Laia Maynou and John Cairns

What is driving HTA decision-making? Evidence from cancer drug reimbursement decisions from 6 European countries

Article (Accepted version) (Refereed)

Original citation:
Maynou, Laia and Cairns, John (2018) What is driving HTA decision-making? Evidence from cancer drug reimbursement decisions from 6 European countries. Health Policy. ISSN 0168-8510 (In Press)

DOI: https://doi.org/10.1016/j.healthpol.2018.11.003

What is driving HTA decision-making? Evidence from cancer drug reimbursement decisions from 6 European countries

Laia Maynou[1,2,3,4], John Cairns[4,5]

[1]*London School of Economics and Political Science, Health Policy*
[2]*Center for Research in Health and Economics (CRES), University Pompeu Fabra*
[3] *Research Group on Statistics, Econometrics and Health (GRECS), University of Girona*
[4]*London School of Hygiene and Tropical Medicine*
[5] *CCBIO, University of Bergen*

Corresponding author:

Laia Maynou, PhD.
London School of Economics and Political Science, Health Policy
Houghton Street, London, WC2A 2AE
e-mail: l.maynou-pujolras@lse.ac.uk

Funding: This research was funded under the European 7th Framework Programme with Advance-HTA (nº 305983). The results presented reflect the author's views. The EC is not liable for any use of the information communicated.

Acknowledgements

This paper was developed within the research project funded by the European Commission's Research Framework Programme (FP7), Advance-HTA (nº 305983). The authors would like to thank the Advance-HTA Consortium members and the experts from the National HTA Agencies for their support on the data collection process. Moreover, the authors appreciate the good feedback received in the different conferences where the WP1 research has been presented (HESG, EvaluAES, AES, HTAi, iHEA, internal seminars at LSHTM and CRES, UPF). We would also like to thank Prof. Marc Saez. We would like to thank the comments of two anonymous reviewers of a previous version of this work who, without doubt, helped us to improve our work.

Conflicts of interest

There are no conflicts of interest for any of the authors. All authors freely disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work.

What is driving HTA decision-making? Evidence from cancer drug reimbursement decisions from 6 European countries

Abstract

Background: Decisions on the reimbursement of the same cancer drugs are different across European countries, but empirical work on the reasons behind these differences has been scarce. The main objective of this paper is to make a methodological contribution to existing research, specifically by outlining the systematic process of analysis to address such questions and determining the factors that might lead to different drug reimbursement decisions, and to explore its application in the field of oncology.

Methods: Reimbursement decisions on cancer drugs in six European countries (Belgium, England, Poland, Portugal, Scotland, and Sweden) between 2006 and 2014 were included in the study. A taxonomy was developed, comprising two groups of variables (system-level and product-specific) and an econometric model was specified (multilevel mixed-effects ordered probit).

Results: Only one in six evaluations in the sample reach the same reimbursement recommendation. Most health system variables were not determinants of a higher or lower probability of a positive reimbursement recommendation. However, the probability of reimbursement was higher when a drug was considered cost-effective by NICE/SMC and when there was a financial Managed Entry Agreement. This work also demonstrated a possible econometric approach for analysing differences in reimbursement decisions and contributes a structured approach for collecting and preparing data for such analyses.

Conclusions: Drug reimbursement decisions can be analysed in detail along a set of factors that are related to each decision. This information is essential, not only for understanding why a particular drug is accepted in one country and not in another but also when trying to implement a new HTA system or reform an existing one. This analysis provides policy makers and stakeholders with a model that enables a better understanding of the factors that drive HTA decisions and is adaptable to answer similar questions. Moreover, the data collection limitations encountered and described in this work shed light on the need for greater accessibility and transparency in HTA systems and regarding HTA outcomes.

Key words: Drug reimbursement, cancer drugs, Health Technology Assessment (HTA), Multilevel mixed-effects Ordered Probit.

Background

Health Technology Assessment (HTA) is gaining importance because of the growing number of new medical technologies and limitations in health care budgets. All health care systems need to make choices regarding which services and products to pay for from public resources. As a result, most developed countries have HTA processes for informing drug reimbursement decisions. For the purpose of this work, drug reimbursement does not refer to the reimbursement of patients for costs incurred when purchasing drugs, but rather to the decision-making process in a country's health care system that determines which drugs will be made routinely available to patients from public funds. In the last stage of the process, countries make different decisions regarding which treatments to provide (for a review of these processes see [1]). These decisions, which usually combine clinical and economic evidence with value judgements, are extremely important, not only to patients but also to manufacturers and health care professionals.

Drug reimbursement processes have attracted attention from several authors. Various comparative analyses have been recently published describing a number of different national models [indicatively 2-10]. Moreover, a number of descriptive and comparative studies have specifically analysed reimbursement decisions [1,11-22]. However, few empirical analyses exist and they mainly focus on the UK or include few observations [23-29].

Differences in drug reimbursement decisions across European countries matter, in part because the clinical evidence reviewed is largely the same, and countries, while not of equal wealth, are of broadly comparable levels of economic development. As a result, one might expect broadly similar decisions (positive or negative) on drug reimbursement to be taken. However, this is not the case [e.g. 11, 15, 30]. So, why do these countries reach different conclusions? Modelling this question drives this paper. Our hypothesis is that these differences may partly reflect differences in HTA procedures across countries.

This research tests this hypothesis using decisions on cancer drugs in six European countries for the period 2006-2014. This therapeutic area was selected because of the high level of public interest in these reimbursement decisions, and because many cancer drugs have been appraised thus providing a rich dataset.

In a preliminary analysis [30], we tested a limited number of hypotheses that could explain the differences in cancer drug reimbursement decisions across ten European countries. While the results showed that HTA system characteristics, drug particularities and a country´s socioeconomic situation could explain some of these differences, a fuller explanation required further, model-based analysis incorporating a wide range of health system characteristics and specific characteristics of the individual drugs.

Our aim in this paper is to meet these requirements and make a methodological contribution to existing research on determining the factors that might lead to different drug reimbursement decisions, especially on cancer drugs. For this purpose, a taxonomy was developed, comprising two groups of variables (i.e. system-level and product-specific), a dataset comprising the corresponding information for included decisions and countries was created and an econometric model was specified (Multilevel mixed-effects Ordered Probit).

Methods

1. Developing a taxonomy of factors potentially influencing reimbursement decisions

In order to achieve the goals of this research, we specifically designed a taxonomy to classify the characteristics of the HTA decision-making systems and outcomes of reimbursement decisions. To create this taxonomy, a detailed analysis of the drug reimbursement systems in six European countries was conducted (Belgium, England, Poland, Portugal, Scotland and Sweden). These countries were selected because they each have a well-defined HTA process, publicly available information on their drug reimbursement decisions and comparable possible outcomes of the HTA process. This analysis involved: 1) a review of policy documents and relevant literature from September 2013 to March 2014 [e.g. 31-34,1-6, 12-15,23,24] and detailed examination of the websites of decision-making bodies in the study countries, 2) discussion with experts on related processes in each of the study countries from September 2013 to March 2014. In this second process, we primarily relied on Consortium members of the EU-funded project Advance-HTA (7th Framework Programme Grant Nr. No. 305983) representing some of the studied countries.

