UNIVERSITY OF GOTHENBURG
SCHOOL OF BUSINESS, ECONOMICS AND LAW

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An Analysis of the Decision-making Process of the TLV and the Willingness to Pay for Healthcare in Sweden

Jens Dahlstrand and Fredrik Sandberg

Supervisor: Andreea Mitrut
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Supervisor: Associate Professor, Andreea Mitrut
University: University of Gothenburg, Department of Economics

Abstract
The Dental and Pharmaceutical Benefits Agency (TLV) is the Swedish government agency who decides if a new medicine should be included in the benefit scheme or not. This study investigates which implicit factors influence the agency's reimbursement decisions and how the TLV values different properties of a medicine. The dataset used for this study consists of 116 observations and was extracted by analyzing all decision documents published on the TLV's website between the years 2008-2015. We model the TLV's reimbursement decisions as binary choices and investigate eight potentially important factors influencing the decisions. Six factors are identified as being of importance in the decision-making process: cost-effectiveness, the severity of the disease, the existence of an alternative treatment, the size of the applying firm and if the medicine is a preventive treatment or an orphan drug. We also estimate the TLV's valuation of four different characteristics often associated with a medicine. The results indicate that the TLV has the highest WTP for medicines categorized as palliative treatments, followed by medicines intended to treat severe diseases, orphan drugs and preventive treatments.

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Keywords: TLV, HTA, ICER, WTP, reimbursement, probit model, Heckman selection.

Contents

List of Tables

List of Figures

1. Introduction

Growing health expenditures is a challenge to the sustainability of many reimbursement systems in the developed countries. In order for the public funders of healthcare systems to control costs, while at the same time providing high quality healthcare, several countries have during the last decades established Health Technology Assessment (HTA) agencies. In Sweden, the TLV is the public agency with the remit to assess new pharmaceutical technologies and decide whether they should be included in the benefit scheme or not. The Swedish reimbursement system is based on a value-based pricing system, where the aim is to give the patients access to innovative and cost-effective treatments during the whole course of a medicine's life cycle. The TLV make decisions on reimbursement based on three principles; cost-effectiveness, need and solidarity and human dignity (TLV, 2015a). Although, these principles are explicitly stated, little is actually known about how they are operationalized. The ambiguity of these principles rather suggests that several implicit criteria are being used in the decision-making process of the TLV. If the purpose of the TLV is to be a transparent and accountable government agency, with the objective to reflect the society's preferences for health, more detailed knowledge is needed about what weight the TLV attaches to cost-effectiveness and what other factors also influence the decision-making process.

According to theory, the public funder of a healthcare system needs a benchmark threshold in order to determine what is "good value for money" (Towse, Pritchard & Devlin 2002). However, the TLV does not currently operate such a cost-effectiveness threshold. Eichler, Kong, Gerth, Mavros and Jonsson (2004) suggest that not operating a threshold could be attractive to decision-makers as it makes more room for arbitrariness and "ad hoc" considerations. Moreover, determining a threshold might be a politically sensitive question as the decision-maker would have to determine the societal willingness to pay for the healthcare of different diseases. On the other hand, if the TLV were to be more explicit about the factors affecting decisions and what weight they give to each of these factors, this could lead to increased efficiency, equity and consistency in decision-making. In addition, more transparency would further enhance the trust to the reimbursement system, both to the public and the pharmaceutical companies.

The first aim of this study is to examine the factors influencing decisions on reimbursement of innovative medicines made by the TLV board. Secondly, we also want to estimate the TLV's economic valuation of different characteristics often associated with these medicines. The study by Svensson, Nilsson and Arnberg (2015) is the only published study that

has attempted to address these questions in a Swedish context. Svensson et al. (2015) investigate the influence of cost-effectiveness and the severity of the disease and find that both factors have a significant impact on past decisions made by the TLV. This study contributes to the existing literature by extending the model of Svensson et al. (2015) and investigate other potentially important factors to decision-making process of the TLV. Moreover, it is also the first study to estimate the TLV's willingness to pay (WTP) for different characteristics associated with medicines.

The data used for this study was created by analyzing all decision documents that were published on the TLV website between the years 2008-2015. During this period, the TLV published a total of 643 reimbursement decisions. Out of these, 116 contained cost-effectiveness calculations, in terms of cost per QALY gained, which qualified them for inclusion into our dataset. We construct eight variables, which we hypothesize have an influence on decisions made by the TLV. These eight variables will constitute our main specification. Additionally, we construct four variables, each representing a specific group of patients, which we include in a second specification to test if certain patient groups are more likely to have their medicines approved than others.

In this study, we employ a probit model to estimate the impact of our set of variables on the likelihood of receiving an approval from the TLV board. In a second stage, we infer only on the approved decisions, and apply an OLS model to estimate the economic values given to different properties of the medicines. In order to control for possible sample selection bias, we also use a two-step Heckman Selection model. Our results confirm previous findings by Svensson et al. (2015), i.e. that cost-effectiveness and the severity of the disease are factors influencing reimbursement decision made by the TLV. Furthermore, we find that preventive treatments, orphan drugs and medicines produced by big firms are more likely to be reimbursed, whereas medicines with an alternative treatment have a lower likelihood of receiving an approval. The results also suggest that the TLV has a SEK150,000 higher WTP for medicines characterized as preventive treatments and over SEK200,000 for medicines targeted for severe diseases, palliative treatments and orphan drugs.

The rest of the paper is structured as follows. Section 2 provides a literature review of the previous empirical research of HTA decision-making. In section 3, we explain more in detail the concept cost-effectiveness and decision-making process of the TLV. In section 4, we formulate our two research questions. In section 5, the data extraction process is described and descriptive statistics are presented. Section 6 discusses the empirical strategy and in section 7 we present the results. Section 8 consists of a short discussion of the conclusions from our

results. Finally, in section 9 we discuss the limitations of our study and suggestions for further research.

2. Literature Review

During the last decade, several studies have investigated the decision-making process of HTA agencies and the role of cost-effectiveness. One of the first studies to perform empirical analysis on HTA agency decision-making was conducted by Devlin and Parkin (2004). The study used a binary choice analysis on decisions made by the UK National Institute for Health and Care Excellence (NICE) and hypothesized that the agency operated a probabilistic threshold range, rather than a strict value. Six variables were considered and the study found that cost-effectiveness, the burden of the disease and uncertainty had an impact on the decisions made by NICE. Moreover, the study showed that NICE practiced a threshold range above the publicly stated £20,000– £30,000. The analytical framework developed by Devlin and Parkin (2004) constitutes the basis to many of the following studies performed on HTA decision-making. An extension to this model was also developed by Dakin, Devlin and Odeyemi (2006) where NICE decisions were categorized into three categories; recommended, restricted and not recommended. The study used a multinomial logistic regression and found that patient groups, clinical evidence and the type of the pharmaceutical technology were also important variables in the decisions made by NICE.

The perspective of the threshold as a probability range, rather than a single value, has dominated the empirical literature on HTA decision-making since Devlin and Parkin (2004) published their study. The subsequent studies have either treated HTA decisions as binary choices or employed a multinomial modeling approach. Some authors have also tried alternative approaches, such as experimental studies, and explored the stated preferences of individual appraisal committee members in HTA agencies. These studies have confirmed previous empirical findings and support the notion of a probabilistic threshold (Tappenden, Brazier, Ratcliffe & Chilcott, 2012). It has also been shown that committee members have a willingness to trade-off economic efficiency for other attributes (Linley & Hughes, 2012)

The empirical literature on HTA decision-making has primarily focused on NICE decisions and there have, until recently, only existed a few empirical studies on HTA decision-making, see also (Harris, Hill, Chin, Li & Walkom, 2008). This is partly explained by the limited access of data on HTA decisions in other countries. Although, NICE introduced the use of CUAs relatively early, the study of Devlin and Parkin (2004) only had 39 observations,

where 33 were used in their model. The study of Dakin et al. (2006) was based on only 60 observations with a reported cost-effectiveness ratio.

