014.
36. EUnetHTA. Work Package 5 - Life cycle approach to improve Evidence Generation. 2017.

37. Wilsdon; T, Serota A, for Charles River Associates contracted by EFPIA, PhRMA, Medicines Australia and EuropaBio A comparative analysis of the role and impact of Health Technology Assessment. 2011 May 2011.
38. Wilsdon; T, Fiz; E, Haderi; A, 2013 Final Report by Charles River Associates for PhRMA and EFPIA. Project No. D19197-00. A comparative analysis of the role and impact of Health Technology Assessment.
39. Hirako M, McAuslane N, Salek S, Anderson C, Walker S. A Comparison of the Drug Review Process at Five International Regulatory Agencies. Drug Inf J. 2007;41(3):291-308.
40. EUnetHTA. European network for Health Technology Assessment National uptake 2016.
41. Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nature reviews Drug discovery. 2008;7(10):818-26.
42. Martinalbo J, Bowen D, Camarero J, Chapelin M, Demolis P, Foggi P, et al. Early market access of cancer drugs in the EU. Ann Oncol. 2016;27(1):96-105.
43. Schelleman H, Dupree R, Kristensen FB, Goettsch W. Why we should have more collaboration on HTA in Europe: the example of sofosbuvir. Journal of Pharmaceutical Policy and Practice. 2015;8(1):O13.
44. Mueller D, Gutierrez-Ibarluzea I, Schuller T, Chiumente M, Ahn J, Pichon-Riviere A, et al. Capacity Building in Agencies for Efficient and Effective Health Technology Assessment. Int J Technol Assess Health Care. 2016;32(4):292-9.
45. Kleijnen S, Toenders W, de Groot F, Huic M, George E, Wieseler B, et al. European collaboration on relative effectiveness assessments: What is needed to be successful? Health Policy. 2015(0).
46. Jaramillo HEC, Moreno-Mattar O, Osorio-Cuevas D. Emergence Of "Drivers" For The Implementation Of Health Technology Assessment. Int J Technol Assess Health Care. 2016;32(4):300-6.
47. Towse A, Garau M, Mohr P, Messner DA. Futurescapes: expectations in Europe for relative effectiveness evidence for drugs in 2020. Journal of comparative effectiveness research. 2015:1-18.
48. Tsoi B, O'Reilly D, Masucci L, Drummond M, Goeree R. Harmonization of HTA--based reimbursement and regulatory approval activities: a qualitative study. J Popul Ther Clin Pharmacol. 2015;22(1):e78-89.
49. Drummond MF. Will there ever be a European drug pricing and reimbursement agency? The European Journal of Health Economics. 2003;4(2):67-9.
50. European Commission; DG SANCO Strengthening of the EU cooperation on Health Technology Assessment (HTA). 2016.
51. Charles River Associates. European cooperation on HTA impact assessment. 2017.
52. Nachtnebel A, Mayer J, Erdos J, Lampe K, Kleijnen S, Schnell-Inderst P, et al. [HTA goes Europe: European collaboration on joint assessment and methodological issues becomes reality]. Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen. 2015;109(4-5):291-9.
53. Wilsdon; T, Pistollato; M, Li; L, Haderi A, Report prepared by Charles River Associates for EFPIA Project No. D21304-00D21304-00. An analysis of the EUnetHTA pilot assessments. 2015
54. Kawalec P, Malinowski KP. Relating Health Technology Assessment recommendations and reimbursement decisions in Poland in years 2012–2014, a retrospective analysis. Health Policy. 2016;120(11):1240-8.
55. Drummond M, Neumann P, Jonsson B, Luce B, Schwartz JS, Siebert U, et al. Can we reliably benchmark health technology assessment organizations? Int J Technol Assess Health Care. 2012;28(2):159-65.
56. Fuchs S, Olberg B, Panteli D, Perleth M, Busse R. HTA of medical devices: Challenges and ideas for the future from a European perspective. Health Policy. 2017;121(3):215-29.

Addendum &

SUMMARY

Health Technology Assessment (HTA) is an increasingly important policy tool in the decision making on financing health technologies. HTA plays an important role in the reimbursement of new medicines in particular in Europe to ensure the most rational way of spending scarce resources.

A marketing authorization issued by the European Medicines Agency is a necessary but no longer sufficient condition for the availability of new drugs for European patients. Thus the HTA requirement for new drugs to represent good value for money is sometimes described as the fourth hurdle to medicines' availability, in addition to the medicine's quality, efficacy and safety, which are considered by regulatory agencies. The key issue is to spend available health care resources in the best possible way and determine how to achieve the best value for money available and dedicated to health care. HTA can contribute to achieving this goal by evidence based decision making process and by improving health outcomes and thus spending available resources in the best possible way.

This raises the question: if HTA is so important and plays such a prominent role in evidence based decision making in health care why it still remains controversial and even more importantly why there are such substantial differences in HTA recommendations across jurisdictions?

In this thesis we have studied the variation in HTA of new medicines (in Poland, in Europe and globally). We have explored in details HTA processes, outcomes and timelines for new drugs across jurisdictions included in our research with the main focus on Europe and Poland. In this thesis we investigated HTA bodies approach to oncology versus non-oncology drugs in Europe and in Poland and also the impact of regulatory pathways on HTA recommendations for oncology drugs in Europe.

Timelines between the regulatory approval by EMA and HTA recommendations influence patients' access to new drugs and thus is perceived as an access gap. Therefore in this thesis we also investigated the timelines from regulatory approval to HTA recommendations in the context of jurisdiction specific HTA processes.

Part A focuses on international perspective on HTA, Part B explores HTA recommendations for new oncology medicines and Part C focuses on Poland as the example of one country which has successfully implemented a pragmatic HTA model and whose experience could be utilized by other countries with limited resources. Finally the discussion section discusses the main findings and put them in the context of existing research.

Part A: International perspective on HTA

In chapter 2 we investigated how HTA agencies differ in their approach to new drugs with a special focus on their approach to oncology versus non-oncology drugs. We also explored timelines from regulatory approval to HTA recommendations (defined as access gap) in the context of jurisdiction specific HTA processes. To allow

international comparison a trichotomous classification of HTA recommendations was developed based on jurisdiction specific process maps. We collected the data on HTA outcomes for new active substances approved by EMA between 2007 and 2013 based on publicly available information. We included 470 HTA reports from six European jurisdictions (England, France, Germany, Netherlands, Poland and Scotland). Almost 40% of all HTA recommendations were negative while over 60% were positive and positive with restrictions across all six jurisdictions included in our study. Median timing from MA approval by EMA to HTA recommendation was 211 days for all drugs across all jurisdictions and it was 220 and 197 days for oncology and non-oncology drugs respectively. In this chapter we concluded that HTA agencies differ in their approach to oncology and non-oncology drugs, with Germany issuing more positive recommendations for oncology drugs and England issuing more positive recommendations for non-oncology drugs. The Netherlands was the only studied jurisdiction with recommendations that were consistent across oncology and non-oncology drugs. Timelines vary considerably across jurisdictions, which can be a barrier for joint EU assessments.

In chapter 3 the development of a methodology for benchmarking HTA agencies is described detailing the challenges and opportunities, the common milestones of an HTA review process and the type of information required to enable comparative analysis . Timelines of HTA processes were also presented however based on detailed information provided by HTA agencies (and in many cases not available in the public domain). Data for 109 HTA reviews from five HTA agencies were analysed in this study. There were no substantial differences in the HTA methodology applied by these jurisdictions. Our study showed considerable differences among the median timelines from submission to final HTA recommendation. In the group of agencies analysed in our study only one agency had more than 75% of its resources dedicated to HTA activities and this agency had the shortest median timelines. We concluded that it was feasible to find consensus among HTA agencies regarding the common milestones of the HTA review process in order to map jurisdiction-specific processes against agreed generic processes, along with the detailed characteristics of each agency that enables results to be interpreted in the right context. There may be promising potential in HTA agency benchmarking across jurisdictions.