We used insights from this analysis in combination with the Hutton Framework [31] to describe the drug reimbursement decision processes and inductively design the taxonomy. The aim of the Hutton Framework is to systematize the understanding of so-called 'fourth hurdle' systems using HTA. The term 'fourth hurdle' describes the additional requirement that a new drug has to demonstrate value for money before being reimbursed (on top of being of good quality, effective and safe, which are requirements for gaining market access). The Hutton Framework identifies two main levels of the reimbursement system: the policy implementation level (the system level) and the technology decision level (the drug level) [4].

The resulting taxonomy adopts this division between system-wide and product-specific factors and describes the main characteristics of the drug reimbursement system in each country (organisational, process and method) and the main features of each drug (general and country-specific). Table I defines the taxonomy variables and Table II categorises them. The taxonomy was used to generate explanatory variables for the econometric model (see below).

2. Creating the dataset for the econometric model

The dataset for this study comprises cancer drug reimbursement decisions, analysed along the variables described above. The Scottish Medicines Consortium (SMC) was the starting point of our study because it appraises all drugs approved by either the Medicine and Healthcare Product Regulatory Agency (MHRA) or the European Medicines Agency (EMA). The drugs selected were classified under "malignant disease and immunosuppression" on the SMC website. The list of drugs was validated by reviewing National Institute for Health and Care Excellence (NICE) decisions for any additional observations (especially on further indications for included drugs). This process produced 81 drugs and 161 drug-indications (to account for multiple cancer indications of included drugs, as reimbursement decisions may vary for different indications of the same drug).

This sample includes the technology appraisals for cancer drugs from January 2006 to November 2014 in the six selected countries (Belgium, England, Poland, Portugal, Scotland, and Sweden). The dataset was restricted to these six countries to ensure public availability of information and comparability of the possible decision outcome variable used in this study (see below). For example Germany and France were not included because the outcome of the HTA process is

different in nature from the other selected countries and Spain was not included because drugs are usually accepted into routine practice at the national level, but regions ("Comunidades Autonómas") can impose variable restrictions. Drugs appraised from 2006 onwards were included since, by that point, many Europeans countries had introduced formal HTA systems and had started collaborating at European level. As some of the analysed drugs have more than one indication, we treat each indication as a separate observation in order to capture all possible differences in HTA outcomes. We considered 161 drug-indications per country, but decisions made before 2006 and decisions with missing dates were not included since there was no possibility of linking them with the time variables included in the model.

Table III shows the data source for each country. For some countries, all decisions were publicly available through official websites, but for others, assistance was required from the National HTA Agencies or Health Departments, who were contacted via official contact points and/or the authors' networks. Data collection took place between October 2013 and December 2014.

The dataset contains the outcome of the decision, the date when the decision was published and all the variables defined in the taxonomy. The decision outcome describes the final decision regarding the adoption of the technology. For this specific analysis, we define the outcome as Non-Favourable, Favourable with restrictions and Favourable. These are the three main categories of the HTA decision. To distinguish between "Favourable with restrictions" and "Favourable", the decision is considered to be restricted only when it differs from the indication detailed in the marketing authorisation (e.g. when reimbursement is limited to a sub-population of the patients for whom the drug has been authorized).

In order to capture all possible decisions, we included two further categories in the decision variable: Non-submission and Non-assessment. Non-submission captures decisions where the reimbursement body explicitly asked the manufacturer to make a submission but they failed to do so. This information is only documented for NICE and SMC decisions, as the other four countries do not provide such data. Non-submission is considered a Non-Favourable decision for NICE or SMC, but it was classified separately because this negative decision is the result of a different process. Non-assessment, on the other hand can be the result of different circumstances, like the manufacturer deciding not to apply for reimbursement in the first place or the decision-maker not requiring the HTA agency to assess the drug. It is important to note the difference between the non-submission and non-assessed categories. Decisions categorized as either non-submission or non-assessment were not included in the econometric model. Because the exclusion of these categories could introduce sample selection bias and endogeneity problems in the estimation as a result of using a non-randomly selected sample [35] further analyses (i.e. robustness checks) were performed (see below).

Owing largely to data limitations, some assumptions were required in order to produce comparable data. If a country's reimbursement process changed between January 2006 and November 2014, the same variable was recorded differently depending on the year considered (see online Appendix). For this specific dataset, this only applied to Poland. Some countries make re-evaluations of previous decisions (e.g. England) or they allow for a re-submission after a negative decision (e.g. Scotland). When a later decision changed the outcome, the latest decision for a particular drug-indication was included in the dataset. This was done to comply with our econometric specification of only one decision for each drug-indication and to account for the decision based on the most evidence and most recently applicable in the country. We expected a very small number of cases with this constellation, containing the potential bias introduced by this decision.

Finally, the incremental cost-effectiveness ratio (ICER) was not reported for each decision in each country. As a result, the best option was to work with an approximation of this ICER taking NICE's ICER for each drug-indication (or SMC's ICER if NICE did not report it). This does not assume that the ICER will be the same in other countries but rather that estimated cost-effectiveness will tend to be positively correlated across countries.

3. Econometric Model

The objective in designing the model was to determine empirically which of the taxonomy variables are associated with a higher or lower probability of reimbursement. Previous empirical studies [23-29] show evidence of a significant impact of clinical evidence and the ICER on drug reimbursement decisions.

A multilevel mixed-effects model was chosen. A panel data design was not feasible given the nature of reimbursement processes, as there is one decision per drug-indication per country in a particular year as opposed to annual decisions [36]. However, the year of decision was considered to construct the time dependent variables (see below), as were time-specific effects.

Although the dependent variable (probability of reimbursement) is unobserved, it can be approximated for the included countries through a categorical variable corresponding to the final decision: 0. Non-Favourable. 1. Favourable with restrictions. 2. Favourable. Thus, the response (Y) cannot be modelled as a linear combination of explanatory variables plus an error, but uses probabilities instead. Relevant literature has treated the categorical dependent variable "reimbursement decision" as nominal [24,26]. However, it could also be considered ordinal since the "Favourable with restriction" outcome represents an intermediate point between "Favourable" and "Non-Favourable" decisions. In this analysis we treat it as ordinal believing that this specification allows us to capture more information regarding the decision outcome.