It is not until the last two years that a couple of studies have been conducted in other European countries than the UK. The availability of larger amounts of data, during the last couple of years, has enabled researchers to hypothesize and test a wider range of factors, which could influence HTA decisions. As a result, many of the recent studies have taken exploratory approaches, where different selection procedures have been used in order to identify the influential factors to build their models upon. Charokopou, Majer, Raad, Broekhuizen, Postma and Heeg (2015) hypothesize about 18 variables and use a backward elimination procedure. Other authors have excluded insignificant variables in a univariate analysis and then only included the variables that are also significant in the multinomial regression model in their final specification (Cerri, Knapp & Fernandez, 2014; 2013).

Cerri et al. (2013) use a multinomial approach on decisions made by the College Voor Zorgverzekeringen (CVZ) in the Netherlands, between the years 2004-2009. Their study finds that factors such as therapy type, budget impact, size of the patient population and inclusion of patient submissions impact on the decisions made by the CVZ. The study of Charokopou et al. (2015) uses the same strategy on the Scottish Medicines Consortium (SMC) and show that the company size, medicines for the nervous system and medicines that are not intended for chronic use have a positive impact on decisions made by the SMC. Moreover, they also show that medicines with cost-effectiveness evidence have the highest odds of receiving a positive recommendation.

Although several papers have been published on HTA decision-making during the last couple of years, the results from the studies on HTA decision-making in other countries may not contribute that much to the understanding of the process behind the reimbursement decisions made by the TLV. As the appraisal criteria varies among countries, many of the findings in other countries are not relevant in a Swedish context. The study by Svensson et al. (2015) is the only study that has tried to evaluate reimbursement decisions made in Sweden. Svensson et al. (2015) model the TLV decisions as binary choices and estimate the impact of cost-effectiveness and the severity of the disease on the likelihood of receiving an approval from the TLV. Their dataset covers the years of 2005-2011 and comprises 102 observations. Their results show that both factors have an influence on the reimbursement decisions made by the TLV. The objective of this study is to improve the knowledge of the decisions-making process of the TLV by examining more factors than the previous study of Svensson et al. (2015) and also estimating the TLV's WTP for healthcare.

3. Background & Theory

3.1 Health Economic Analysis

The most common tools for economic evaluations in healthcare are cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). CEA and CUA are different methods of comparing two, or more healthcare treatments, where costs are related to a single health outcome measure. When two treatments achieve the same outcome, a simple comparison could instead be based on cost-minimization analysis (CMA). An economic evaluation is considered as a CEA when the health outcome is expressed in physical units, e.g. *life years gained.* In CUA the outcome is expressed by a utility factor, which in a healthcare setting usually is stated as *Quality-adjusted life year (QALY).* The QALY is a generic health outcome, which captures both the reduced morbidity and the perceived quality gains resulting from a treatment. Hence, it measures two dimensions of health, where the length of a life is adjusted by the patient's expected health status in each state proceeding after a pharmaceutical intervention. In a healthcare setting, what is considered as costs depend on the viewpoint of the decision-maker. With a narrow perspective, costs could be defined as the resources consumed from providing the treatment, e.g. medicines, doctor visits and hospital equipment. With a societal perspective, costs could also include the resources used in other public agencies or patient out-of-pocket expenses, such as sickness benefits or loss of earnings. (Drummond, Sculpher, Torrance, O'Brien & Stoddart, 2005)

Using the QALY as a measure, the difference in health effects between two treatments is expressed in terms of "cost per QALYs gained", which is often summarized as the incremental cost-effectiveness ratio (ICER). This is illustrated in equation (1). Depending on the costs and benefits of a new medicine, the ICER could have four outcomes. When a new medicine is less effective and more costly the medicine is said to be dominated by the old medicine, whereas a more effective and less costly medicine dominates the alternative. From this perspective, it is easy to comprehend that the public funder ought to reject the former medicine and invest in the latter one. However, as medicines could also be more effective and more costly, or less effective and less costly, the question of whether to implement the treatment or not will depend on the public funder's WTP for the treatments. This maximum acceptable ICER is also often referred to as the cost-effectiveness threshold. (Drummond et al., 2005)

$$(1)\quad ICER = \frac{\text{Costs}_{\text{New}} - \text{Costs}_{\text{Old}}}{\text{Benefits}_{\text{New}} - \text{Benefits}_{\text{Old}}}$$

3.2 The Concept of a Threshold

The economic literature offers two broad approaches on how the threshold ought to be set. In the first model, the decision-maker is assumed to be perfectly informed and face an exogenously fixed budget. If the aim is to maximize health outcomes, interventions are implemented in descending order, based on cost-effectiveness, until the budget is totally exhausted. The threshold is then identified at the level where no further interventions are implemented (Morris, Devlin & Parker, 2012). In the other approach, the threshold is set as to reflect the society's WTP for health. The appropriate threshold could, for example, be determined by research on WTP for health studies, or be linked to some fixed level of the GDP per capita. If the threshold could be properly identified, all technologies with an ICER lower than this value ought to be reimbursed and the resulting budget would have to be the sum of all implemented technologies (McCabe, Claxton & Culyer, 2012).

The concept of a single, or strict, cost-effectiveness threshold relies on the premises that the decision-maker has access to perfect information and bases the decision solely on the cost-effectiveness of a technology. However, in practice, healthcare providers have limited access to information and decisions have to be made with uncertainty (Claxton, 2007). Moreover, criteria other than cost-effectiveness are also likely to affect reimbursement decisions, such as the medical need, severity of the disease and the rarity of the disease (Franken, le Polain, Cleemput & Koopmanschap, 2012). If these criteria are also practiced, this means that the decision-maker is willing to trade-off some economic efficiency for other political goals. Furthermore, it also implies that there exists no single threshold, but rather a threshold range within which other factors, than only the cost-effectiveness, are also likely to affect the decision outcome (Devlin & Parkin 2004).

3.3 The TLV Decision-Making

The TLV is the Swedish governmental agency with the responsibility to decide which pharmaceutical products, medical devices and dental care procedure to include in the reimbursement system or not. The Swedish healthcare system is mainly financed by the county councils, who have the responsibility to provide and finance the healthcare, but the system is also partly funded by government grants and co-payments by patients (Anell, H Glenngård & Merkur, 2012). Since 2002, Sweden has a Value Based Pricing (VBP) system for innovative outpatient drugs. VBP is a pricing system where the price of a product is determined by the perceived benefits to its consumers. In a healthcare setting, consumers are represented by the

patients and prices are dependent on the decision-makers WTP for the added value generated by an innovative medicine. When no added value is claimed by the pharmaceutical firm, medicines will compete over prices. It is the applying pharmaceutical company that sets the price of the medicine, from which the TLV then makes a joint decision on both price and reimbursement (Persson, Willis & Ödegaard, 2009).