Part B: HTA recommendations – focus on oncology

The focus of part B of this thesis was on oncology as oncology drugs constitute a high proportion of all new drugs approved by licencing bodies (in our research the proportion of oncology drugs approved by EMA was almost 40%).

In chapter 4 we investigated the impact of regulatory pathways (conditional versus standard) on HTA recommendations for new cancer drugs in Europe and our research showed little to no difference in HTA recommendations for new oncology drugs by regulatory pathway (conditional versus standard). Special regulatory pathways were

developed and introduced to increase the early uptake of potentially beneficial medicines in clinical practise. However our study suggested that the use of the EMA conditional regulatory pathway did not increase the likelihood of positive HTA recommendation.

In chapter 5 we studied the extent to which the value of end points for cancer medicines differs among European decision makers. The relevance of commonly used end points in trials, especially overall survival (OS), progression-free survival (PFS) and quality of life (QoL), varies, leading to the available evidence being valued differently. Guidelines and relative effectiveness assessments (REAs) were compared for pricing or reimbursement decisions in England, France, Germany, The Netherlands, Poland, and Scotland. Anticancer medicines were evaluated that received a marketing authorization in Europe between 2011 and 2013 and had at least four available national REAs. A total of 79 REAs were included. HTA guidelines indicate a preference for clinically and patient relevant end points such as OS and QoL above surrogate end points. Most guidelines did not specify whether PFS was considered a surrogate or patient-relevant end point. OS data were included in all REAs and were the preferred end point by HTA agencies, but these data were not always mature or robust. European decision-making on relative effectiveness of anticancer medicines seemed to be affected by a gap in requested versus available clinical evidence, mainly because the EMA was willing to accept some degree of clinical uncertainty. A multi-stakeholder debate would be essential to align concrete robust evidence requirements in oncology and a collectively shared definition for relevant clinical benefit, which will benefit patients and society in general.

Furthermore in chapter 6 the impact of OS and PFS gains on HTA recommendations for new anticancer drugs was investigated. Therefore, we compared publicly available HTA reports produced by six European HTA agencies to investigate how the magnitude of OS and PFS influenced HTA recommendations for 14 new anticancer medicines. A dichotomous classification of HTA recommendations was developed to allow cross-jurisdiction comparison and compared the data for effect magnitudes of OS and PFS against a threshold of 3 months' incremental gains for OS and PFS and HR = 0·7 (for OS and PFS). In this study we included 72 HTA recommendations for 14 anticancer drugs. The described OS incremental gains varied from no improvement/OS data not mature to 10·4 months. The PFS incremental gains ranged from 1.4 months to 6·1 months. We noted divergence in HTA recommendations despite the fact that in general, the same effect magnitudes for OS and PFS were referenced by different jurisdictions for the same medicine. HTA guidelines did not contain a clearly defined threshold for clinically relevant improvements of OS or PFS as a prerequisite for positive HTA recommendations We concluded that HTA agencies faced difficulties when determining the clinical relevance of new anticancer medicines. Defining a disease-specific minimum standard for what could be considered a clinically relevant OS and PFS gain could support consistent, transparent, and informed decision making in the rapidly evolving field of oncology.

Part C: Focus on Poland

The focus of chapter 7 and 8 was on Poland as the example of a country with limited resources in which HTA was successfully implemented in the decision making processes in particular on new drugs, however there is still room for improvement. Polish HTA recommendations for new oncology and non-oncology drugs are explored in particular in the context of a changing HTA environment. The reasons for restrictions and negative HTA recommendations are analysed and timelines (access gap and HTA review time) are investigated and discussed as they considerably impact patients' access to new drugs.

In chapter 7 the Polish experience in implementing HTA was described and how this approach may be considered by other countries with limited resources. Thus, the evolution of the HTA system and processes in Poland over the last decade and current developments based on publicly available information were analysed. We found out that the role of HTA in the drug-reimbursement process in Poland has increased substantially over the recent decade, starting in 2005 with the formation the Agency for Health Technology Assessment and Tariff System (AOTMiT). The key success factors in this development were effective capacity building based on the use of international expertise, the implementation of transparent criteria into the drug reimbursement processes and the selective approach to the adoption of innovative medicines based on the cost-effectiveness threshold among other criteria. While Poland is regarded as a leader in Central and Eastern Europe, there is room for improvement, especially with regard to the quality of HTA processes and the consistency of HTA guidelines with reimbursement law. In the "pragmatic" HTA model use by AOTMiT, the pharmaceutical company is responsible for the preparation of a reimbursement dossier of good quality in line with HTA guidelines while the assessment team in AOTMiT is responsible for critical review of that dossier. Adoption of this model may be considered by other countries with limited resources to balance differing priorities and ensure transparent and objective access to medicines for patients who need them.

In chapter 8 we further explored HTA recommendations for new drugs in Poland with the focus on oncology and non-oncology drugs. The objective of this study was to compare AOTMiT outcomes, determinants of outcomes and timelines of decision making between 2012 and 2015 for new oncology drugs with non-oncology drugs. AOTMiT recommendations were classified as positive, positive with restrictions and negative and defined reasons for restrictions as well as for negative recommendations as clinical, economic, both clinical and economic, and organisational. Results for oncology and non-oncology products were differentiated. We found out that AOTMiT assessed only 39% of all NASs approved by EMA from 2012-2015. Most (57%) received a negative recommendation (48%, oncology; 64%, non-oncology). Only 4% received a purely positive recommendation. The main rationale for restricted recommendations was economic (50%, oncology, 75%, non-oncology). A mixture of economic and clinical reasons was the most common rationale for rejection (85%)

for all drugs and the only rationale for rejection in oncology drugs. Median timing for reviews exceeded legal requirements, slightly less so for oncology medicines. We concluded that despite improved processes and transparency at AOTMiT, timely patient access to medicines was threatened as only the minority of NASs are assessed and the majority assessed are evaluated negatively, although oncology drugs were evaluated slightly less negatively.

Discussion

Chapter 9 summarizes the main findings and discusses the variations in HTA processes and outcomes for new medicines and put them in the broader context of existing research. We discuss the challenges and opportunities such variations constitute for the evidence based decision making process on the reimbursement of new drugs in particular in the context of oncology and non-oncology drugs and the context of changing HTA environment in countries with limited resources like Poland.

HTA processes and outcomes vary across jurisdictions impacting the timely access to new medicines for patients. There are many possible determinants for these variations. The recommendations are made in a complicated multi stakeholder field thus many factors are taken into account. Variations in HTA processes and outcomes can be explained by jurisdiction and agency specific determinants as well as by drug and disease specific determinants.

Effective HTA processes require more cooperation between regulatory agencies and HTA agencies to enable timely patients' access to new drugs. Collaboration between regulators and HTA bodies throughout the product life cycle may improve the evidence generation required at different stages and may reduce overlap between regulators and HTA bodies as well as may reduce access gap.

Polish experience in successful implementation of HTA in decision-making processes on drug reimbursement (pragmatic model) could be utilized by countries with limited resources.

