# Declined acceptance rates of medicine taken into the Dutch reimbursement system after the introduction of the new Zorginstituut Nederland guideline on the 26th of June 2015.

Reza Bandraz
Department of Pharmaco-therapy, - Epidemiology and - Economics
University of Groningen
s-2122901
Mentors: Prof. dr. Maarten Postma, Drs. Evgeni Dvortsin

# Abstract

**Background:** The ZIN introduced a new guideline on the 26th of June 2015 for the reimbursement of medicine into the Dutch healthcare system. This guideline was introduced to provide more clearance on the reimbursement criteria and to emphasize the importance of costs-effectiveness as a criterion. After the introduction of this guideline no known data has been published on its effects on the reimbursement of medicine. This study therefore outlined the trends on cost-effectiveness decisions made by the ZIN from March 2006 until April 2017 and searched for trends around the introduction of the new guideline.

**Methods:** A database research on medicine with a cost-effectiveness analysis was performed. The data was extracted from the ZIN website and included medicine offered for reimbursement between March 2006 and April 2017. Descriptive statistics were performed to search for overall trends. The Pearson Chi-square Test and the Fisher's Exact Test were used to assess the difference in acceptance rates of medicine offered for reimbursement before and after the introduction of the new ZIN guidelines.

**Results:** The median acceptance rate of all medicine offered for reimbursement declined significantly with 53% after the introduction of the new ZIN guideline (p=0.009 and power=0.92). For cancer medicine specifically, the acceptance rates declined with 61% (p=0.015).

**Discussion/Conclusion:** The new ZIN guideline emphasizes cost-effectiveness and contains additional criterion on cost-effectiveness, which makes it more challenging for medicine to obtain reimbursement, resulting in declined acceptance rates. The ZIN makes exceptions on cost-effectiveness as major criterion in cases of add-on medicine and orphan drugs.

# Introduction

The total expenditure by healthcare providers in the Netherlands has doubled from €50 billion in 2001 to €100 billion in 2018.[1] In this time period, the Dutch healthcare system has been subjected to multiple changes concerning the reimbursement of medical interventions. The costs, effectiveness, quality and safety of medical interventions have become core concepts within this reimbursement system.[2,3] The first change concerning the reimbursement of medical interventions was introduced in 2006, in which the Dutch National Healthcare Institute, *Zorginstituut Nederland* (ZIN), started publishing recommendations on the reimbursement of medicines based on clinical and cost-effectiveness criteria.[2] The pharmaco-economic assessment of these recommendations consisted of three different directives: (1) Guidelines for pharmaco-economic research (2006), (2) Guidance on outcome research (2006) and (3) Cost research manual (2010).[2,3] The use of three different directives, published in different years, was considered to be unclear because the recommendations did not always correlate. Furthermore, the directives could not be applied when evaluating non-drugs and did not longer conform to recent scientific knowledge. Cost-effectiveness as criterion was also considered to be inadequate.[2,3] Therefore, the Dutch government decided to develop a new directive that brings the Dutch guidelines together, is widely applicable, makes unambiguous recommendations and emphasizes cost-effectiveness as a criterion in the medical package management. To establish this, criteria had to be operationalized and proposals for a legal anchoring of cost-effectiveness had to be made. The ZIN was appointed for this purpose and published their findings in a report on the 26$^{th}$ of June 2015. In their report, the ZIN concluded that cost-effectiveness is of great importance, because its application provides insight into the amount of health gain provided by medical intervention in relation to its costs.[2,3] By selecting the most cost-effective care, the health gain for the entire population can be maximized.[2] The ZIN therefore proposed using reference values to assess the cost-effectiveness of an intervention. These reference values correspond to the values that the *Raad voor de Volksgezondheid en Zorg* (RVZ) set in 2006.[2] The reference values consist of three ranges in which the disease burden of an intervention is linked to the maximal additional cost per quality-adjusted life year (QALY). These reference values are: €20,000/QALY for interventions with a disease burden of 0.1-0.4, €50,000/QALY for interventions with a disease burden of 0.41-0.7 and €80,000/QALY for interventions with a disease burden of 0.71-1.0.[2] After

comparing the costs in QALY to the reference value, three other criteria are taken into consideration: effectiveness, practicability and necessity.[2,3]

To further assess cost-effectiveness, the requirements for cost-effectiveness data had to be documented. The ZIN provided these requirements by presenting a guideline for pharmaco-economic research. In this guideline multiple factors were discussed, such as: modelling of the outcomes, which costs should be included and which perspective should be used. The guideline is based on a social perspective. This means that as well as direct costs and effects inside healthcare, factors outside healthcare such as: unemployment allowances, absenteeism and transportation costs are taken into account when the value of a new healthcare innovation is calculated.[2]