The final decision on reimbursement is taken by a board comprising experts from different fields and members of the county councils. The board considers a societal perspective and takes into account a wider set of economic benefits and costs, which are generated by the innovative medicine, such as primary treatment costs, patient earnings and out-of-pocket costs. Hence, the reimbursement decision is not based on the actual price of an innovative medicine, but rather on the economic costs to society, which is captured by the ICER (TLV, 2015b). The applying firm is responsible for providing the TLV with economic and clinical evidence to prove the cost-effectiveness of its medicine. In its general guidelines, the TLV recommends the use of CUA to prove a medicine's added therapeutically value, where QALYs is the preferred health outcome measure. However, when two medicines are equal in health effects, reimbursement decisions are instead based on CMAs, i.e. price comparisons over actual prices (TLV, 2015c).

The Swedish reimbursement system is a product oriented system, where one decision is supposed to apply for a medicine's whole indicated population. However, if a drug has several indications, or if it is only considered as cost-effective to a limited group of patients, the TLV is mandated to give the medicine a restricted reimbursement. By analyzing the marginal utility of a drug, the TLV could either restrict the approval to a particular indication or a subgroup of patients (Persson et al., 2009).

The TLV does not have an explicit cost-effectiveness threshold, although, one often cited figure is the SEK500,000 per QALYs gained, which have been developed by the National Board of Health and Welfare (Socialstyrelsen, 2011). In its decisions, the TLV sometimes make value-based statements about the cost-effectiveness, which seem to indicate that these recommendations are practiced as some sort of benchmark. As two examples, the TLV has stated that SEK360,000 is to be considered as a moderate cost, whereas SEK500,000-600,000 is considered as a relatively high cost, see for example (TLV, 2012a; TVL, 2011).

In order to decide whether a medicine ought to be included in the reimbursement system or not the TLV is guided by an ethical platform, which can be summarized in three principles; (1) human dignity, (2) need and solidarity, and (3) the cost-effectiveness principle. The principle of human dignity stipulates that the healthcare ought to respect all people's equal

value and that no one should be discriminated against. The second principle implies that those who are in greater need should be allocated more of the resources within the healthcare system. The third and last principle states that the costs of a drug or treatment should be reasonable from a socioeconomic, humanitarian and medical point of view (TLV, 2012b). According to the three principles of the TLV, it is quite clear that the TLV base the reimbursement decisions on a multi-criteria analysis, where the cost-effectiveness of a medicine plays an important role in determining the outcome of the decision. However, it is not entirely obvious how the other principles are operated or which other criteria the principles aim to cover.

4. Research Questions

The first focus of this study is to identify the factors influencing the reimbursement decisions made by the TLV board. It is stated by the TLV that both the cost-effectiveness and the severity of the disease are two factors that are considered jointly when making decisions on reimbursement (TLV, 2015a). However, based on the three principles of the TLV, there is reason to believe that other factors are also of significant importance to the decision-making process. After we have identified these factors, the second focus of this study will be to estimate the TLV's valuation of various characteristics often associated with a medicine. The two objectives of this study are specified by the following two research questions:

1. Which factors influence reimbursement decisions made by the TLV board?
2. How does the TLV value different properties of a medicine?

5. Data & Descriptive Statistics

The data that we use in this study was obtained by analyzing all public decisions documents that were published on the TLV webpage between the years 2008 - 2015. For some of the variables in our model, the data was extracted directly through explicit statements made by the TLV board. However, information on patients' medicine usage, as well as firm employees and firm turnover, also had to be collected from different databases

5.1 Variables

5.1.1 The Decision Outcome

The reimbursement decisions made by the TLV board, in practice, have more than two outcomes[1]. However, in this study we treat all approved decisions as one category. This method has been applied in several previous studies on HTA decision-making and was also used and validated on the TLV decision-making in the study of Svensson et al. (2015). The reimbursement decision thus becomes a binary choice, which can be characterized as a "Yes" or "No" to approval of the medicine. We have chosen to call our dependent variable *approval*, which takes on value 1 if there is a "Yes" and 0 if there is a "No".

5.1.2 The ICER

As described above, the ICER represents a ratio between two treatments, where the difference in costs is divided by the difference in health effects. This variable could also be thought of as representing the incremental costs to society, resulting from the implementation of a new medicine. Since the TLV recommends the use of QALYs in health economic evaluations, this variable is expressed as *the cost per QALY gained*. However, for the simplicity of writing, we will instead use the analogues term *ICER*. The *ICER* is a continuous variable, which is denominated in 1000s of SEK. The TLV does generally present the ICER as a single figure in its decisions, however, in cases where it has been stated as an interval, we have instead used the mean of this interval.

5.1.3 Independent Variables

The TLV has stated that lower ICERs are accepted, when there are factors causing uncertainty regarding, for example, the actual usage of a medicine or the clinical effects (TLV, 2015a). When there is uncertainty about the actual economic outcomes of a medicine this is sometimes expressed as ICER intervals, rather than precise figures. Although, there is no established method of estimating these kinds of uncertainties in the literature, Devlin and Parkin (2004) and Dakin, Devlin, Feng, Rice, O'Neill and Parkin (2015) have developed a method of capturing the uncertainties surrounding the ICER calculations. We use a similar approach and construct the variable *ICER range*. The variable is a ratio, where the distance between the upper and lower bound of the ICER estimate is divided by the mean of the interval. When no ICER interval is stated in a decision this variable takes on value zero.

We also construct a dummy variable called *big firm* based on the definition for small and medium-sized enterprises (SME), which is developed by the European Commission

[1] Reimbursement decisions made by the TLV board in practice have three outcomes; full, restricted or no reimbursement. Reimbursement could, for example, be restricted to a certain patient group or to a specific usage.

(2016). The data for this variable was collected from Retriever Business database (Retriever, 2016). As the SME does not have a formal definition of what is considered as a big firm we have defined all firms larger than medium firms as big firms, i.e. having 250 or more employees or a turnover of more than €50 billion the year prior to when the decision was made.

The remaining independent variables are dummy variables, which indicates whether a specific characteristic is associated with the medicine or not. We have chosen to include the variable *high severity*, since this variable was found significant in the previous study of Svensson et al. (2015). We have also used their strategy to categorize the severity of disease, since the TLV does not have any formal definition of when a disease is to be considered as severe or not. A disease has been categorized as severe whenever it is stated by the TLV as "high" or "very high", or where there is a high risk of death or disability.

The variables *palliative treatment* and *preventive treatment* are used to capture the general purpose of the medicine. A medicine is defined as *preventive treatment* only when it is designed to protect or prevent the occurrence of a disease, e.g. vaccines or prophylaxis. The variable *palliative treatment* captures medicines intended for people who have serious illnesses, where the aim is to reduce pain or treat the side effects of treatments for diseases that cannot be cured. As there exists no strict definition of what is considered as palliative treatment in Swedish healthcare (Socialstyrelsen, 2013), we base the variable *palliative treatment* on explicit statements made by the TLV, where the board has expressed that a medicine is intended for palliative treatment.

The variable *orphan drug* captures medicines that are intended to treat rare diseases. The TLV uses the same definition of orphan drugs as the European Medicines Agency (EMA), which is that diseases should not have a prevalence of less than five out of 10.000 individuals (EMA, 2016). Finally, the variable *alternative treatment* states whether there already is a comparable treatment covered in the benefit scheme or not.

We have also created four variables, which describes the composition of the patient group associated with a medicine. Since there exists no public data on patients' usage of specific medicines in Sweden, we instead use data based on the medicine's substance as a proxy. The data was collected from the Swedish National Board of Health and Welfare database and four patient groups were identified; *men, women, children* and *old60+* (older than 60). A patient group is defined as *men, women, children* and *old60+* when one of these groups have received a clear majority of the prescriptions on medicines containing the relevant substance. It is worth noticing that a medicine could be intended for men, women or both.