The dependent variable Y can be considered as a latent variable y_i^* ,

$$y_i^* = \beta_0 + \beta_1 x_i + \varepsilon_i$$

While the latent variable y_i^* is unobserved, y_i can be observed,

$$\begin{aligned} y_i &= 0 \quad if\ y_i^* \le 0 \\ y_i &= 1 \quad if\ 0 < y_i^* \le \mu_1 \\ y_i &= 2 \quad if\ \mu_1 < y_i^* \le \mu_2 \end{aligned}$$

assuming that ε_i is normally distributed (with zero mean and unit variance). There are two main options for specifying the model when the dependent variable is ordered: *ordered probit* and the *proportional odds ratio model/cumulative logit model* [37]. While both options account for non-linear distributions, the probit specification relies on a normal distribution of the error terms, while the logit follows a standard logistic distribution. For this particular case, we assume, for simplicity, the errors are normally distributed. As a result, we specify an ordered probit model.

$$\Pr ob(y_i = 0 | x_i) = \Phi(-(\beta_0 + \beta_1 x_i))$$
$$\Pr ob(y_i = 1 | x_i) = \Phi(\mu_{i,1} - (\beta_0 + \beta_1 x_i)) - \Phi(\beta_0 + \beta_1 x_i)$$
$$\Pr ob(y_i = 2 | x_i) = \Phi(\mu_{i,2} - (\beta_0 + \beta_1 x_i)) - \Phi(\mu_{i,1} - (\beta_0 + \beta_1 x_i))$$

where $\Phi(.)$ denotes the cumulative normal distribution. For all the probabilities to be positive the following restriction must be fulfilled, $0<\mu_{i,1}<\mu_{i,2}<1$.

Our multilevel mixed-effects model [24,25] can be specified as follows,

$$Y_{ij}^{*} = \alpha_{ij} + \beta x_{ij} + e_{ij}$$

where α denotes the intercept, β the coefficients, x a matrix of explanatory variables, e the error term and subscripts, i and j denote drug-indication and country.

When using a complex design with multiple levels (drug-indication and country) and dimensions (spatial and temporal), there is important heterogeneity in the initial conditions (i.e. intercept). Failure to account for heterogeneous quantities in the model may introduce serious bias into the model estimators. In our case, heterogeneity can be controlled introducing *random-effects* in the intercept (α_{ij}) (varying at country level j and drug-indication i). In other words, the multilevel mixed-effects model involves clustering at country and drug-indication level.

The year of the decision is a time effect that needs to be considered. Year dummy variables are used in our model to control for temporal dependency and avoid problems of serial autocorrelation (i.e. error terms in time series transfer from one period to another; the error for time period t is correlated with the error for a subsequent time period $t+1$).

The original model included all variables from the taxonomy, some continuous variables to control for the principal socioeconomic and demographic characteristics of each country (incidence rate for each condition, Gross Domestic Product (GDP) growth and percentage population >65 years old) and the time-specific variables. However, there was correlation across variables and some insufficient variability in the categories of some categorical variables. Therefore, the t-test and the log-likelihood test were used to find the best model, with the final model specification being a m*ulti-level mixed-effects ordered probit [38,39]:*

$$\Pr ob(Y_{ij} = 0 | x_{ij}) = \Phi(-\eta_{ij})$$
$$\Pr ob(Y_{ij} = 1 | x_{ij}) = \Phi(\mu_{ij,1} - \eta_{ij}) - \Phi(\eta_{ij})$$
$$\Pr ob(Y_{ij} = 2 | x_{ij}) = 1 - \Phi(\mu_{ij,2} - \eta_{ij})$$

where K= 0, 1, 2 (decision), i=drug-indication, j=country; and η_{ij} denotes a linear predictor.

For each observation, the linear predictor (η_{ij}) contains:

$$\eta_{ij} = \alpha_{ij} + \beta_1(Healthsystem_j) + \beta_2(Evidence_j) + \beta_3(Initiator_{jt}) + \beta_4(Stakeholders < 2_j) + \beta_5(EconomicEvaluation_j) +$$
$$\beta_6(Budget\,Impact_j) + \beta_7(Pricingdecision = 1_j) + \beta_8(Pricingdecision = 2_j) + \beta_9(MEA = 1_{ij}) + \beta_{10}(ICER = 1_i) + \beta_{11}(Endoflife_i = 1) +$$
$$\beta_{12}(Endoflife_i = 2) + \beta_{13}(Incidencerate_{ij}) + \beta_{14}(GDPgrowth_{jt}) + \beta_{15}(Pop > 65_{jt}) + \beta_{16}(yeardummies_{jt})$$

where *t* denotes years (2006-2014). This subscript appears in the linear prediction because some of these variables are time-variant.

For the final model, some explanatory variables, mainly system-level, were removed or were regrouped, as they were irrelevant according to t-tests or were correlated with other variables.

Under ordered categorical data, there is an important assumption to fulfil, namely the proportional odds assumption. This assumption states that the location parameters (slope coefficients) are the same across response categories. This assumption is tested through the test of parallel lines (i.e. Brant test). For our specific model, the result of the test showed that the assumption was violated. One possible explanation is that the sample is not balanced; there is not a decision for each drug-indication for each country (i.e. not all drug-indications were assessed in all countries). To overcome the potential bias in the estimates, we followed the strategy suggested by Liu and Agresti [40] which entails fitting models for the separate categories taking into account ordinary sampling variability rather than relying purely on testing. As a result, instead of moving to a multinomial model, where the same problem with Independence of Irrelevant Alternatives (IIA) would persist, a solution is to introduce some random-effects in the model specification. As noted above, our model has random-effects in the intercept, accounting for drug-indication and country. This approach improves the efficiency of the model.

We used Stata 14 and the specific commands for Multi-level mixed-effects Ordered Probit (*meoprobit*) [39] to run the model.

Results

1. **Size and composition of the dataset**

For the 161 identified drug-indications, our dataset comprised 908 observations; 23% of them were favourable decisions, while 12% were rejected and 17% were restricted. The non-submission category only accounted for 5% of the total sample. The remaining 43% of the observations were non-assessed drug-indications. There were 475 decisions (excluding the non-submitted and non-assessed categories) that fit our categorical variable of interest (favourable, non-favourable and reject decisions). Table IV disaggregates the information by country for the sample of 475 decisions. Scotland and Belgium have assessed most cancer drug-indications, while Belgium, Poland and Scotland have the highest rates of restricted decisions.

Analysing the dataset for the possible decision outcomes, we observe that in most cases the outcome of the HTA decision is different by drug-indication and country. Only for 1 in 6 (16%) drug-indications pairs were the decisions identical across all countries. This information confirms evidence of differences reported in previous work [e.g. 11, 15, 30].

Tables V and VI report descriptive statistics for the variables defined in the taxonomy. The outcomes of system-wide variables for each country are included in the online appendix. Table V shows the results of the categorical variables for 475 decisions (favourable, non-favourable and rejected decisions). It also demonstrates that for some variables, such as, type of patient, disease stage, Incremental Cost-Effectiveness Ratio (ICER), initiator, decision level, transparency, Managed Entry Agreement (MEA), some categories have few observations leading to their exclusion from the final

econometric model due to lack of variation. Table VI shows statistics on the continuous variables for the 475 decisions per country. The variables, except for incidence rate, are time dependent and range from 2006 to 2014.