The research presented in this PhD thesis was conducted under the umbrella of the Utrecht-World Health Organization (WHO) Collaborating Centre for Pharmaceutical Policy and Regulation, which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands. This research was (partly) accomplished in collaboration with the Centre for Innovation in Regulatory Science, London, The United Kingdom.

SAMENVATTING

Health Technology Assessment (HTA) is een steeds belangrijker wordend beleidsinstrument in de beslissing over de financiering van nieuwe technologie in de gezondheidszorg. HTA speelt een belangrijke rol in de vergoeding van nieuwe geneesmiddelen, in het bijzonder in Europa, om de meest rationele manier van verdeling van schaarse middelen te verzekeren.

Een marktautorisatie van de EMA (*European Medicines Authority*) is een noodzakelijke, maar niet meer voldoende, voorwaarde voor de beschikbaarheid van nieuwe geneesmiddelen voor Europese patiënten. Vergoedingsautoriteiten (HTA organisaties) evalueren voor nieuwe geneesmiddelen onder andere de bewijsvoering op het gebied van doelmatigheid. Dit wordt soms beschreven als de vierde hindernis na de evaluatie van kwaliteit, werkzaamheid en veiligheid van het geneesmiddel, die door de registratieautoriteiten zoals de EMA worden uitgevoerd.

Dit leidt tot de vraag: als HTA zo belangrijk is en zo'n prominente rol speelt in de besluitvorming in de gezondheidszorg, waarom is het nog steeds controversieel en nog belangrijker, waarom zijn er zoveel verschillen in HTA-aanbevelingen over jurisdicties?

In dit proefschrift werd de variatie in HTA van nieuwe geneesmiddelen bestudeerd (in Polen, in Europa en wereldwijd). HTA processen, uitkomsten en tijdlijnen voor nieuwe geneesmiddelen werden bekeken in verschillende jurisdicties die in dit onderzoek zijn opgenomen, met de nadruk op Europa en Polen.

In dit proefschrift werden verder de verschillen in benadering van oncologie versus non-oncologie geneesmiddelen en ook de impact van regulatoire routes binnen de EMA op HTA-aanbevelingen voor oncologie geneesmiddelen in Europa onderzocht.

Tijdlijnen tussen marktautorisatie door de EMA en de aanbevelingen door vergoedingsautoriteiten beïnvloeden de toegankelijkheid van nieuwe geneesmiddelen voor patiënten. De periode tussen beide beslismomenten wordt dus beschouwd als kloof in toegang tot geneesmiddelen. Daarom werd in dit proefschrift ook de tijd tussen marktautorisatie en HTA-aanbevelingen onderzocht.

Deel A richt zich op het internationale perspectief binnen HTA. Deel B onderzoekt HTA-aanbevelingen voor nieuwe oncologische geneesmiddelen en deel C richt zich op Polen als voorbeeld van een land met een succesvolle implementatie van een pragmatisch model van HTA. Deze ervaring zou kunnen worden gebruikt door andere landen met beperkte middelen. Tenslotte worden in de discussie sectie de belangrijkste bevindingen besproken en worden ze in de context van de huidige stand van de wetenschap geplaatst.

Deel A: HTA aanbevelingen: internationaal perspectief

In hoofdstuk 2 werd onderzocht hoe HTA agentschappen verschillen in hun benadering van nieuwe geneesmiddelen, met speciale aandacht voor het verschil tussen oncologie en niet-oncologie geneesmiddelen. Daarnaast zijn tijdlijnen tussen

regulatoire goedkeuring en HTA-aanbevelingen onderzocht. Om internationale vergelijking mogelijk te maken, werd een trichotome indeling van HTA aanbevelingen per jurisdictie ontwikkeld. De gegevens over HTA-uitkomsten werden verzameld voor nieuwe geneesmiddelen die door de EMA tussen 2007 en 2013 zijn goedgekeurd. Alle data werden verzameld op basis van publieke informatie. In totaal werden 470 HTA-rapporten van zes Europese jurisdicties (Engeland, Frankrijk, Duitsland, Nederland, Polen en Schotland) geincludeerd. Bijna 40% van alle HTA-aanbevelingen waren negatief, terwijl meer dan 60% positief en positief waren met restricties. De mediane duur tussen marktautorisatie door EMA en een HTA aanbeveling was 211 dagen voor alle geneesmiddelen in alle jurisdicties en het was 220 en 197 dagen voor respectievelijk oncologie en niet-oncologie geneesmiddelen. In dit hoofdstuk is geconcludeerd dat HTA-organisaties verschillen in hun aanpak van oncologie en niet-oncologie geneesmiddelen, waarbij Duitsland meer positieve aanbevelingen voor oncologie geneesmiddelen gaf en Engeland meer positieve aanbevelingen voor non-oncologie geneesmiddelen gaf. Nederland was de enige bestudeerde jurisdictie waar geen verschillen waren tussen oncologie en niet-oncologiegeneesmiddelen. Tijdslijnen varieerden sterk over jurisdicties, wat een belemmering kan vormen voor gezamenlijke EU-beoordelingen.

In hoofdstuk 3 werd de ontwikkeling gepresenteerd van een hulpmiddel dat benchmarking van HTA-organisaties mogeljk maakt. Daarbij werden uitdagingen en kansen, de gemeenschappelijke mijlpalen van het HTA-beoordelingsproces en het soort informatie die nodig was om vergelijkende analyse mogelijk te maken weergegeven. Tijdlijnen van HTA-processen werden ook gepresenteerd op basis van informatie die door HTA-organisaties werd verstrekt. Gegevens van vijf verschillende HTA agentschappen over het proces end e uitomsten van in totaal 109 HTA aanbevelingen werden geanalyseerd in deze studie. Er waren geen substantiële verschillen in de HTA-methodologie die door deze jurisdicties werd. In de groep agentschappen die in onze studie werden geanalyseerd, had slechts één agentschap meer dan 75% van zijn middelen gewijd aan HTA-activiteiten en dit agentschap had de kortste mediaan tijdlijnen. Het zou dus mogelijk kunnen zijn om consensus te vinden tussen HTA-organisaties met betrekking tot de gemeenschappelijke mijlpalen van het HTA-herzieningsproces. Er kan veelbelovend potentieel zijn in het benchmarking van HTA-organisaties over jurisdicties.

Deel B: HTA aanbevelingen: focus op oncologische geneesmiddelen

De focus van deel B van dit proefschrift was op de oncologie, omdat oncologie geneesmiddelen een groot deel vormen van alle nieuwe geneesmiddelen die door registratieautoriteiten zijn goedgekeurd. In dit onderzoek was het aantal oncologische geneesmiddelen die door EMA goedgekeurd bijna 40%.

In hoofdstuk 4 werd de invloed van regulatoire routes (voorwaardelijke markttoelating versus standaard) op HTA-aanbevelingen voor nieuwe oncologie geneesmiddelen in

Europa onderzocht. Geneesmiddelen bleken even vaak een positief of negatief advies te krijgen na een voorwaardelijke marktautorisatie als na een standaard autorisatie. Bijzondere regulatoire routes zijn ontwikkeld en geïntroduceerd om de vroege opname van potentieel goede geneesmiddelen in de klinische praktijk te verhogen. Deze studie liet echter zien dat het gebruik van deze voorwaardelijke regulatoire route de waarschijnlijkheid van positieve HTA-aanbeveling niet verhoogde.