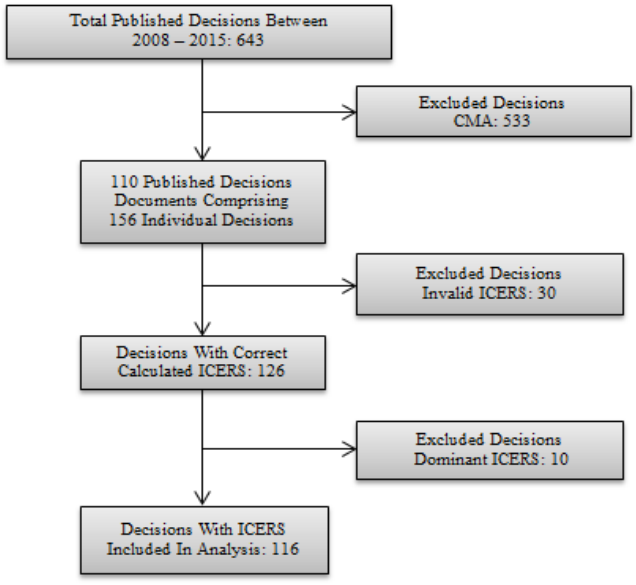
Thus, when *men* and *women* are included in the model, "both" is to be considered as the base group. A similar interpretation can also be used for *children* and *old60+*.

5.2 Descriptive Statistics

In figure one, the selection process is reported for all published decisions that were analyzed during the data extraction process. Between the years of 2008-2015, a total of 643 decision documents were published on the TLV website, where 317 decisions were granted full reimbursement and 211 were approved with a restriction. Altogether, 528 published decisions received a positive decision outcome, whereas 105 applications were declined reimbursement. A detailed overview of the distribution of the published decision by year is found in the Appendix in table 5. In order to identify the relevant decisions for this study, i.e. where decisions were based on an ICER estimate, all 643 decisions were analyzed individually. Out of the 643 published decision documents, 533 documents were excluded, due to the fact that they were based on CMAs rather than CUAs i.e. price comparison of the actual price of the medicine and not the ICER.

Whenever a decision document contained more than one decision, it was sub-divided into four separate decisions. The fragmentation of 110 decision documents resulted in a total of 156 individual decisions. Out of these, 30 individual decisions were excluded, as the ICER estimates in these decisions were rejected by the TLV board. Furthermore, 10 individual decisions were also excluded since the medicines were either dominated, dominant or had an ICER interval ranging between dominant and some positive value. The dataset was finally reduced down to comprising a total of 116 individual decisions.

Figure 1 - Flow Diagram for the Selection Process



In table 1, the descriptive statistics are presented and categorized by the decision outcome. Only the means are presented for the dummy variables, whereas the standard deviation is also presented for the *ICER* and the *ICER range*. Moreover, we have nine missing observations for the variables *men*, *women*, *children* and *old60+*. Since these nine observations constitute a relatively large share of the total number of observations, we present summary statistics for both the full and the restricted sample.

Table 1. Summary Tables

	FULL SAMPLE						RESTRICTED SAMPLE					
	Decision outcome						Decision outcome					
VARIABLE	Declined		Approved		Total		Declined		Approved		Total	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
ICER (1000s)	1936	2147	411	293	740	1194	1950	2276	404	293	722	1220
ICER Range	0.23	0.47	0.19	0.40	0.20	0.42	0.26	0.50	0.20	0.42	0.21	0.43
Dummy variables												
High Severity	0.52		0.55		0.54		0.45		0.55		0.53	
Orphan Drug	0.24		0.24		0.24		0.18		0.21		0.21	
Palliative Treatment	0.08		0.04		0.05		0.09		0.05		0.06	
Preventive Treatment	0.08		0.24		0.21		0.05		0.26		0.21	
Alternative Treatment	0.36		0.34		0.34		0.32		0.34		0.34	
Big Firm	0.56		0.63		0.61		0.50		0.61		0.59	
Men							0.14		0.19		0.18	
Women							0.14		0.24		0.21	
Children							0.23		0.04		0.07	
Old60+							0.27		0.41		0.38	
Observations	25		91		116		22		85		107	

As can be seen in table 1, the average ICERs are almost five times higher for the declined medicines, than for the approved medicines. The mean ICERs for the approved medicines in the full sample is SEK411,000 compared to SEK1,936,000 for the medicines that were declined. Approximately half of the medicines in our samples concern diseases that are classified as severe and this share is seemingly consistent for both outcomes. This also applies for orphan drugs, which constitutes 24% of observations in both outcomes, and 36-34% for medicines with an alternative treatment. The drop of nine observations does not seem to change the results very much as the differences between the two samples are very small.

Preventive treatments seem to be approved more often, where 24% of the approved decisions are preventive treatments, compared to 8% in the declined decisions. Palliative treatments constitute the smallest share of the observations, with only 5% of the medicines

being palliative, whereas 61% of the companies in our dataset are classified as big firms. Moreover, medicines intended for children only constitute 7% of the observations in the dataset. The largest patient group is people who are 60 years or older, where 38% of the medicines are associated with this group of patients.

6. Empirical Strategy

In this section, we present the econometric methods that we use to answer the two research questions specified above. The first two models aim to answer the two questions respectively, whereas the third model is used to control for potential sample selection bias in the second model.

6.1 Probit Model

As we have chosen to characterize the reimbursement decisions made by the TLV board as binary choices, we identify the factors influencing reimbursement decisions by employing a probit model. In order to answer the first research question, we fit the following model to the data:

(1) $Approval_i = \beta_0 + \beta_i X' + \beta_i \theta' + \varepsilon_i$

In Equation (2), $Approval_i$ is binary variable, which takes on value 1 if a medicine is approved and 0 if it is declined. The term X' is a vector of explanatory variables, containing *ICER*, *high severity, orphan drug, palliative treatment, preventive treatment, alternative treatment, ICER range* and *big firm*. The vector θ' contains year controls, together with *men, women, children* and *old60+,* and ε_i is the error term.

6.2 OLS Model

In order to answer the second research question, we use an OLS model to estimate the TLV's economic valuation of various characteristics associated with the medicines. The strategy we use is based on two crucial assumptions. First, we assume that both the TLV and the applying firms have access to perfect information, meaning that the calculated ICERs represent the actual costs of health to society and that the TLV's demand curve is known to the firms. Secondly, we assume that all firms that apply for reimbursement are profit maximizers. If both these conditions are met, the pharmaceutical companies will set their prices such that each accepted ICER must represent the TLV's maximum WTP for each specific medicine.

Consequently, by estimating the impact of different characteristics only on the accepted ICERs, we assume that what we observe is the TLV's valuation of each of these factors. In order to answer the second research question the following model is used:

(2) $ICER_i = \alpha_0 + \alpha_i Z' + \nu_i$

In equation (3), Z' is a vector of explanatory variables containing *high severity, palliative treatment, orphan drug, preventive treatment* and *alternative treatment*. ν_i is the error term.