2. Insights from the empirical analyses

Both the descriptive and empirical analyses carried out for this work, showed substantial evidence of different reimbursement decisions for the same drug-indication across the six countries. The results of the econometric model are shown in Table VII; variables that have a statistically significant effect on the probability of reimbursement are flagged with asterisks (*).

Table VII presents two models, which include a different number of system-level variables, in order to see differences in the estimation. The number of observations for both models is 393. The drop from 475 to 393 is due to missing observations in some particular explanatory variables. As can be seen in the table, the reported likelihood-ratio test favors a mixed-effects Ordered Probit regression over a Standard Ordered Probit regression. Moreover, the Variance Partitioning Coefficient (VPC), which is 0.16 for Model 1 and 0.18 for Model 2, being different from 0 or 1, shows the relevance of the clustering. These results indicate the need to control for the different levels (country and drug-indication) of the dataset and further highlight the relevance of the clustering. On one hand, the random-effect (i.e. random slope parameter) used to capture country heterogeneity is not significant. This result shows that the specification of the econometric model seems to be able to control for the most important differences across countries. On the other hand, the drug-indication random-effect shows significant variability. In other words, there is some relevant variation across drug-indication that the random-effect is controlling for.

The results of Model 1 show that being in a system based on social health insurance increases the probability of reimbursement, while Model 2 shows no significant effect for the system-level variables. In terms of product-specific variables, both models find that a drug considered cost-effective by NICE/SMC or which has been introduced under financial MEA is associated with a higher probability of reimbursement. However, a higher incidence rate is associated with a lower probability of reimbursement.

Regarding the time variables, Model 1 shows a positive and statistically significant relationship of GDP growth and percentage of population above 65 with the probability of reimbursement. For Model 2, these time variables are not significant. This finding can be due to the inclusion of the system-level variables into the model. Moreover, the results of the year dummy variables show a significantly lower probability of reimbursement from 2010 onwards. This coincides with the financial crisis from 2008 onwards, which introduced additional constraints for health systems reducing the probability of reimbursement.

3. Model robustness checks

The main robustness check was to specify the econometric model as a two-part model, which followed the initial specification, i.e. Multilevel mixed-effects Ordered Probit, in order to test for sample selection regarding the assessment. The first part of the model defines whether the drug-indication was assessed or not. The model is a Multi-level mixed-effects Probit with a binary variable (0 Non-assessed /1 Assessed) with a set of explanatory variables that can explain the assessment decision (i.e. Evidence, Initiator, Economic Evaluation, Health system and Budget impact). The second part

of the model is the Multi-level mixed-effects Ordered Probit previously defined. The second part includes a variable that captures the predicted values of the model predictions of the first part (based on fixed effects and posterior means of random effects). The results of the model did not show any statistical difference for the second part (i.e. efficiency and significance did not change) compared to the original analysis. Moreover, the predicted values of the first part were not significant. In other words, the ordered model that we estimated initially is robust.

We also checked whether the exclusion of non-submission decisions from the main analysis was appropriate. When the non-submission decisions were treated as non-favourable (rather than excluded) the results changed significantly and the model lost efficiency, confirming that these two types of decision are best considered separately. Furthermore, the two-part model showed no difference when controlling for the assessment variable. So, selection bias does not seem to arise from the non-assessment category. Regarding the non-submission category, the model did not show significant differences from the main models. Finally, being aware that the Cancer Drug Fund provided patients with some of the drugs rejected by NICE, the models were run without introducing the NICE decisions. The results were similar to the main models shown above. Tables with the results of the robustness checks can be obtained from the authors on request.

Discussion

The main objective of this paper was to test a possible model for determining the factors that may lead to different drug reimbursement decisions across countries, providing insight on what drives HTA decision-making. This entailed designing a taxonomy, creating a dataset and estimating a Multilevel mixed-effects Ordered Probit. The dataset itself is also a contribution of this work.

First, according to previous literature [e.g. 11, 15, 30].and our dataset, differences exist in the final reimbursement decisions across the six countries analysed. Second, the tests on the econometric specification showed that a Multilevel mixed-effects Ordered Probit was better than a Standard Ordered Probit, highlighting the need to allow for clustering by country and drug-indication. Moreover, despite differences in the final reimbursement decision across countries, the econometric specification was able to control for the most important differences across countries, as demonstrated by the country random-effect.

The empirical results showed that a positive recommendation by NICE/SMC, a financial MEA or a SHI system are associated with a higher probability of reimbursement. Another result is that a higher incidence rate might be associated with a lower probability of reimbursement because, other things equal, it is associated with a larger budget impact. As with previous studies [23-26], the ICER is important for HTA decision-making. In particular, these studies and our results, show that a lower ICER (better cost-effectiveness) increases the probability of reimbursement.

With the exception of the way the health system is financed (tax-based vs. SHI), no system-level variable was a significant determinant of the reimbursement decision. However, the possibility remains that differences in other variables, such as MEAs, which were significant, derive from or are influenced by system-level differences. Apart from that, the socioeconomic characteristics of the country show a significant effect on the reimbursement decisions.

While the findings on cost-effectiveness and Health System are in line with the results from our preliminary analysis of factors influencing reimbursement decisions [30], the economic evaluation variable was not significant in this particular

model. Compared to the previous study, which did not include an econometric analysis, this work allowed us to investigate simultaneously the effect of different potential factors on the final reimbursement decisions.

In addition, the results of the year dummy variables showed a lower probability of reimbursement from 2010 onwards, which coincides with a period of austerity measures in Europe. This result confirms the findings of our preliminary analysis, which showed that the global financial crisis is related to a lower probability of reimbursement [30]. Evidence of an increase in health inequalities from 2010 onwards, coinciding with the austerity measures, has also been shown elsewhere [41].

The main findings have several policy implications. First of all, this research provides a model for better understanding the main determinants of drug reimbursement decisions. As a result, policy-makers will be more aware of the factors that drive HTA decisions (i.e. estimated cost-effectiveness, financial MEA, SHI system, incidence rate and socioeconomic characteristics). When introducing or reforming an existing HTA process, this analysis can help shaping its characteristics. It can also contribute to the comprehension of diverging reimbursement decisions across countries for the HTA community, including patients groups and health care professionals.

Secondly, the data collection for this work, highlighted substantial differences in transparency and accessibility of related information in the different countries. Assembling the dataset for this analysis was both time consuming and complicated, as not all countries make their decisions publicly available or provide sufficient detail. We overcame these issues by contacting national experts who helped complete and validate our data. However, there is an overall need for greater accessibility to information and transparency in this area to improve all stakeholders' knowledge and understanding of differences in HTA outcomes between countries.