In hoofdstuk 5 werd onderzocht in hoeverre de waarde van eindpunten voor oncologie geneesmiddelen verschilt tussen Europese jurisdicties. De relevantie van veelgebruikte eindpunten in klinische trials varieert, met name algehele overleving (OS), voortgangsvrije overleving (PFS) en kwaliteit van leven (QoL), waardoor het beschikbare bewijs verschillend gewaardeerd wordt. In deze studie werden richtlijnen en relatieve effectiviteitsbeoordelingen (REA's) van geneesmiddelen vergeleken voor prijsstelling of vergoeding in Engeland, Frankrijk, Duitsland, Nederland, Polen en Schotland. Oncologische geneesmiddelen die tussen 2011 en 2013 een marktautorisatie kregen van de EMA, en met ten minste vier beschikbare nationale REA's, werden geincludeerd in deze studie. Er werden in totaal 79 REA's opgenomen. HTA richtlijnen lijken een voorkeur te geven aan klinische en patiënt relevante eindpunten zoals OS en QoL boven surrogaat eindpunten. De meeste richtlijnen hebben niet aangegeven of PFS als een surrogaat of patiënt relevant eindpunt werd beschouwd. Data over OS waren opgenomen in alle REA's en waren altijd het gewenste eindpunt door HTA agentschappen, maar deze gegevens waren niet altijd beschikbaar of robuust. Europese besluitvorming over de relatieve effectiviteit van geneesmiddelen tegen kanker lijkt te worden beïnvloed door een kloof in gevraagde versus beschikbare klinische bewijzen, vooral omdat de EMA bereid was een zekere mate van klinische onzekerheid te accepteren. Een debat met meerdere belanghebbenden zou essentieel zijn om betrouwbare eisen aan de bewijsvoering in de oncologie en een gezamenlijk gedeelde definitie voor relevante klinische uitkomsten af te stemmen, die de patiënten en de maatschappij in het algemeen ten goede komen.

Daarnaast werd in hoofdstuk 6 de impact van de mate van verbetering van OS- en PFS- op HTA-aanbevelingen voor nieuwe oncologische geneesmiddelen onderzocht. Daarom werden de beschikbare HTA-rapporten vergeleken die door zes Europese HTA-organisaties werden geproduceerd, Een dichotome indeling van HTA-aanbevelingen werd ontwikkeld om gegevens voor effectmagneten van OS en PFS te vergelijken tussen de zes jurisdicties. Daarnaast werden de aanbevelingen vergeleken tussen geneesmiddelen met meer dan 3 maanden verbetering in OS en PFS en een hazard ratio van 0,7 of hoger en geneesmiddelen met minder gunstige grootte van effect. In deze studie zijn 72 HTA-aanbevelingen geincludeerd voor 14 oncologische geneesmiddelen. De verbetering van OS zoals beschreven in de rapporten varieerde van geen verbetering / OS data niet compleet tot een verbetering van 10,4 maanden. De verbetering in PFS varieerde van 1,4 maanden tot 6,1 maanden. Resultaten lieten een divergentie in HTA-aanbevelingen zien, ondanks het gebruik van dezelfde

effectgroottes voor OS en PFS per geneesmiddel door de verschillende jurisdicties. HTA richtlijnen bevatten geen duidelijk gedefinieerde drempel voor klinisch relevante verbeteringen van OS of PFS als voorwaarde voor positieve HTA aanbevelingen. HTA-organisaties kunnen mogelijk baat hebben bij een duidelijkere bepaling van klinische relevantie van nieuwe oncologische geneesmiddelen. Het definiëren van een ziekte-specifieke minimumstandaard voor wat kan worden beschouwd als een klinisch relevante OS en PFS verbetering zou consistente en transparante besluitvorming kunnen ondersteunen.

Deel C: Focus op Polen

De focus van hoofdstukken 7 en 8 was op Polen als voorbeeld van een land met beperkte middelen waarin HTA succesvol is geïmplementeerd in de besluitvormingsprocessen, maar er is nog ruimte voor verbetering. In hoofdstuk 7 werd de ervaring in Polen beschreven van de implementatie van HTA en hoe deze aanpak door andere landen van beperkte middelen zou kunnen worden overwogen. De evolutie van het HTA-systeem en bijbehorende processen in Polen van het afgelopen decennium en de huidige ontwikkelingen werd geanalyseerd gebaseerd op publiek beschikbare informatie. De rol van HTA in het geneesmiddelvergoedingsproces in Polen is aanzienlijk toegenomen in het afgelopen decennium, beginnend in 2005 met de oprichting van het agentschap voor HTA (AOTMiT). De belangrijkste succesfactoren in deze ontwikkeling waren effectieve capaciteitsopbouw, gebaseerd op het gebruik van internationale expertise, de implementatie van transparante criteria in de geneesmiddelvergoedingsprocessen en de selectieve aanpak van de vergoeding van innovatieve geneesmiddelen op basis van een kosteneffectiviteitsdrempel. Hoewel Polen als leider in Midden- en Oost-Europa wordt beschouwd, is er nog wel ruimte voor verbetering, met name wat betreft de kwaliteit van HTA-processen en de consistentie van HTA-richtlijnen met vergoedingswetgeving. In het "pragmatische" HTA-model dat door AOTMiT wordt gebruikt, is het farmaceutisch bedrijf verantwoordelijk voor de voorbereiding van een vergoedingsdossier van goede kwaliteit in overeenstemming met HTA-richtlijnen. Het beoordelingsteam in AOTMiT is verantwoordelijk is voor kritische beoordeling van dat dossier. Aanvaarding van dit model kan door andere landen met beperkte middelen worden overwogen om verschillende prioriteiten in evenwicht te brengen en transparante en objectieve toegang tot geneesmiddelen te waarborgen voor patiënten die ze nodig hebben.

In hoofdstuk 8 werden HTA-aanbevelingen voor nieuwe geneesmiddelen in Polen verder onderzocht met de nadruk op oncologie en non-oncologie geneesmiddelen. De doelstelling van deze studie was het vergelijken van AOTMiT-uitkomsten, determinanten van uitkomsten en tijdlijnen van besluitvorming tussen 2012 en 2015 voor nieuwe oncologische geneesmiddelen met niet-oncologische geneesmiddelen. AOTMiT aanbevelingen werden geclassificeerd als positief, positief met restricties en negatief. De redenen voor restricties en voor negatieve aanbevelingen

werden geclassificeerd als klinisch, economisch, zowel klinisch als economisch en organisatorisch. Resultaten voor oncologie en non-oncologische producten werden gedifferentieerd. We hebben geconstateerd dat AOTMiT vanaf 2012-2015 slechts 39% van alle NAS's, die marktautorisatie kregen van EMA, heeft beoordeeld. De meeste (57%) kregen een negatieve aanbeveling (48%, oncologie, 64%, non-oncologie). Slechts 4% kreeg een positieve aanbeveling zonder restricties. De belangrijkste reden voor positieve aanbevelingen met restricties was economisch (50%, oncologie, 75%, non-oncologie). Een combinatie van economische en klinische redenen was de meest voorkomende reden voor afwijzing (85%) voor alle geneesmiddelen en de enige reden voor afwijzing in oncologie geneesmiddelen. Mediane tijdslijnen voor aanbevelingen overschreden de wettelijke vereisten, hoewel dit ets minder het geval was voor oncologie geneesmiddelen. Hieruit kan geconcludeerd worden dat ondanks verbeterde processen en transparantie bij AOTMiT, tijdige toegang tot geneesmiddelen bedreigd werd, omdat alleen de minderheid van de NAS's wordt beoordeeld, de beoordelingen niet aan de tijdslijnen voldoen en de meerderheid van de beoordelingen negatief is.