6.3 Heckman Selection Model

We exclude decisions that are non-randomly selected in the OLS model, which may introduce bias into the model. This could lead us to either over- or underestimate the effects in the OLS regression. In order to control for potential sample selection bias, we also apply a two-step Heckman Selection model (Heckman, 1979). The Heckman correction is a two-equation model, where the decisions on reimbursement and price are assumed to be taken simultaneously. The model treats the sample selection problem as an example of omitted variable bias and lets us use the information from the declined decisions to correct for the biased estimates in the OLS regression. The Heckman correction procedure takes place in two stages. In the first stage, we estimate a selection model on the full sample, which in our case is the probit model specified in equation (2). Secondly, we estimate the inverse Mills ratio, λ_i, for each individual decision and include it in the OLS regression as an independent variable. The new regression equation that is estimated takes the following form:

(3) $ICER_i = \gamma_0 + \gamma_i Z' + \sigma_\varepsilon \rho \lambda_i (I_i - \beta_i X') + \mu_i$

In equation (4), Z' is the same vector as in equation (3), containing *high severity, palliative treatment, orphan drug, preventive treatment* and *alternative treatment*. σ_ε stands for the standard deviation of ε_i, whereas ρ is the correlation between the unobserved effects of ε_i and ν_i. The Heckman model assumes that the two error terms are jointly normally distributed. The term I_i is the threshold value for when an approval is observed. The inverse Mills ratio, λ_i, is estimated for each decision i, by dividing the normal density function by one minus the normal cumulative distribution function. The formal equation of the inverse Mills ratio is presented in equation (4), where the denominator is interpreted as I_i minus the predicted probability of each observation i.

(4) $\lambda_i(I_i - \beta_i X') = \frac{f(I_i - \beta_i X')}{1 - F(I_i - \beta_i X')}$ $\quad I_i = \begin{cases} 1 \; if \; Approval_i = YES \\ 0 \; if \; Approval_i = NO \end{cases}$

As the standard deviation is positive by assumption and ρ is assumed to be the correlation between the unobserved effects of the two error terms, we have that the λ_i can only be zero when two unobserved error terms are zero. When λ_i is positive, this is a sign that we have sample selection bias in the OLS regression.

7. Results

7.1.1 Factors Influencing Reimbursement Decisions

Table 2 presents the results from the probit model. In the first column, we have chosen to present the same specification as was used in the study of Svensson et al. (2015). The second column presents the results from our main specification, whereas in column (3) we also control for yearly effects. In column (4), we have included four variables controlling for the gender and age of the patient groups associated with the medicine. As mentioned above, the inclusion of these variables leads to a drop of observations from 116 to 107, due to nine missing observations. In column (5), we also control for yearly effects on the restricted sample. Since we cannot directly interpret the magnitude of the estimated coefficients in a probit model, only the signs and the significance levels of each coefficient are discussed in this section. The results of the marginal effects are also presented below (see section 7.1.2). A full table also showing the yearly effects can be found in Appendix table 6 and 7.

Table 2. Probability of Approved Reimbursement Decision

Variable	Coefficients			
	(1)	(2)	(3)	(4)
Approval	Probit	Probit	Probit	Probit
ICER	-0.00378***	-0.00568***	-0.00757***	-0.00893***
	(0.000928)	(0.00134)	(0.00166)	(0.00209)
High Severity	1.485**	1.841**	3.508***	2.656***
	(0.636)	(0.761)	(1.064)	(0.824)
Orphan Drug		0.850**	0.718	1.729***
		(0.406)	(0.598)	(0.506)
Palliative Treatment		0.492	0.439	0.840
		(0.628)	(0.611)	(0.594)
Preventive Treatment		1.720***	1.911**	4.891***
		(0.564)	(0.825)	(1.630)
Alternative Treatment		-1.171**	-1.659**	-1.587**
		(0.541)	(0.735)	(0.777)
Big Firm		1.365***	1.539**	2.228***
		(0.455)	(0.624)	(0.655)
ICER Range		-0.895	-0.942	-1.643**
		(0.593)	(0.674)	(0.735)
Men				3.159***
				(1.108)
Women				-1.059*
				(0.567)
Children				0.285
				(0.902)
Old60+				-2.168**
				(0.972)
Year Dummies	NO	NO	YES	NO
Observations	116	116	116	107
Pseudo R-Squared	0.590	0.705	0.780	0.746

Standard errors in parentheses *** p<0.01, ** p<0.05, * p<0.1

As can been seen in column (1), (2), (3) and (4), the direction of the *ICER* is negative, whereas for *high severity* the direction is positive. The signs of the coefficients for these variables are consistent and significant throughout all specifications. The results confirm the previous findings by Svensson et al. (2015), i.e. that the TLV is more likely to approve medicines that are intended to treat severe diseases than for non-severe diseases and that the likelihood of receiving an approval decreases as the ICER increases.

In columns (2) and (3), where the full sample is used, *palliative treatment* and *ICER range* are insignificant, regardless of whether we control for years or not. *Orphan drug* becomes insignificant when year controls are also included in the model. The results are rather consistent in columns (2) and (3), although, as we also control for years, there is a quite

substantial change in the size of the coefficient of *high severity,* and *orphan drug* becomes insignificant. The overall results from the columns (4) and (5) show that medicines that prevent diseases have a positive impact on the probability of receiving an approval. Medicines have a lower likelihood of being approved when there already exists a comparable alternative treatment within the benefit scheme, whereas being a big firm increases the probability of receiving a positive decision outcome. As the results are mixed for the coefficients of *orphan drug* in columns (2) and (3), we are not confident to definitely state whether it has an influence on the decisions made by the TLV or not. However, as it is significant in our main specification, in column (2), and the coefficient stays relatively consistent in both specifications, it is likely that this factor also have a positive influence on the likelihood of receiving an approval.

In column (4), where patient groups are also included, the estimated sizes for *orphan drug* and *ICER range* increase and both variables becomes significant, at a one and five percent level respectively. The results show that *orphan drug* has a positive impact on the probability of being reimbursed. The effect of the *ICER range* is negative, implying that as the uncertainty concerning the ICER calculations increase the likelihood of being approved decreases. As the estimations in column (4) are made on a restricted sample it is possible that some of the changes in these variables arise due to the dropped variables. However, when also estimating the specification in column (2) on the restricted sample no significant differences in effects are found (see column (6), table 6 in Appendix). When including the controls for the age and the gender of the patient groups in column (4), *men*, *women* and *old60+* become significant. The results from column (4) indicate that medicines are more likely to be approved when men constitutes a majority of the patient population associated with the medicine, whereas patient groups comprising a majority of women, or patients aged 60+, have a negative influence on the likelihood of getting the medicine approved for reimbursement. However, no such effect is found in the case of children.

In addition to the specifications in columns (1), (2) and (3) we also estimated a model including year controls and *men, women, children* and *old60+* combined. The estimations were made on the restricted sample, where all variables except for the *ICER range, children* and the year controls were significant. However, as we introduce 19 parameters into the model, with a dataset only comprising 107 observations, it is possible that we have induced too many parameters relatively to the number of observations. Thus, as we believe that this specification may suffer from problems of overfitting the results were excluded from the table. Therefore, they are instead presented in the Appendix (see column (5), in table 6).