Although the results are satisfactory, during this research we encountered a number of challenges. In addition to the data availability issues described above, some assumptions were needed in order to combine all these data in a single analysis. Furthermore, while the price of included drugs would have been a useful variable for the analysis, related information is usually not readily available and only pertains to official (list) prices, not actual prices paid by health systems. Another important challenge was the model specification. We defined our dependent variable as an ordered categorical variable, necessitating the fulfilment of the parallel lines assumption to produce reliable results. While our model did not fulfil this assumption, we used the strategy of Liu and Agresti to address this problem [40]. Finally, in order to test for some of the limitations stemming from the data and assumptions in our work (i.e. sample selection bias and endogeneity) and validate our results, we performed a number of robustness checks. These increased confidence in the validity of the model.

In this study, we have only looked at cancer drugs. Future research should also compare across therapeutic areas, in order to explore whether the type of drug is an additional determinant of the probability of reimbursement.

Conclusions

The aim of this research was to understand what is driving HTA decision-making and why countries make different decisions and set foundations for future methodology exploring such questions. The general conclusion is that drug reimbursement decisions can be analysed in detail and that there are a set of factors that are related to each decision. Significant associations with drug reimbursement decisions were demonstrated for a drug´s estimated cost-effectiveness, the existence of a financial MEA, a health system based on social health insurance, the condition´s incidence rate and the

socioeconomic characteristics of the country. This information is essential, not only for understanding why a particular drug is accepted in one country and not in another but also when trying to implement a new HTA system or reform an existing one.

Another important conclusion is that despite differences in the final reimbursement decision across countries, documented in this study and in previous literature, the econometric specification was able to control for the most important differences across countries. The best model was a Multilevel mixed-effect Ordered Probit which showed the relevance of clustering at the country and drug-indication level.

Thus, this research provides policy makers with a model that allows a better understanding of the factors that drive HTA decisions. The analyses highlight differences in drug reimbursement decisions across countries, thus improving HTA stakeholders' understanding of these complex processes. Finally, the data collection challenges highlight the need for greater accessibility and transparency in the HTA systems in order to improve stakeholders' understanding and knowledge of differences in outcome between countries.

References

[1] Fischer, K.: A systematic review of coverage decision-making on health technologies-Evidence from the real world. Health Policy 107, 218-230 (2012).

[2] Sorenson, C., Drummond, M., Kanavos, P.: Ensuring value for money in health care: the role of health technology assessment in the European Union. European Observatory on Health Systems and Policies, Copenhagen (2008).

[3] Wilsdon, T., Serota, A.: A comparative role and impact of health technology assessment. Charles River Associates, London (2011).

[4] Franken, M., Le Polain, M., Koopmanschap, M., Cleemput, I.: Similarities and differences between five European drug reimbursement systems. International Journal of Technology Assessment in Health Care 28(4), 349–357 (2012).

[5] Paris, V., Belloni, A.: Value in Pharmaceutical Pricing. OECD Health Working Papers 63 (2013).

[6] Barneih, L., Manns, B., Harris, A., Blom, M., Donaldson, C., Klarenbach, S., Husereau, D., Lorenzetti, D., Clement, F.: A synthesis of Drug Reimbursement Decision-Making Processes in Organisation for Economic Co-operation and Development countries. Value in Health, 17, 98-108 (2014).

[7] Franken, M., Stolk, E., Scharringhausen, T., de Boer, A., Koopmanschap, M.: A comparative study of the role of disease severity in drug reimbursement decision making in four European countries. Health Policy, 119(2),195–202 (2015).

[8] Panteli, D., Eckhardt, H., Nolting, A., Busse, R., & Kulig, M.: From market access to patient access: overview of evidence-based approaches for the reimbursement and pricing of pharmaceuticals in 36 European countries. Health research policy and systems, 13:39 (2015).

[9] Ferrario, A.: Time to entry for cancer new medicines: from European Union-wide marketing authorization to patients access in Belgium, Estonia, Scotland and Sweden. Value in Health (2018) https://doi.org/10.1016/j.jval.2018.01.003

[10] Oortwijn, W., Determann, D., Schiffers, K., Tan, S. And van der Tuin, J.: Towards Integrated Health Technology Assessment for Improving Decision Making in Selected Countries. Value in Health, 20(8),1121-1130 (2017).

[11] Allen, N., Liberti, L., Walker, S. R., & Salek, S.: A Comparison of Reimbursement Recommendations by European HTA Agencies: Is There Opportunity for Further Alignment? Frontiers in Pharmacology, 8-384 (2007).

[12] Mason, AR., Drummond, MF.: Public funding of new cancer drugs: Is NICE getting nastier?. European Journal of Cancer 45(7), 1188–1192 (2009).

[13] Clement, F., Harris, A., Li, J., Yong, K., Lee, K., Manns, B.: Using effectiveness and cost-effectiveness to make drug coverage decisions: a comparison of Britain, Australia, and Canada. JAMA 302(13), 1437–1443 (2009).

[14] Kanavos, P., Nicod, E., Van den Aardweg, S., Pomedli, S.: The impact of health technology assessments: an international comparison. Euro Observer 12(4), 1–7 (2010). [15] Nicod, E., Kanavos, P.: Commonalities and differences in HTA outcomes: A comparative analysis of five countries and implications for coverage decisions. Health Policy 108,167–177 (2012).

[16] Franken, M.G., Nilsson, F., Sandmann, F.G., Boer, A.D., & Koopmanschap, M.A.: Unravelling Drug Reimbursement Outcomes: A Comparative Study of the Role of Pharmacoeconomic Evidence in Dutch and Swedish Reimbursement Decision Making. PharmacoEconomics, 31,781-797 (2013).

[17] Spinner, D.S., Birt, J., Walter, J.W., Bowman, L., Mauskopf, J., Drummond, M.F., Copley-Merriman, C.: Do different clinical evidence bases lead to discordant health-technology assessment decisions? An in- depth case series across three jurisdictions. Clinicoecon Outcomes Res. 2013 5,69–85 (2013).

[18] Lim, C.S., Lee, Y., Koh, Y., Heo, D.S.: International comparison of the factors influencing reimbursement of targeted anti-cancer drugs. BMC Health Services Research, 29,14:595 (2014).

[19] Grepstad, M., Kanavos, P.: A comparative analysis of coverage decisions for outpatient pharmaceuticals: evidence from Denmark, Norway and Sweden. Health Policy, 119(2),203–11 (2015).

[20] Nicod, E., Kanavos, P.: Developing an evidence-based methodological framework to systematically compare HTA coverage decisions across countries: a mixed methods study. Health Policy, 120(1),35–45 (2016).

[21] 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, 18(6),715-730 (2017).

[22] Allen, N.J., Walker, S.R., Liberti, L.E., & Salek, S.: Health Technology Assessment (HTA) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland. Value in Health, 20(3),320-328 (2017).