Discussie

In hoofdstuk 9 werden de variaties in HTA processen en resultaten voor nieuwe geneesmiddelen besproken.

HTA processen en uitkomsten variëren over jurisdicties die de tijdige toegang tot nieuwe medicijnen voor patiënten beïnvloeden. Er zijn veel mogelijke determinanten voor deze variaties. Variaties in HTA-processen en resultaten kunnen worden zowel verklaard door jurisdictie- en agentschapsspecifieke determinanten, evenals door geneesmiddel- en ziektespecifieke determinanten.

Effectieve HTA-processen vereisen meer samenwerking tussen registratie- en HTA-organisaties om tijdig patiënten toegang te kunnen geven tot nieuwe geneesmiddelen. Samenwerking tussen registratie- en HTA-organisaties gedurende de gehele levenscyclus van een geneesmiddelen kan de bewijsvoering in verschillende stadia van de levensyclus verbeteren. Daarnaast kan hiermee de mogelijke overlap tussen registratie- en HTA organisaties verminderd worden. De beschreven ervaring van Polen in de succesvolle implementatie van HTA in de besluitvormingsprocessen inzake drugsvergoeding kan worden gebruikt door landen met beperkte middelen.

Dit proefschrift is geschreven in het kader van het World Health Organization (WHO) Collaborating Centre for Pharmaceutical Policy and Regulation binnen de afdeling Farmacoepidemiologie en Klinische Farmacologie, Utrecht Instituut voor Farmaceutische Wetenschappen, Faculteit Beta Wetenschappen, Universiteit Utrecht. Dit onderzoek is daarnaast uitgevoerd in samenwerking met het Centre voor Innovation in Regulatory Science, Londen, Verenigd Koninkrijk.

STRESZCZENIE

Ocena technologii medycznych (ang. skrót HTA) jest coraz ważniejszym narzędziem w procesie podejmowania decyzji dotyczących finansowania leków. Szczególnie w Europie ocena technologii medycznych odgrywa ważną rolę przy refundacji nowych leków i zapewnia wybór najbardziej racjonalnych metod dysponowania środkami publicznymi w opiece zdrowotnej.

Decyzja o dopuszczeniu leków do obrotu wydawana przez Europejską Agencję Leków jest koniecznym, ale już nie jedynym warunkiem dostępności nowych leków dla europejskich pacjentów. Wymóg, aby nowa terapia była racjonalna ekonomicznie jest często opisywany jako czwarty warunek udostępnienia leku pacjentom, jeśli lek spełnia jednocześnie warunki jakości, skuteczności i bezpieczeństwa oceniane przy dopuszczaniu leku do obrotu przez agencje regulujące rynek leków. Coraz częściej kluczową kwestią jest uzyskanie jak najlepszej relacji skuteczności leku do jego ceny. Ocena technologii medycznych (HTA) przyczynia się do osiągnięcia tego celu. Dzięki wykorzystaniu w HTA miarodajnych i popartych badaniami danych naukowych publiczne środki finansowe są wykorzystywanie w optymalny sposób a leczenie jest skuteczniejsze.

Tu rodzi się pytanie: jeśli poparta dowodami naukowymi ocena technologii medycznych odgrywa tak wielką rolę w podejmowaniu decyzji dotyczących finansowania terapii, dlaczego budzi wciąż tyle kontrowersji, a co ważniejsze - skąd biorą się tak istotne różnice w rekomendacjach HTA w poszczególnych jurysdykcjach?

W niniejszej publikacji analizie poddano różnice w ocenie technologii medycznych nowo wdrażanych leków (w Polsce, Europie i na świecie). Z uwagą przestudiowano szczegóły procedury HTA, jej wyniki i czas oczekiwania na wprowadzenie leku do refundacji w różnych jurysdykcjach ze szczególnym uwzględnieniem Polski i Europy. W niniejszej pracy zbadano podejście agencji HTA do leków onkologicznych i nieonkologicznych w Polsce i w Europie, oraz wpływ procedury stosowanej przez agencję regulującą na rekomendacje HTA dotyczące leków onkologicznych w Europie.

Czas od dopuszczenia leku do obrotu przez Europejską Agencję Leków do wydania rekomendacji w ramach HTA jest bardzo istotny z punktu widzenia pacjentów i jest określany jako access gap, czas oczekiwania na wprowadzenie leku do refundacji. W niniejszej publikacji analizowana jest jego długość w kontekście procesów HTA właściwych dla poszczególnych jurysdykcji.

Część A skupia się na międzynarodowej perspektywie HTA, część B na rekomendacjach dotyczących leków onkologicznych, część C opisuje doświadczenia polskie, gdzie z pozytywnym skutkiem wprowadzono pragmatyczny model HTA. Polskie doświadczenia mogą służyć innym krajom z ograniczonymi środkami w systemie opieki zdrowotnej. Ostatni rozdział, poświęcony dyskusji, prezentuje niniejsze rozważania w kontekście istniejących badań.

Część A: HTA w perspektywie międzynarodowej

W rozdziale drugim analizowane są różnice w podejściu do nowych leków przez agencje HTA, z rozróżnieniem na leki onkologiczne i nieonkologiczne. Przedmiotem badania jest czas upływający od zatwierdzenia leków przez stosowne instytucje regulujące do wydania rekomendacji przez agencje HTA (zdefiniowany jako czas oczekiwania na wprowadzenie leku do refundacji) w kontekście działań HTA właściwych dla poszczególnych jurysdykcji. W celach porównawczych zastosowano trójdzielną klasyfikację rekomendacji HTA właściwych dla poszczególnych jurysdykcji. Zebrane tutaj dane na temat wyników działań HTA dla nowych substancji czynnych zatwierdzonych do obrotu przez Europejską Agencję Leków w latach 2007-2013 pochodzą z domeny publicznej. Uwzględniono 470 raportów HTA z sześciu europejskich jurysdykcji (Anglia, Niemcy, Holandia, Francja, Polska i Szkocja). Prawie 40% leków zostało przez HTA zaopiniowanych negatywnie. Opinie pozytywne lub pozytywne warunkowo otrzymało 60% badanych leków. Średni czas od dopuszczenia leku do obrotu przez Europejską Agencję Leków do wydania rekomendacji przez agencje HTA wynosił 211 dni we wszystkich jurysdykcjach. Czas ten wynosił 220 dni dla leków onkologicznych i 197 dni dla leków pozostałych. Konkludując można stwierdzić, że agencje HTA w każdym z opisywanych krajów opiniują leki inaczej. W Niemczech wydaje się najwięcej pozytywnych rekomendacji dla leków onkologicznych. W Anglii agencje HTA rekomendują pozytywnie więcej leków nieonkologicznych. W Holandii ilość rekomendacji dla leków onkologicznych i nieonkologicznych jest podobna. Czas oceny leków nie jest jednolity w badanych krajach, co może być istotną barierą w stworzeniu wspólnych europejskich regulacji prawnych w tej materii.