7.1.2 Marginal Effects

Table 3. Marginal Effects at Means

VARIABLE	Coefficients			
	(1)	(2)	(3)	(4)
Approval	Margins	Margins	Margins	Margins
ICER	-0.00114***	-0.00156***	-0.00166***	-0.00149**
	(0.000261)	(0.000355)	(0.000417)	(0.000597)
High Severity	0.448**	0.506**	0.771***	0.443**
	(0.181)	(0.210)	(0.235)	(0.188)
Orphan Drug		0.234*	0.158	0.289*
		(0.123)	(0.145)	(0.156)
Palliative Treatment		0.135	0.0965	0.140
		(0.171)	(0.137)	(0.111)
Preventive Treatment		0.473***	0.420***	0.816***
		(0.149)	(0.134)	(0.268)
Alternative Treatment		-0.322**	-0.364***	-0.265***
		(0.138)	(0.129)	(0.0988)
Big Firm		0.375***	0.338**	0.372**
		(0.145)	(0.146)	(0.175)
ICER Range		-0.246	-0.207	-0.274*
		(0.158)	(0.127)	(0.143)
Men				0.527**
				(0.219)
Women				-0.177
				(0.120)
Children				0.0476
				(0.156)
Old60+				-0.362***
				(0.119)
Year Dummies	NO	NO	YES	NO
Observations	116	116	116	107

Standard errors in parentheses *** p<0.01, ** p<0.05, * p<0.1

Table 3 present the marginal effects estimated from the probit results. The marginal effects are calculated when holding all other variables at their means. According to the results in columns (2), (3) and (4), the probability of receiving an approval from the TLV decreases by 0.16 percentage points as the *ICER* increases by SEK1000s. The highest increase in the probability of receiving an approval is observed for medicines targeting severe diseases, which is 51 percentage points higher than for non-severe diseases. A comparison of the results in columns (1) with the overall results seems to suggest that only including *the ICER* and *high severity* in the model would lead to an underestimation of the effects for these two variables, implying that previous findings have been downward biased.

The effect is also substantial for preventive treatments, where belonging to this category increases the probability of being approved by 47 percentage points. Medicines with an alternative treatment already being subsidized have a 27-37 percentage point lower probability of being reimbursed, compared to where no alternative exists. The results show that medicines are 34-38 percentage points more likely to be reimbursed if the applying company is considered as a big firm. The effect of the orphan drugs seem to be positive, but is more uncertain as it is only significance on a five percent level in columns (2) and (4) and insignificant in column (3).

Out of the four variables representing the patient groups only the effects of *men* and *old60+* are significant, although women were significant in the probit regression. The effect for *men* is rather substantial, suggesting that medicines intended for men have 53 percentage points higher likelihood of being subsidized compared to others. The opposite effect is found for people older than 60, where the probability decreases by 36 percentage points

7.1.3 The Impact of Each Factor on the Accepted ICER

In table 4, the results are presented for the OLS-model and the two-step Heckman selection model. Column (1) show the results from the OLS-model, whereas columns (2), (3) and (4) show the results from the Heckman model. In column (2), the selection equation, i.e. the probit model, corresponds to the main specification used in table 2, column (2). Furthermore, year dummies are added to the selection equation in column (3), whereas the four patient group variables are added in column (4). As nine observations are dropped when we include *men, women, children* and *old60+,* the restricted sample is used in column (4).

Table 4. OLS and Heckman Selection Models

VARIABLE	Coefficients			
	(1)	(2)	(3)	(4)
ICER	OLS	Heckman	Heckman	Heckman
High Severity	185.8***	211.8***	204.5***	219.5***
	(60.54)	(49.32)	(55.21)	(55.89)
Palliative Treatment	209.8***	244.2***	240.5***	257.7***
	(57.66)	(41.52)	(56.66)	(50.64)
Orphan Drug	237.3***	209.4***	238.8***	243.8***
	(75.88)	(63.42)	(71.26)	(74.05)
Preventive Treatment	93.86	149.9**	113.9*	140.5**
	(73.03)	(63.00)	(64.87)	(67.90)
Alternative Treatment	-10.42	-91.32**	-39.97	-52.25
	(53.41)	(40.57)	(49.09)	(46.41)
Lambda		765.6***	426.1*	623.3***
		(164.7)	(226.5)	(178.1)
Constant	223.2***	146.9***	182.4***	145.0***
	(41.01)	(38.79)	(41.36)	(39.78)
Included in the selection equation:				
Patient Groups				YES
Year Dummies			YES	
Observations	91	91	91	85
R-Squared	0.287	0.507	0.369	0.403

Robust standard errors in parentheses *** p<0.01, ** p<0.05, * p<0.1

The results in table 4 show that *high severity, palliative treatment* and *orphan drugs* are statistically significant at a one percent level in all specifications. *Preventive treatment* becomes significant when we also control for sample selection bias, whereas *alternative treatment* is only significant in column (2). The overall pattern observed is that the sizes of the coefficients increase as we estimate the model using the two-step Heckman selection model. The only exception is the coefficient of *orphan drug* in column (2), which becomes smaller. As the lambda is statistically significant in all specifications, this indicates that the OLS regression suffer from sample selection bias. The results imply that we would underestimate the TLV's valuation of the different characteristics of the medicines if we were to only consider the results from the OLS-model. Moreover, it would also lead us reject the economic significance of *preventive treatment*, which may not be correct.

The column (2) is where we have used our main specification in the selection equation. By judging from the R-squares in the table, this is also the model that best fits the data. Using the results from column (2) as our basis, the TLV has the highest valuation for palliative

treatments, where they are willing to accept ICERs that are SEK244,000 higher than if a treatment is not of palliative character. In contrast, the TLV seems to lower the WTP when there already exists an alternative treatment in the benefit scheme. However, the variable *alternative treatment* is significant in column (2), but insignificant in all other columns. Thus, this result should be interpreted with caution. The TLV also have high valuations of orphan drugs and medicines targeted to treat severe diseases, nearly SEK210,000 for both. The TLV's WTP for preventive treatments is estimated to be SEK150,000 higher than for other treatments.

7.2 Robustness Checks

In this section we investigate if our probit models are robust to exclusions of variables or changes in the definitions of variables. Only the main specifications is discussed in this section.

The definition of palliative treatment in our dataset has no strict definition compared to the other variables. Therefore, results without this variable are presented in the Appendix, in table 8 in column (2), and the result shows that there is no change for statically significance of the coefficients in column (2) compared with our main model in column (1). We also choose to change the definition for the variable *big firm*. Instead of using the SME-definition we use the number of patents for each firm. The threshold that is being used to identify a big firm in our dataset is 500 patents or above. This alternative measure investigates the power behind the whole corporate group for getting a positive reimbursement decision whereas the SME-definition measures the subsidiary firm strength for approval. The results are presented in table 8 in Appendix column (3). All variables that were significant in the original model remain significant, besides *orphan drug,* when we use patents as a proxy for a big firm. However, there are changes in the significance level for *high severity, alternative treatment*. Notably, *ICER range* becomes significant at the ten percent level when we use patents. Also, we investigate the total number of patents instead of using a threshold in column (4) in table 8 in Appendix. Yet, we see no significant changes when using this specification compared to the model when a threshold is used for patents.

To smooth the distribution of the *ICER* and to transform the data into normality and reduce potential issue of outliers, we transform the numeric value of the *ICER* into the logarithmic value of the *ICER*. The results with log-ICER are presented in table 8, column (5). The results with a log-ICER are similar as our main probit model. Yet, the variable *alternative*

treatment is now insignificant, the significance level increases slightly for *high severity* and *ICER range* is significant at the ten percent level.

In our dataset we have two observations that lie extremely above our mean for the ICER of declined decisions (7000SEK & 10000SEK). In column (6) in table 8 we see no changes at all in contrast to our main model in column (1), when these two extreme values are excluded. We also have an extremely low value of 7SEK for approved decisions in our dataset and this observation is excluded in column (7) and we see no significant changes in the result.

Finally, we perform a robustness check on the Heckman Selection model. According to Bushway, Johnson and Slocum (2007) there is problem with inflated standard errors when there is no exclusion of variables in the first step in the Heckman procedure. In table 9 in Appendix we present results where we have excluded *ICER range* in the first step. We exclude this variable since it is insignificant in the first step. Our results in column (3) show no differences in statistically significance when looking at the original Heckman model in column (2). The magnitudes of the coefficients increases, besides *Orphan* which decreases, as we estimate the model using this Heckman model which support that our results in the main Heckman model.