[23] Devlin, N., Parkin, D.: Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Economics 13(5), 437–452 (2004).

[24] Dakin, H., Devlin, N., Odeyemi, I.: ‘‘Yes’’, ‘‘No’’ or ‘‘Yes, but’’? Multinomial modelling of NICE decision-making. Health Policy 77, 352–367 (2006).

[25] Dakin, H., Devlin, N., Feng, Y., Rice, N., O'Neill, P., Parkin, D.: The Influence of Cost-effectiveness and Other Factors on NICE Decisions. Health Economics 24, 1256-71 (2015).

[26] Cerri, K., Knapp, M., Fernandez, JL.: Decision making by NICE: examining the influences of evidence, process and context. Health Economics, Policy and Law 9, 119-41 (2014).

[27] Fischer, K., Rogowski, W., Leidl, R., Stollenwerk, B.: Transparency vs. closed-door policy: Do process characteristics have an impact on the outcomes of coverage decisions? A statistical analysis. Health Policy 112, 187-196 (2013).

[28] Charokopou, M., Majer, IM., Raad, J., Broekhuizen, S., Postma, M., Heeg, B.: Which Factors Enhance Positive Drug Reimbursement Recommendation in Scotland? A Retrospective Analysis 2006–2013. Value in Health 18(2), 284-91 (2015).

[29] Salas-Vega, S., Bertling, A. and Mossialos, E.: A comparative study of drug listing recommendations and the decision-making process in Australia, the Netherlands, Sweden, and the UK. Health Policy, 120(10),1104-1114 (2016).

[30] Maynou, L., Cairns, J.: Why do some countries approve a cancer drug and others don’t? Journal of Cancer Policy 4, 21-25 (2015).

[31] 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). International Journal of Technology Assessment in Health Care 22(1), 10-8 (2006).

[32] Garrido, M.V., Kristensen, F. B., Busse, R., Nielsen, C. P.: Health technology assessment and health policy-making in Europe. Current status, challenges and potential. Observatory Studies Series, Nº 14 (2008).

[33] EUnetHTA Work Package 8: EUnetHTA Handbook on Health Technology Assessment Capacity Building. Barcelona (Spain): Catalan Agency for Health Technology Assessment and Research. Catalan Health Service. Department of Health Autonomous Government of Catalonia (2008).

[34] Banta, D., Kristensen, F.B., Jonsson, E.:A history of health technology assessment at the European level. International Journal of Technology Assessment in Health Care, 25(1), 68–73 (2009).

[35] Heckman, J.: Sample Selection Bias as a Specification Error. Econometrica, 47(1): 153-161 (1979)

[36] Frees, E.: Longitudinal and Panel Data: Analysis and Applications for the Social Sciences, Cambridge University Press (2004).

[37] Zavoina, R., McElvey, W.: A statistical model for the analysis of ordinal level dependent variables. Journal of Mathematical Sociology 103-120 (1975).

[38] Garson D.: Hierarchical Linear Modelling: Guide and Applications. SAGE Publications, Inc (2013).

[39] Stata Corp.: Stata Multilevel mixed-effects reference manual, Release 13. Stata Press. Available at https://www.stata.com/manuals13/me.pdf (last access 21st September 2016).

[40] Liu, I. Agresti, A.: The Analysis of Ordered Categorical Data: An Overview and a Survey of Recent Developments. Test 14(1), 1-73 (2005).

[41] Maynou, L. and Saez, M. (2016). Economic crisis and health inequalities: evidence from the European Union. International Journal for Equity in Health, 15(135). DOI: 10.1186/s12939-016-0425-6

Table I. Taxonomy

1. System-wide variables	
	1.1. Organisational
Evidence	Whether the assessment is produced or reviewed inside the body dealing with the drug reimbursement (agency) or, by contrast, this evidence is produced or reviewed by an independent body (outside the agency), for instance, universities, or independent committees.
Body Independence	The body in charge of the drug reimbursement is an independent scientific body or the government manages it. Moreover, if it is independent from the Ministry of Health (MoH), does it make recommendations or the final decision?
Decision level	This variable indicates if the decision and recommendation is taken at a national or regional level.
Health System	This variable collects whether the country health system is based on a Social Health Insurance (SHI) or a Tax-based system.
	1.2. Process
Initiator	In most cases the manufacturer applies for reimbursement, however, in some countries, the initiative comes from the Department of Health, from the body in charge of HTA or it is an automatic procedure. In these last cases, then, the manufacturer is asked to make a specific submission.
Stakeholders	The different systems have a diverse degree of involvement of stakeholders. In some countries, they are fully involved in the whole procedure, while in other countries their presence is just limited to some comments at the early assessment.
Transparency	This variable indicates the transparency of the system, in terms of documentation publicly available, without taking into account the information of price negotiations.
Appeal	This variable records whether or not there is a formal system to appeal the final decision taken by the decision-making body.
	1.3. Method
Economic Evaluation	This variable indicates whether an economic evaluation (cost effectiveness, cost utility or cost-benefit analysis) is required for the decision-making process. It can be that it is always needed for the assessment or that it is only required for some group of drugs (e.g. drugs which increase the therapeutic value) or non-required.
Budget Impact	This variable shows if a budget impact analysis is required for the decision-making process.
Pricing location	This variable indicates what type of institution deals with price setting (inside the Ministry of Health (MoH), external body or none of them, price set by manufacturer).
Pricing decision	The variable records how the pricing decision is taken in each of the previous cases. It can be a price negotiation, it can be based on referencing pricing or, by contrast, it can be set by the manufacturer in the submission and used for the corresponding calculations.

Source: own construction

Table I. (Continued)