W rozdziale trzecim przedstawiono metodologię porównywania procedur agencji HTA, opisując szczegółowo wyzwania, możliwości i najważniejsze punkty w procesie opiniowania HTA oraz rodzaj danych niezbędnych do przeprowadzenia analizy porównawczej. Czas wydawania rekomendacji HTA został oceniony na podstawie szczegółowych informacji dostarczonych przez opisywane agencje (choć nie zawsze dostępnych w domenie publicznej). W niniejszej publikacji przeanalizowano dane dotyczące stu dziewięciu badanych leków pochodzące z pięciu agencji. Metodologia oceny leków nie różniła się zasadniczo w analizowanych jurysdykcjach. Niniejsze badania uwidoczniły jednak różnice w długości procesu opiniowania. Spośród agencji analizowanych tylko jedna poświęcała 75% swojego potencjału na działania związane z oceną technologii medycznych. Ta agencja opiniowała w najkrótszym czasie. Konkluzją rozdziału jest stwierdzenie, że osiągnięcie konsensusu dotyczącego wspólnych punktów referencyjnych w ocenie leków poprzez różne agencje jest możliwy. Miałoby to na celu dostosowanie procesów oceny do uwarunkowań prawnych, przyjętych procedur ogólnych i specyfiki każdej z agencji HTA. Istnieje spory potencjał dla jednolitego porównania agencji HTA we wszystkich jurysdykcjach.

Część B: Rekomendacje HTA w onkologii

Część B niniejszej pracy skupia się na onkologii, ponieważ leki onkologiczne stanowią wysoki odsetek wszystkich nowych leków dopuszczonych do obrotu przez decydujące o tym instytucje (w niniejszej pracy badawczej leki onkologiczne stanowiły 40% leków dopuszczonych do obrotu przez Europejską Agencję Leków).

W rozdziale czwartym zbadano wpływ procedur regulacyjnych (warunkowych i standardowych) na rekomendacje HTA dotyczące nowych leków onkologicznych w Europie. Z niniejszych dociekań wynika, że wpływ ścieżki regulacyjnej (warunkowej czy standardowej) na rekomendacje leków przez HTA w poszczególnych krajach Europy nie różni się zasadniczo. Specjalne warunkowe procedury regulacyjne umożliwiały wcześniejsze wprowadzenie leków potencjalnie korzystnych w praktyce klinicznej. Jednocześnie stwierdzono, że wybór warunkowej ścieżki legislacyjnej Europejskiej Agencji Leków nie zwiększa prawdopodobieństwa wydania pozytywnej rekomendacji HTA dla leku.

W rozdziale piątym omówiono do jakiego stopnia punkty końcowe dla leków onkologicznych wpływają na decyzje instytucji regulacyjnych w Europie. Rola powszechnie przyjętych punktów końcowych takich jak przeżycie całkowicie (ang. overall survival, w skrócie OS), przeżycie wolne od progresji choroby (ang. progression free survival, w skrócie PFS) i jakość życia (ang. Quality of Life, w skrócie QoL) nie jest oceniana jednolicie, co sprawia, że dostępne dane są różnie interpretowane. Porównano obowiązujące wytyczne i względną ocenę efektywności klinicznej (ang. relative effectiveness assessment, w skrócie REA) w świetle podejmowania decyzji o refundowaniu i wycenie leków w Anglii, Francji, Niemczech, Holandii, Polsce i Szkocji. Oceniono leki onkologiczne które zostały dopuszczone do obrotu w Europie pomiędzy 2011 a 2013 i miały co najmniej cztery dostępne krajowe oceny względnej efektywności (REA). W tej pracy uwzględniono 79 takich ocen. Wytyczne HTA kładły nacisk na takie punkty końcowe jak przeżycie całkowite (OS) i jakość życia raczej niż surogaty punktów końcowych. Większość wytycznych HTA nie precyzowała, czy przeżycie wolne od progresji choroby (PFS) stanowi istotny z punktu widzenia pacjenta punkt końcowy czy jedynie surogat. Dane dotyczące całkowitego przeżycia pacjentów były ujęte we wszystkich ocenach względnej efektywności i były najważniejszymi punktami końcowymi branym pod uwagę przez agencje HTA, ale dane te nie zawsze były wystarczające. Na proces podejmowania decyzji dotyczących względnej efektywności leków onkologicznych w Europie wpływa rozdźwięk między potrzebną a dostępną ilością danych klinicznych. Wynika ona z tego, że Europejska Agencja Leków dopuszczała margines niepewności w badaniach klinicznych. Dopiero debata wielu uczestników systemu mogłaby ujednolicić wymogi dotyczące danych klinicznych w onkologii i stworzyć wspólne kryteria, które mogłyby służyć zdrowiu pacjentów i społeczeństwa.

W rozdziale szóstym omówiono wpływ wzrostu OS (przeżycia całkowitego) i PFS (przeżycia wolnego od progresji choroby) na rekomendacje HTA dla nowych leków onkologicznych. Aby ocenić jak wielkość efektu zdrowotnego w zakresie OS i PFS wpłynęła na kolejne rekomendacje HTA dla 14 leków onkologicznych porównano tu dostępne w domenie publicznej raporty pochodzące od sześciu europejskich agencji HTA. Ustalono dwudzielną klasyfikację rekomendacji HTA i porównano je w różnych jurysdykcjach zestawiając wielkość efektu zdrowotnego w zakresie OS i PFS na tle 3-miesięcznej różnicy w wartości inkrementalnej dla OS i PFS oraz współczynnika ryzyka wynoszącego 0,7 (dla OS i PFS). W tej analizie wzięto pod uwagę 72 rekomendacje HTA dla 14 leków onkologicznych. Opisane różnice inkrementalne wynosiły od braku poprawy/ niewystarczające dane na temat OS do 10, 4 miesięcy OS. Dla PFS różnice inkrementalne wynosiły od 1,4 miesiąca do 6,1 miesięcy. Zauważono rozbieżność w rekomendacjach HTA pomimo faktu, że te same wielkości efektu zdrowotnego w zakresie OS i PFS stanowiły punkt odniesienia dla oceny tego samego leku w różnych jurysdykcjach. Wytyczne HTA nie zawierały ściśle określonego dolnego progu dla klinicznie udowodnionej poprawy u pacjentów OS i PFS, który stanowiłby warunek konieczny dla wydania pozytywnej rekomendacji przez agencję HTA. Wysunięto wniosek, że agencje HTA miały trudności w określeniu przydatności klinicznej nowych leków onkologicznych. Określenie standardów minimalnych korzyści u pacjentów OS i PFS dla określonej choroby mogłoby stworzyć spójny i przejrzysty system podejmowania decyzji w szybko rozwijającej się dziedzinie onkologii.

&

Część C: Sytuacja w Polsce

W rozdziałach siódmym i ósmym skupiono się na Polsce jako przykładzie kraju z ograniczonymi środkami w systemie opieki zdrowotnej, w którym HTA została z powodzeniem wykorzystana przy podejmowaniu decyzji o wprowadzeniu nowych leków do refundacji. Wciąż jest tu jednak miejsce na poprawę. Polskie rekomendacje HTA dla nowych leków onkologicznych i nieonkologicznych są analizowane w kontekście zmieniającego się środowiska HTA. Przyczyny negatywnych lub warunkowych opinii dla leków oraz rzeczywisty czas dostępu pacjentów do leku (czas oczekiwania na refundację leku i czas oceny HTA) są tu omówione jako czynniki mające wpływ na dostęp pacjentów do nowych leków.