8. Conclusions and Discussion

The objectives of this study was to identify the implicit factors influencing reimbursement decisions made by the TLV and estimate the economic values given to different characteristics often associated with medicines. Our results confirm the previous findings by Svensson et al. (2015), i.e. that both the ICER and the severity of the diseases are two influential factors when the TLV makes decisions of reimbursement. However, the results show a two to three times larger effect of the ICER, and even more for the severity of the disease, indicating that the previous estimates in the study of Svensson et al. (2015) probably are downward biased, as a consequence of omitting important variables in the model. However, this problem is also acknowledged and discussed in their paper.

This empirical study uses a main specification of eight variables, including the two variables mentioned above, to explain the decision-making process of the TLV. In addition to the ICER and the severity of the disease, this study also finds that treatments characterized preventive increases the likelihood of receiving an approval from the TLV, whereas the existence of an alternative treatment already being subsidized reduces the likelihood of being approved. As we already expected the severity of disease to be important in the appraisal

criteria, one of the interesting finding here is the impact of preventive treatments. The true benefits of a preventive treatment are sometimes difficult to account for in health economic evaluations, as the economic effects are discounted and since there is often a high uncertainty about the outcomes in the long-term. However, it has been shown that Swedish tax-payers have a higher WTP for prophylaxis than for on-demand treatment (Carlsson, Höjgård, Lethagen, Lindgren, Berntorp & Lindgren, 2009). The second principle states that more resources should allocated to those in greater need. Based on this principle, it seems reasonable that the TLV would have a lower willingness to approve medicines when there already exist alternative treatments in the benefit scheme. The variable *big firm* was included in our model as a measure of firm power and political influence. The results for the impact of big firms seem rather robust and the estimated effects are quite large. As none of the alternative definitions changed the overall results and both definitions were significant, it is possible that this variable also captures the human capital aspect of the pharmaceutical companies. Furthermore, the results also suggest that medicines have a higher probability of receiving an approval if they are orphan drugs, although these results are not as robust as for the other variables.

Out of the eight variables that were tested in our main specification in the probit model, only palliative care and the variable capturing the uncertainty of the ICER estimate, i.e. *ICER range,* were not found to have an impact on the decision-making process of the TLV. It is worth noticing that the definitions used for these variables may not be optimal. We have defined the variable *ICER range* as a ratio of the intervals of the ICER estimates and zero when no interval is presented. However, the TLV sometimes make statements about the uncertainty when no interval is presented. Thus, it is possible that this variable fails to capture the uncertainty surrounding the ICER calculations in a sufficient way. The variable *palliative treatment* is not based on a strict definition, where treatments were only considered as palliative when it was explicitly stated by the TLV. This resulted in only 6 treatments being categorized as palliative and may have led to too little variation in the data. As we had to assume that medicines were only palliative treatments when it was stated by the TLV, it is possible that we failed to identify several medicines that were relevant for this definition.

We included the four patient group variables as a way of testing the possible influence of age and gender of the patient population on the reimbursement decisions made by the TLV board. The data for these variables are based on the substances of the medicines and not the medicine itself. Therefore, we want to be cautious with drawing any conclusion from these results, as we cannot test how good these variables are as proxies for the actual patient groups associated with the medicines. However, if the results are valid, they suggest that medicines

where men constitutes a majority of the patient population are more likely to have their medicines approved, whereas the case is the opposite for medicines where the majority of the patient population is either women or people aged 60 or more.

In order to answer our second research question we estimate the impact of various medicine characteristics on the accepted ICERs. Our results show that the TLV has the highest WTP for medicines targeted for severe diseases, palliative treatment and orphan drug. According to our estimates, the TLV have a WTP of approximately SEK200,000 or more for these characteristics. The fact that the TLV has a highest valuation of palliative treatments may be derived from the principle of need and solidarity, as these treatments are often intended to relieve symptoms and help people to live longer, even though they cannot be cured. Further, the results from the two-step Heckman model suggest that the OLS regression suffer from sample selection bias, where all estimates are also larger in the Heckman regression. When using the Heckman model the variable preventive also becomes significant, with an estimated WTP for preventive treatment of over SEK100,000. This approach however, relies on the two crucial assumptions, i.e. perfect information and profit maximization. We acknowledge that the assumption of perfect information could be criticized based on two arguments. Firstly, there is often high uncertainties regarding the actual outcomes of the ICER estimates. Secondly, although firms may learn about the behavior of the TLV by experience, it is still difficult for the firms to know the exact WTP for each specific medicine. Nevertheless, we believe that this approach could add to the understanding of how the TLV make decisions and give a new perspective on how the WTP of other HTA agencies could be estimated.

9. Limitations and further research

This study analyze all decision between the years 2008-2015. As we started the data extraction process, we were certain to obtain more observations than the previous study conducted on TLV decision-making, which contained 102 observations. However, ICER estimates could not be extracted for several decisions, even though the information in these published decision documents indicated that the TLV probably made the decisions based on an ICER estimate. The information provided by the TLV in the published decisions is often inconsistent and does not always necessarily contain all the information relevant to the actual decision. Collecting a sufficient amount of observations thus becomes a huge amount work, which may explain why very few studies have been conducted within this field of research. A low amount of observations limits the possibility of testing several other important factors, as we run the risk

of having an excessive number of parameters in the model, relative to the number of observations. Therefore, for further research on the decision-making of the TLV, we believe that an effort to collect a substantially larger amount of observations is needed.

The possibility for us to test different variables has also been restricted as we have had limited access to relevant data-bases. If information on patient's usage of medicines were accessible this would enable us test several other potentially important factors, such as budget impact or the number of patients using the medicine. Having access to more observations would also allow us to investigate how specific diseases are valued by the TLV and if the composition of board members impact on the decision outcome.

In this study we base our analysis on the behavior of the TLV. However, for further research we believe that the same dataset could also be used in order to investigate how firms behave in the market for pharmaceutical products. By assuming that the firms know the demand curve of the TLV, i.e. the probability ranged threshold, it would be possible to estimate the level of risk that each firm chooses when applying for inclusion in the benefit scheme. In this case, the level of risk would be the same as the estimated predicted probability for each medicine in the probit model that we have used.

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11. Appendix

Table 5. All Published Decisions and All Included Decisions

ALL DECISIONS	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**TOT**
All decisions	103	61	69	93	73	65	88	91	643
Included decisions	13	3	18	14	14	13	18	23	116
No. of Approved Decisions included	11	2	15	11	9	8	14	21	91
No. of Declined Decisions included	2	1	3	3	5	5	4	2	25
Total	103	61	69	93	73	65	88	91	643