2. Product-specific variables	
	2.1. General drug characteristics
Type of patient	This variable identifies whether the drug-indication is for adults, for children or for both.
Orphan	This variable indicates whether or not a drug is designated as an orphan by European Medicine Agency (EMA)[1]. A drug is qualified under orphan when it fulfils the following criteria (EMA, orphan designation): 1) it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; 2) the prevalence of the condition in the European Union (EU) must not be more than 5 in 10,000; 3) no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.
Incidence rate	This variable tries to collect an estimate the number of patients for whom the drug is indicated. From the technology appraisals, it is not always feasible to know for how many patients are eligible for that drug in each country. This variable is approximated through the incidence rate. The information is taken from the age-standardised incidence rate per 100,000 for each therapeutic area and country[2]. For cancer, the incidence rate is disaggregated per type of cancer and country (GLOBOCAN 2012 project).
Disease stage	This variable determines whether the drug-indication is a treatment for an early stage or late stage of the condition.
ICER	This variable indicates whether the Incremental Cost-Effectiveness Ratio (ICER) determined by NICE is above or below £30,000 per QALY. When the drug indication has not been appraised by NICE, the SMC ICER is taken to define this variable. NICE generally performs a more detailed analysis than SMC in calculating the ICER, while SMC usually accepts the ICER identified by the manufacturer. ICER variable is not a continuous variable because of two main reasons. Firstly, NICE and SMC are the bodies that always document this value (transparency). Secondly, for simplicity, it is used as an indicator of cost-effectiveness (i.e. threshold from NICE). A categorical variable is able to show the relationship between cost-effectiveness and the probability of reimbursement, while a continuous variable will not take into account the specific criteria of cost-effectiveness. Moreover, this approach was taken because not all countries specified an ICER or another measure that account for cost-effectiveness.
End of life	Was the drug-indication accepted by NICE as an end of life treatment? For the drug-indications assessed before 2009 (year of implementation of the criteria), it is categorised with another code.
	2.2. ***Specific drug-country characteristics***
Managed Entry Agreement (MEA)	This variable indicates the existence of a MEA during the decision-making process. A MEA is an arrangement between a manufacturer and payer/provider that enables access to reimbursement of a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use, or limit their budget impact. This variable collects the different types of MEA: financial, performance-based or a combination of both.
Alternative	This variable shows whether or not there are alternative active treatments for this drug-indication already available in the positive list of each of the countries. It is not considered to be an alternative treatment when the comparator is best supportive care, standard chemotherapy or standard care.

[1] European Medicines Agency, Human medicines, Orphan designations. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&mid=WC0b01ac05800240ce. Accessed 30 September 2015
[2] http://globocan.iarc.fr/Default.aspx. Accessed 30 September 2015

Table II. Variables categorised

SYSTEM-LEVEL VARIABLES	
Evidence	0. Internal (done inside the agency) 1. External (review body outside the agency)
Body Independence	0. Inside Ministry of Health 1. Independent body only does a recommendation 2. Independent body who decides
Decision level	0. Recommendation and decision at National level 1. Recommendation National / decision Regional 2. Recommendation Regional/decision National 3. Recommendation and decision National, freedom for implementation at Regional
Health system	0. Tax-based system 1. Social Health Insurance system
Initiator	0. Department of Health 1. Manufacturer submission 2. Body in charge of the HTA 3. Automatic 4. Both, manufacturer and Department of Health
Stakeholders	0. Non-involved 1. Only comments at an early stage 2. Involved but not in the final meeting 3. Fully involved
Transparency	0. Nothing 1. Some documents 2. Everything
Appeal	0. No 1. Yes
Economic evaluation	0. Never 1. Only for some drugs 2. Yes, for all cases
Budget impact	0. No 1. Yes
Pricing location	0. No negotiation (e.g. price set by Manufacturer) 1. External body 2. Inside Ministry of Health
Pricing decision	0. Based on a negotiation 1. Calculation based on price referencing 2. Set by the manufacturer
PRODUCT-SPECIFIC VARIABLES	
Type of patient	0. Adults 1. Children 2. Both
Orphan	0. No 1. Yes
Incidence rate	Numeric variable
Disease stage	0. Early treatment 1. Late treatment 2. Not specified
ICER	0. Above £30,000 per QALY 1. Below £30,000 per QALY 2. Non submission 3. Non data
End of life	0. No 1. Yes 2. Not determined (before 2009)

Managed Entry Agreement (MEA)	0. 1. 2. 3.	No Yes (financial schemes) Yes (performance-based) Yes (combination of both)
Alternative	0. 1.	No Yes

Source: own construction and World Bank Data

Table III. Decision data by country (sources)

Country	Institution/Dataset	Data source
Scotland	SMC	HTA decisions from the SMC website
England	NICE	HTA decisions from the NICE website
Belgium	RIZIV INAMI	HTA decisions from the INAMI dataset (online). Validation of the data and information on MEA from the INAMI team.
Sweden	TLV / NLT	HTA decisions from the TLV/NLT website. Validation from the TLV team.
Poland	AHTAPol	Dataset created by AHTAPol
Portugal	INFARMED	HTA decisions from INFARMED dataset (online). Information on the MEA from the INFARMED team.

NICE - National Institute for Health and Care Excellence; SMC - Scottish Medicine Consortium; TLV - The Dental and Pharmaceutical Benefits Agency, NLT - New pharmaceutical product therapies, RIZIV-INAMI - Belgium Health Insurance Agency; INFARMED - National Authority of Medicines and Health Products, IP; AHTAPol - Agency for Health Technology Assessment in Poland.. ***Source: own construction***

Table IV. Decision outcome per country[1]

	Scotland		England		Belgium	
Non-Favourable	32	(23.53%)	34	(22.82%)	4	(2.74%)
Restricted	35	(25.74%)	20	(13.42%)	45	(30.82%)
Favourable	24	(17.65%)	32	(21.48%)	66	(45.21%)
Non-submission	36	(26.47%)	7	(4.7%)	0	(0%)
Non-assessed	9	(6.62%)	56	(37.58%)	31	(21.23%)
Total	**136**	**100%**	**149**	**100%**	**146**	**100%**

	Sweden		Poland		Portugal	
Non-Favourable	5	(3.23%)	27	(16.73%)	7	(4.35%)
Restricted	6	(3.87%)	47	(29.19%)	3	(1.86%)
Favourable	34	(21.94%)	20	(12.42%)	34	(21.12%)
Non-submission	0	(0%)	0	(0%)	0	(0%)
Non-assessed	110	(70.97%)	67	(41.61%)	117	(72.67%)
Total	**155**	**(100%)**	**161**	**100%**	**161**	**100%**

[1] *We considered 161 drug-indications per country, however, decisions before 2006, and decisions when the date was missing, are not included (no possibility of linking them with time variables). Source: own construction*

Table V. Descriptive statistics: categorical variables (for 475 decisions)