W rozdziale siódmym opisano polskie doświadczenia w implementacji HTA i przedstawiono, jak mogą one posłużyć innym krajom z ograniczonymi środkami w systemie opieki zdrowotnej. W oparciu o publicznie dostępne dane na ten temat z okresu ostatnich dziesięciu lat przeanalizowano ewolucję systemu HTA w Polsce, ustalając, że rola HTA w refundacji leków w Polsce znacznie wzrosła od 2005 roku, co miało związek z powołaniem Agencji Oceny Technologii Medycznych i Taryfikacji (AOTMiT). Do sukcesu przyczyniło się wykorzystanie doświadczenia międzynarodowych ekspertów, wprowadzenie przejrzystych kryteriów w procesie

refundowania leków i wybiórcze podejście do innowacyjnych leków - oparte na stworzeniu progu efektywności kosztowej jako jednego z kryteriów. Mimo iż Polska uważana jest za lidera w Europie centralnej i wschodniej nadal jest miejsce na poprawę, zwłaszcza w zakresie jakości procesów HTA i dostosowania wytycznych HTA do przepisów określających podstawy refundacji leków. W pragmatycznym modelu HTA stosowanym przez AOTMiT za przygotowanie dokumentacji dotyczącego refundacji leków i jej zgodność z prawem i wytycznymi HTA odpowiada firma farmaceutyczna, zaś AOTMiT odpowiada za krytyczną analizę tego dossier. Kraje z ograniczonymi środkami w systemie opieki zdrowotnej mogą rozważyć przyjęcie takiego modelu, aby sprecyzować własne priorytety i zapewnić przejrzysty i obiektywny dostęp do leków dla pacjentów ich potrzebujących.

W rozdziale ósmym zbadano rekomendacje HTA dla nowych leków w Polsce z naciskiem na leki onkologiczne i nieonkologiczne. Zadaniem tego rozdziału było porównanie wyników oceny leków i czasu trwania procesu decyzyjnego w AOTMiT w latach 2012 - 2015 dla leków onkologicznych i nieonkologicznych. Rekomendacje AOTMiT zostały sklasyfikowane jako pozytywne, pozytywne warunkowo, i negatywne. Powody zastrzeżeń i negatywnych rekomendacji były oparte na przyczynach klinicznych, ekonomicznych, kliniczno-ekonomicznych oraz organizacyjnych. Zróżnicowano wyniki dla leków onkologicznych i nieonkologicznych. Niniejsza publikacja dowodzi, że AOTMiT oceniło tylko 39% wszystkich nowych substancji aktywnych (ang. New Active Substances, w skrócie NAS) dopuszczonych do obrotu przez Europejską Agencję Leków w latach 2012-2015. Większość, 57%, uzyskała negatywną ocenę (48 % onkologicznych, 64% nieonkologicznych leków). Tylko 4% nowych cząstek otrzymało w pełni pozytywną ocenę. Głównym powodem zastrzeżeń przy rekomendacjach były czynniki ekonomiczne (w 50% leków onkologicznych i w 75% nieonkologicznych). Połączenie czynników ekonomicznych i klinicznych było głównym powodem niezakwalifikowania do refundacji leków (85%) dla wszystkich leków i jedynym powodem - w przypadku leków onkologicznych. Średni czas oceny leku przekraczał wymogi prawne, choć w mniejszym stopniu dotyczyło to leków onkologicznych. Wysunięto więc wniosek, że pomimo poprawy efektywności działań i przejrzystości procedur AOTMiT, terminowy dostęp pacjentów do leków był zagrożony, gdyż oceniono tylko małą część nowych substancji. Większość z nich została zaopiniowana negatywnie, z tym zastrzeżeniem, że leki onkologiczne opiniowano negatywnie nieco rzadziej.

Dyskusja

Rozdział dziewiąty podsumowuje główne ustalenia niniejszej pracy i omawia różnice w procesach i wynikach HTA dla nowych leków. Następnie przedstawia je w kontekście istniejących badań naukowych. W rozdziale tym omówiono wyzwania i szanse jakie daje zróżnicowane HTA w procesie decyzyjnym opartym na danych naukowych poprzedzającym refundację nowych leków, w szczególności onkologicznych

i nieonkologicznych, wobec zmieniającego się środowiska HTA w krajach z ograniczonym budżetem służby zdrowia, takich jak Polska.

Działania i wyniki HTA różnią się w zależności od jurysdykcji w ten sposób wpływając na dostęp pacjentów do nowych leków. Różnice te mają wiele uwarunkowań. Leki opiniuje się w gronie wielu uczestników systemu, co każe brać pod uwagę mnogość czynników. Rozbieżności w procesie oceny i wynikach prezentowanych przez HTA wynikają z różnic prawnych, z czynników wewnątrz agencyjnych oraz uwarunkowań związanych z przebiegiem choroby.

Aby przyspieszyć dostęp pacjentów do nowych leków potrzebna jest większa efektywność działań HTA i większa współpraca między agencjami regulującymi rynek leków a agencjami HTA. Współpraca tychże przez cały cykl życia leku może usprawnić gromadzenie danych wymaganych w kolejnych etapach tego procesu. To może z kolei zmniejszyć dystans pomiędzy instytucjami regulującymi i agencjami HTA i skrócić czas oczekiwania pacjentów na wprowadzenie leku do refundacji.

Pozytywne polskie doświadczenia z HTA przy wprowadzaniu na rynek nowych leków refundowanych (model pragmatyczny) mogą zostać wykorzystane przez inne kraje z ograniczonymi środkami w systemie opieki zdrowotnej.

Badania zaprezentowane w niniejszej pracy doktorskiej zostały przeprowadzone w ramach współpracy z Centrum Badań nad Polityką Regulacji Farmaceutycznej przy Światowej Organizacji Zdrowia (World Health Organization Collaborating Centre for Pharmaceutical Policy and Regulation), z siedzibą w Utrechcie, mieszczącym się przy Katedrze Farmakoepidemiologii i Farmacji Klinicznej Instytutu Nauk Farmaceutycznych na Wydziale Nauki Uniwersytetu w Utrechcie (Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science). Część badań została zrealizowana przy współpracy z Centrum Innowacji Nauk Regulacyjnych (Centre for Innovation in Regulatory Science) w Londynie.

ACKNOWLEDGEMENTS

I would like to thank Prof Dr Bert Leufkens for his support and inspiration, reminding me constantly about the bigger picture and international perspective when I was so deeply absorbed by the details of data from hundreds HTA recommendations from all over the world. I am sincerely grateful to Drs Anke Hövels and Neil McAuslane – co-promoters of this thesis. Anke was my every day contact point at Utrecht University and supported me in my journey between Poland, the Netherlands and the UK. Anke, thank you for your continuous support and motivation during this journey, I will always remember the scientific guidance you provided as well as our female leadership discussions. Neil was always available, including during his holidays, to support me and discuss the details of the research, assisting me in interpreting data while maintaining a global focus. My thanks also go to colleagues from CIRS, Dr Lawrence Liberti for all his support and Patricia Connelly for her willingness to help.

I extend my thanks to Dr Sarah Kleijnen, Teresa Leonardo Alves and Dr Wim Goettsch, with whom I very much enjoyed working on our oncology study and to Dr Jarno Hoekman for the opportunity to explore regulatory-HTA interface in greater detail. I also wish to thank all co-authors of the publications included in this thesis. I would like to thank my former colleagues from HTA agencies around the world with whom I meet regularly and whose curiosity about progress toward my doctorate continuously motivated me, including Dr Brian O'Rourke, Dr François Meyer, Dr Mirjana Huić, Dr Mairin Ryan, Prof Dr Irina Cleemput, Dr Anne Lee, Dr Alric Ruether, Dr Meindert Boysen, Prof Dr Rabia Kahveci and many others and my special thanks go to the former EUnetHTA team Prof Dr Finn Børlum Kristensen, Julia Chamova and Lidia Becla.

I am also very grateful to Dr Zbigniew J. Król for convincing me to start my research when we both worked at AOTM and to Jan Czeczot for his belief in me from the first day of my professional career. I also extend special thanks to Dr Andrzej Jacyna, Maciej Miłkowski and colleagues at NFZ who supported my research at its final stage.