Table 6. Probability of Approved Reimbursement Decision

Variables	**Coefficients**					
	(1)	**(2)**	**(3)**	**(4)**	**(5)**	**(6)**
Approval	**Probit**	**Probit**	**Probit**	**Probit**	**Probit**	**Probit**
ICER	-0.00378***	-0.00568***	-0.00757***	-0.00893***	-0.0140***	-0.00536***
	(0.000928)	(0.00134)	(0.00166)	(0.00209)	(0.00369)	(0.00128)
High Severity	1.485**	1.841**	3.508***	2.656***	4.083***	1.722**
	(0.636)	(0.761)	(1.064)	(0.824)	(1.433)	(0.702)
Orphan Drug		0.850**	0.718	1.729***	2.218**	0.869*
		(0.406)	(0.598)	(0.506)	(0.916)	(0.464)
Palliative Treatment		0.492	0.439	0.840	1.682**	0.404
		(0.628)	(0.611)	(0.594)	(0.777)	(0.641)
Preventive Treatment		1.720***	1.911**	4.891***	6.650***	1.627***
		(0.564)	(0.825)	(1.630)	(2.158)	(0.550)
Alternative Treatment		-1.171**	-1.659**	-1.587**	-2.286***	-1.049*
		(0.541)	(0.735)	(0.777)	(0.824)	(0.567)
Big Firm		1.365***	1.539**	2.228***	2.731**	1.326***
		(0.455)	(0.624)	(0.655)	(1.138)	(0.437)
ICER Range		-0.895	-0.942	-1.643**	-2.054	-0.859
		(0.593)	(0.674)	(0.735)	(1.311)	(0.578)
Year-08			-2.429**		-0.968	
			(1.095)		(0.946)	
Year-09			-1.244		-0.365	
			(0.853)		(1.148)	
Year-10			0.680		1.597	
			(0.779)		(1.170)	
Year-11			-0.252		0.843	
			(0.752)		(0.970)	
Year-12			-0.872		0.0156	
			(0.663)		(0.613)	
Year-13			-1.287		-1.734	
			(0.795)		(1.391)	
Year-14			-0.479		1.295	
			(0.694)		(0.876)	
Men				3.159***	5.061***	
				(1.108)	(1.727)	
Women				-1.059*	-2.007**	
				(0.567)	(0.829)	
Children				0.285	1.298	
				(0.902)	(1.893)	
Old60				-2.168**	-3.513***	
				(0.972)	(1.042)	
Observations	116	116	116	107	107	107
Year dummies	NO	NO	YES	NO	YES	NO
Pseudo R-squared	0.590	0.705	0.780	0.746	0.817	0.688

Robust standard errors in parentheses *** p<0.01, ** p<0.05, * p<0.1

Table 7. Marginal Effects at Mean

Variables	**Coefficients**				
	(1)	**(2)**	**(3)**	**(4)**	**(5)**
Approval	**Margins**	**Margins**	**Margins**	**Margins**	**Margins**
ICER	-0.00114***	-0.00156***	-0.00166***	-0.00149**	-0.00104*
	(0.000261)	(0.000355)	(0.000417)	(0.000597)	(0.000599)
High Severity	0.448**	0.506**	0.771***	0.443**	0.304
	(0.181)	(0.210)	(0.235)	(0.188)	(0.227)
Orphan Drug		0.234*	0.158	0.289*	0.165
		(0.123)	(0.145)	(0.156)	(0.110)
Palliative Treatment		0.135	0.0965	0.140	0.125
		(0.171)	(0.137)	(0.111)	(0.0954)
Preventive Treatment		0.473***	0.420***	0.816***	0.495*
		(0.149)	(0.134)	(0.268)	(0.274)
Alternative Treatment		-0.322**	-0.364***	-0.265***	-0.170*
		(0.138)	(0.129)	(0.0988)	(0.102)
Big Firm		0.375***	0.338**	0.372**	0.203**
		(0.145)	(0.146)	(0.175)	(0.0995)
ICER Range		-0.246	-0.207	-0.274*	-0.153**
		(0.158)	(0.127)	(0.143)	(0.0718)
Year-08			-0.533**		-0.0721
			(0.228)		(0.0643)
Year-09			-0.273		-0.0272
			(0.175)		(0.0802)
Year-10			0.149		0.119
			(0.185)		(0.143)
Year-11			-0.0553		0.0627
			(0.163)		(0.0678)
Year-12			-0.192		0.00116
			(0.128)		(0.0457)
Year-13			-0.283		-0.129
			(0.199)		(0.127)
Year-14			-0.105		0.0964
			(0.144)		(0.0949)
Men				0.527**	0.377
				(0.219)	(0.230)
Women				-0.177	-0.149*
				(0.120)	(0.0826)
Children				0.0476	0.0966
				(0.156)	(0.120)
Old60				-0.362***	-0.262
				(0.119)	(0.168)
Observations	116	116	116	107	107
Year dummies	NO	NO	YES	NO	YES

Robust standard errors in parentheses *** p<0.01, ** p<0.05, * p<0.1

Table 8. Robustness Checks - Probit

Variables	**Coefficients**						
Approval	**(1) Probit**	**(2) Probit**	**(3) Probit**	**(4) Probit**	**(5) Probit**	**(6) Probit**	**(7) Probit**
ICER	-0.00568***	-0.00562***	-0.00551***	-0.00490***		-0.00568***	-0.00567***
	(0.00134)	(0.00134)	(0.00120)	(0.00131)		(0.00134)	(0.00135)
LOG-ICER					-3.052***		
					(0.813)		
High Severity	1.841**	1.860**	2.139***	1.928***	1.542***	1.841**	1.841**
	(0.761)	(0.779)	(0.756)	(0.726)	(0.584)	(0.761)	(0.761)
Orphan Drug	0.850**	0.835**	0.466	0.397	0.917**	0.850**	0.850**
	(0.406)	(0.414)	(0.498)	(0.433)	(0.376)	(0.406)	(0.406)
Palliative Treatment	0.492		0.680	0.187	0.0372	0.492	0.492
	(0.628)		(0.487)	(0.502)	(0.613)	(0.628)	(0.628)
Preventive Treatment	1.720***	1.675***	1.745***	1.732***	1.914***	1.720***	1.720***
	(0.564)	(0.563)	(0.568)	(0.512)	(0.514)	(0.564)	(0.564)
Alternative Treatment	-1.171**	-1.170**	-0.791*	-0.796*	-0.778	-1.171**	-1.171**
	(0.541)	(0.527)	(0.474)	(0.438)	(0.491)	(0.542)	(0.541)
Patents			1.121**				
			(0.496)				
No. of patents				4.43e-05**			
				(2.08e-05)			
Big Firm	1.365***	1.381***			1.175***	1.365***	1.364***
	(0.455)	(0.447)			(0.428)	(0.455)	(0.455)
ICER range	-0.895	-0.849	-0.975*	-0.931*	-1.142*	-0.895	-0.894
	(0.593)	(0.576)	(0.548)	(0.553)	(0.685)	(0.593)	(0.594)
Year dummies	NO	NO	NO	NO	NO	NO	NO
Observations	116	116	116	116	116	114	113
Pseudo R-squared	0.705	0.704	0.696	0.673	0.643	0.689	0.688

Robust standard errors in parentheses *** p<0.01, ** p<0.05, * p<0.1

Table 9. Robustness Checks - Heckman

Variables	**Coefficients**		
	(1)	(2)	(3)
ICER	**OLS**	**Heckman**	**Heckman**
ICER			
High Severity	185.8***	211.8***	216.5***
	(60.54)	(49.32)	(44.57)
Orphan Drug	237.3***	244.2***	203.7***
	(75.88)	(41.52)	(60.46)
Palliative Treatment	209.8***	209.4***	235.2***
	(57.66)	(63.42)	(39.17)
Preventive Treatment	93.86	149.9**	123.2**
	(73.03)	(63.00)	(53.65)
Alternative Treatment	-10.42	-91.32**	-120.5***
	(53.41)	(40.57)	(37.10)
Big Firm			
ICER range			
lambda		765.6***	890.9***
		(164.7)	(144.6)
Constant	223.2***	146.9***	142.4***
	(41.01)	(38.79)	(36.03)
Year dummies	NO	NO	NO
Observations	91	91	91
R-squared	0.287	0.507	0.592
Pseudo R-squared			

Robust standard errors in parentheses *** p<0.01, ** p<0.05, * p<0.1