Variable	Category	N (%)	Variable	Category	N (%)
Evidence	Internal	378 (79.6%)	**Pricing decision**	Based on a negotiation	11 (2.3%)
	External	93 (20.4%)		Calculation based on price referencing	159 (33.5%)
Body Independence	Inside MoH	44 (9.2%)		Set by the manufacturer	305 (64.2%)
	Indep. Recom.	311 (65.5%)	**Type of patient**	Adults	455 (95.8%)
	Indep. Decision	120 (25.3%)		Children	5 (1%)
Decision level	Recom./Decision National	339 (71.4%)		Both	15 (3.2%)
	Recom. National /Decision Regional	136 (28.6%)	**Orphan**	No	357 (75.2%)
Initiator	Department of Health (DoH)	86 (18.1%)		Yes	118 (24.8%)
	Manufacturer	242 (51%)	**Disease stage**	Early treatment	88 (18.5%)
	Body in charge of HTA	11 (2.3%)		Late treatment	378 (79.6%)
	Automatic	91 (19.2%)		Not specified	9 (1.9%)
	Both, manufacturer and DoH	45 (9.5%)	**ICER**	Above £30,000 per QALY	242 (51%)
Stakeholders	Non-involved	11 (2.3%)		Below £30,000 per QALY	171 (36%)
	Only early assessment	173 (36.4%)		Non-submission	39 (8.2%)
	Involvement, not final meeting	205 (43.2%)		No-data	23 (4.8%)
	Fully involved	86 (18.1%)	**End of life treatment**	No	230 (48.4%)
Transparency	Some documents available	11 (2.3%)		Yes	91 (19.2%)
	Everything publicly available	464 (97.7%)		Not determined (before 2009)	154 (32.42%)
Appeal	No	105 (22.1%)	**Managed Entry Agreement (MEA)**	No	312 (66.4%)
	Yes	370 (77.9%)		Yes, financial scheme	135 (28.7%)
Economic Evaluation	Only for some drugs	115 (24.2%)		Yes, performance-based	20 (4.3%)
	Yes, for all cases	360 (75.8%)		Yes, combination	3 (0.6%)
Budget Impact	No	120 (25.3%)	**Alternative**	No	320 (68.1%)
	Yes	355 (74.7%)		Yes	150 (31.9%)
Pricing location	No negotiation	211 (44.4%)	**Health system**	Tax-based system	266 (56%)
	External body	126 (26.5%)		Social Health Insurance system	209 (44%)
	Inside MoH	138 (29.1%)			

Source: own construction

Table VI. Descriptive statistics: Continuous variables (475 decisions) per country and 2006-2014

Variable	N	Mean (SD)	Min	Max
Incidence rate (all)	**443**	**30.63 (35.06)**	**1.60**	**159.1**
Scotland	86	29.89 (33.80)	3.2	95
England	81	33.87 (35.39)	3.2	95
Belgium	109	38.26 (41.64)	2.6	159.1
Sweden	41	36.83 (45.29)	1.6	119
Poland	88	20.28 (19.36)	1.8	94.2
Portugal	38	20.76 (24.55)	2.3	98.3
GDP growth (all)	**424**	**1.30 (2.29)**	**-5.17**	**6.56**
Scotland	85	0.92 (2.3)	-5.17	3.43
England	79	0.47 (2.52)	-5.17	3.43
Belgium	106	1.03 (1.85)	-2.80	2.88
Sweden	36	2.4 (2.22)	-0.61	6.56
Poland	86	2.98 (1.37)	1.57	5.13
Portugal	32	-0.51 (1.91)	-3.23	2.37
Population > 65 (% total pop.) (all)	**424**	**16.51 (1.49)**	**13.34**	**19.33**
Scotland	85	16.62 (0.48)	16.04	17.49
England	79	16.68 (0.47)	16.04	17.49
Belgium	106	17.27 (0.25)	17.08	17.98
Sweden	36	18.41 (0.68)	17.38	19.33
Poland	86	13.91 (0.35)	13.34	14.43
Portugal	32	18.15 (0.36)	17.46	18.77

Incidence rate is fixed for the whole period. It only changes by country. Source: own construction

Table VII. Results of the model

	MODEL 1		MODEL 2	
	Coeff (SE)	*OR*	*Coeff (SE)*	*OR*
System-wide variables				
Health system (=1 SHI)	0.885 (0.172)	2.422***	7.610 (281.495)	2018.82
Evidence (=1 external review)			-6.076 (281.490)	0.002
Initiator (1= Manufacturer)			-0.289 (0.427)	0.749
Stakeholders (<2 not involved/early stage)			-5.290 (281.487)	0.005
Economic Evaluation			12.143 (562.976)	187861.45
Budget Impact			-6.215 (281.489)	0.002
Pricing decision (1=reference pricing)			-6.103 (281.491)	0.002
Pricing decision (2=set by the manufacturer)			-11.861 (562.979)	7.06e-03
Product-specific variables				
Managed Entry Agreement (1= any type of MEA)	0.968 (0.185)	2.632***	0.889 (0.200)	2.434***
ICER (1=cost-effectiveness)	0.766 (0.197)	2.150***	0.789 (0.202)	2.200***
End of life (1=end of life criteria fulfilled)	0.342 (0.280)	1.408	0.330 (0.292)	1.390
End of life (2= before 2009, criteria not applicable)	0.357 (0.196)	1.429*	0.306 (0.206)	1.358
Incidence rate	-0.006 (0.003)	0.994**	-0.006 (0.003)	0.994**
Time variables				
GDP growth rate	0.203 (0.064)	1.225***	0.070 (0.089)	1.073
Population >65 (% total population)	0.576 (0.076)	1.780***	0.767 (0.690)	2.154
year 2007	-1.106 (0.356)	0.331***	-1.036 (0.373)	0.355***
year 2008	-0.150 (0.358)	0.861	-0.623 (0.437)	0.536
year 2009	0.483 (0.506)	1.622	-0.432 (0.703)	0.649
year 2010	-1.083 (0.323)	0.339***	-1.318 (0.447)	0.268***
year 2011	-0.928 (0.317)	0.395***	-1.399 (0.605)	0.247**
year 2012	-1.068 (0.356)	0.344***	-1.729 (0.839)	0.177**
year 2013	-1.840 (0.380)	0.159***	-2.525 (1.036)	0.080**
Random effects (variance components) [1]				
Var. in Intercepts (i,drug-indication)	0.431(0.192)**		0.464 (0.203)**	
Var. in Intercepts (j, country)	3.78e-34 (6.68e-18)		3.07e-34 (6.48e-18)	
Variance Partitioning coefficient (VPC)	0.16		0.18	
N of observations	393		393	
Study period	2006-2014		2006-2014	
N of countries	6		6	
N of Drug-Indications	139		139	
Log-likelihood	-343.707		-337.232	
LR test (Multilevel mixed-effect Ordered Probit) vs (Ordered Probit)	12.55***		13.37***	

*SE: Standard Errors, OR: Odds Ratio. Both models include year dummies. Significance levels: *p<0.1, **p<0.05,***p<0.01*
Source: own construction

7. Annex

System-level variables

Countries /variables	Agency	Evidence	Body independence	Decision level	Health system	Initiator	Stakeholders	Transparency	Appeal	Economic evaluation	Budget impact	Pricing location	Pricing decision
Belgium	RIZIV INAMI	0	1	0	1	1	2	2	1	1	1	1	1
England	NICE	1	2	0	0	0	3	2	1	2	0	0	2
Poland	AHTAPol	0	1	0	1	1[#]	1	2	0	2	1	2	2
Portugal	INFARMED	0	0	0	0	1	1	2	1	2	1	2	1
Scotland	SMC	0	1	1	0	3	1	2	1	2	1	0	2
Sweden	TLV prescribed	0	2	1	0	1	1	2	1	2	0	0	2
Sweden	NLT hospital	1	1	1	0	2	0	1	0	2	1	1	0

Time changes: [#] 4 – before 2012

Source: own construction. Validated by National experts.