I am deeply grateful to my parents. Mamo, Tato, dziękuję za wszystko, za to, że jesteście! Thank you for all your support and belief in me and for your unconditional love. Dziękuję za Wasze wsparcie, wiarę we mnie i bezwarunkową miłość. And my special thanks go to my son, Wiktor who motivated me in his own unique and specific-to-teenagers way and who gave up family dinners so that I might have time for my scientific research. Additionally, I would like to extend my very special thanks to my triathlon club (Kuźnia Triathlonu). Rafał, Magda, siła! Thanks to you I've experienced many unique moments at the finish line! What does not kill you makes you stronger – so true in triathlons and in life.

Finally, I would like to thank my best friend for being with me, supporting and simply protecting me all the time. You shared all my ups and (especially) downs and motivated me non-stop, sometimes in the most irritating way imaginable and more importantly, you really believed in me. Dziękuję, że mnie wspierałeś zwłaszcza w tym najtrudniejszym okresie. Dostałam więcej niż mogłam oczekiwać.

LIST OF CO-AUTHORS

Affiliations during the conduct of the research

Anne d'Andon
Medicines Evaluation Department, Haute Autorité de Santé (HAS), Paris, France

Anton de Boer
Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands
Medicines Evaluation Board, Utrecht, The Netherlands

Ahmed Elsada
National Institute for Health and Care Excellence (NICE), Manchester, UK

Wim Goettsch
National Health Care Institute (ZIN), Diemen, The Netherlands
Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

Jarno Hoekman
Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

Anke Hövels
Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

Sarah Kleijnen
National Health Care Institute (ZIN), Diemen, The Netherlands
Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

Teresa Leonardo Alves
Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

Hubert G. M. Leufkens
Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands
Medicines Evaluation Board, Utrecht, The Netherlands

Larry Liberti
Centre for Innovation in Regulatory Science (CIRS), London, UK

Neil McAuslane
Centre for Innovation in Regulatory Science (CIRS), London, UK

Kim Meijboom
VU University Amsterdam, Amsterdam, The Netherlands

Angela Timoney
NHS Lothian and Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

Volker Vervölgyi
Department of Drug Assessment, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Cologne (IQWIG), Germany

Tina Wang
Centre for Innovation in Regulatory Science (CIRS), London, UK

LIST OF PUBLICATIONS

Lipska I, Hoekman J, McAuslane N, Leufkens HG, Hövels AM. Does conditional approval for new oncology drugs in Europe lead to differences in health technology assessment decisions? Clinical Pharmacology and Therapeutics. 2015;98(5):489-91.

Lipska I, Hövels AM, McAuslane N. The Association Between European Medicines Agency Approval and Health Technology Assessment Recommendation. Value in Health. 2013;16(7):A455.

Kleijnen S, Lipska I, Leonardo Alves T, Meijboom K, Elsada A, Vervolgyi V, et al. Relative effectiveness assessments of oncology medicines for pricing and reimbursement decisions in European countries. Annals of Oncology. 2016;27(9):1768-75.

Lipska I, McAuslane N, Leufkens HG, Hövels AM. A Decade of Health Technology Assessment in Poland. International Journal of Technology Assessment in Health Care. 2017:1-8.

OTHER PUBLICATIONS

Sagan A, Panteli D, Borkowski W, Dmowski M, Domanski F, Czyzewski M, et al. Poland health system review. Health systems in transition. European Observatory on Health Systems and Policies. 2011;13(8):1-193.

Nowakowska E, et al. Farmakoekonomika. Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, Poznań 2009. ISBN 978-83-7597-061-6.

Zagorska A, Krol Z, Lipska I, Falek A, Sauvage P, Barna A, et al. Implementation of transparent process of drug reimbursement decisions in Poland. Value in Health. 2008;11(6):A348-A9.

Allen N, Lipska I, Liberti L, Salek MS. Do HTA Processes Correlate With Reimbursement Recommendations? Value in Health. 2014;17(7):A797-A8.

Becla L, Osiska B, Malottki K, Lipska I. Clinical effectiveness of bosentan, epoprostenol, iloprost, sildenafil, and treprostinil in the treatment of pulmonary arterial hypertention – a systematic review. Value in Health. 2008;11(6):A382-A3.

Kleijnen S, Leonardo Alves T, Meijboom K, Lipska I, De Boer A, Leufkens HG, et al. The impact of quality-of-life data in relative effectiveness assessments of new anti-cancer drugs in European countries. Quality of Life Research. 2017.

Lipska I: Health Technology Assessment in Poland. PHARMACA 47; (suppl. 1) (1-94) 2009 Zagreb. ISSN 0031-6857.

ABOUT THE AUTHOR

Iga Lipska has broad international and Polish experience in the healthcare sector, with a main focus in recent years on Health Technology Assessment (HTA) and health insurance. She received her medical degree from Warsaw Medical University and post-graduate degrees in business and healthcare management from the Warsaw School of Economics.

Her main field of interest is evidence-based decision making in healthcare and she has worked in the healthcare sector for almost 20 years, starting her professional career as a medical doctor at a cardiology unit at Wolski Hospital in Warsaw in 1997. Then in 1999, she moved to the newly established Polish public health insurance institution (Mazovian Sickness Fund) which was subsequently transformed into National Health Fund – public payer (Narodowy Fundusz Zdrowia/NFZ). When Poland accessed European Union (EU) in 2004 Dr Lipska began working in the International Affairs Office of the Headquarters of NFZ. Between 2004 and 2006 she represented Poland on the Audit Board under the Administrative Commission for Migrant Workers and was responsible for the application of EU regulations in the field of coordination of social security systems. During this time, she was also the Polish project leader of the Transition Facility project financed from EU funds "VITAPOL" which was conducted with the British-Spanish consortium.

In 2006, Dr Lipska started working in the newly established HTA agency in Poland (Agencja Oceny Technologii Medycznych/AOTM). While leading the AOTM HTA department from 2006-2011, she was responsible for the drug assessment processes, supervising the review of industry submissions for new active substances and the preparation of full HTA reports. Dr Lipska was additionally responsible for AOTM international cooperation and between 2006 and 2008 she was the Polish project leader of the Transition Facility project between Poland and France financed from EU funds "Transparency of the National System Drug Reimbursement Decisions". During this time, she also obtained an internationally recognized certificate in project management (PRINCE2 Foundation).

Between 2011 and 2016 Dr Lipska collaborated with the Centre for Innovation in Regulatory Science (CIRS), London, UK as Senior Research Fellow and HTA Steering Committee member. The scope of her responsibility covered CIRS HTA programme activities, including the HTA agencies benchmarking project. At this time she was also the Managing Director of her own consultancy company, Strategies in Health in Warsaw, Poland. In 2015, she also founded and was the first President of the Board of The Foundation Institute of Health Policy in Poland (Fundacja Instytut Polityki Zdrowotnej).

Between 2012 and 2017 she performed doctoral research through the WHO Collaborating Centre for Pharmaceutical Policy and Regulation based in the Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands, where she was researching HTA processes and outcomes for new pharmaceuticals.

In January 2017, Dr Lipska re-joined the Headquarters of NFZ as the acting Director of the Control Department, with her main responsibility being the coordination and implementation of unified procedures in the control process between NFZ and healthcare providers and pharmacies and the supervision of 16 regional NFZ branches.

Dr Lipska is a member of longstanding international scientific societies such as Health Technology Assessment international (HTAi), Guidelines International Network (GIN), International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and its Polish chapter (Polskie Towarzystwo Farmakoekonomiczne).