All these factors combined result in the assessment framework for package advice and the criteria used to determine whether a medical intervention should be taken into the medical reimbursement system.[2,3] However, since the introduction of the ZIN guidelines for economic evaluations in healthcare, no known research has been published regarding its effects on the acceptance of drugs submitted for reimbursement. So it remains unclear whether the implementation of this guideline has been beneficial for assessing and accepting medical interventions into the Dutch reimbursement system. Therefore, the aim of this study was to search for trends in cost-effectiveness decisions made by the ZIN from March 2006 until April 2017.

## Method

A database with data extracted from the 'Zorginstituut Nederland' (ZIN) was produced by Asc Academics. This database was based on publicly available reimbursement dossiers released by the ZIN, including cost-effectiveness analysis from March 2006 until April 2017. The database contained various characteristics of the medicine under consideration, such as: the indication for the medicine reimbursement, model used for analysis, verdict of the ZIN, disease burden, reference QALY threshold, incremental cost-effectiveness ratio (ICER), QALY, drug costs, mean incremental- QALY and life-year gained (LYG), direct- and indirect costs, comparator, mean total costs per patient, the amount of patients that would receive the treatment and other evidence. The list containing all the variables is included in appendix 1.

The database was validated with the documentation of the original source published on the ZIN website.

In order to search for trends in cost-effectiveness decisions made by the ZIN through time, decision reports and advice documents with a cost utility analysis were used for data extraction. The outcomes of these documents were ordered by date and they described the pharmaco-therapeutic and pharmaco-economic evidence and deliberations, the budget impact, and the sensitivity analysis. To meet the inclusion criteria, the case-documents needed to contain data on the additional health and/or cost benefits of the medicine in consideration compared to prior or current treatments. If no raw data was available, graphical data representations (figures, graphs and tables) were used to extract the required data. In cases where a report contained multiple cost-effectiveness analyses (same medicine, different indications), additional entries were made to observe the outcomes of the respective analyses. In these cases, the indication that was offered for reimbursement was used to perform the analyses. If a document was offered for resubmission, a new entry was made to include the resubmitted document. Resubmitted documents emphasize the changes compared to previous submissions and are therefore provided with additional decision reports.

In this paper, the following decision-trends are presented:

- Trends for all ZIN decisions between March 2006 until April 2017;
- Trends in acceptance before and after the introduction of the new ZIN guideline on the 26$^{th}$ of June 2015;
- Trends in acceptance of cancer medicine, since they are the most assessed type of medicine [4];
- Trends in acceptance of the models used for pharmaco-economic analysis.

Furthermore, cost-effectiveness trends in relation to disease burden of submitted interventions are presented. The disease burdens were extracted from the World Health Organization (2004) website.[5] The results present the relation between cost-effectiveness and disease burden in 82 cases. These cases are divided into 3 ranges of disease burdens according to the ZIN guideline: 0.1-0.4, 0.41-0.7 and 0.71-1.0.[2]

### Power Analysis

A power analysis was performed to determine the sample size required to provide reliable evidence. The value for alpha was set at 0.05 and the value for the desired power was set at 0.80.[6,7] The year 2017 contained one submission and was therefore excluded from the power analyses. This submission was therefore also excluded when drawing conclusions.

### Statistics

Descriptive statistics were performed on the dataset to search for overall trends in decisions made by the ZIN between 2006 and 2017 and to search for causality between the introduction of the new policy and the subsequent decisions outcomes. For assessing the difference in acceptance rates for submitted medicines before and after the introduction of the new ZIN guideline, the Pearson Chi-square Test was used. The submitted cancer medicines were assessed separately using the Fisher's Exact Test in order to correct for an expected count less than five. All the analyses were conducted with IBM SPSS statistics version 23 and/or EXCEL and a p-value <0.05 was considered statistically significant.[8,9]

## Results

The ZIN decisions made from March 2006 until April 2017 are illustrated in descriptive charts to present both the overall trends and trends that could be related to the introduction of the new ZIN guideline in June 2015. For the time period under consideration, 82 full submissions were identified, of which 4 were re-submissions. The trends were analyzed according to the results of the decisions: accepted or declined to be taken into the reimbursement system.

### Overall trends in ZIN decisions

Figure 1 shows the decision-trends for all the ZIN decisions, with a cost utility analysis report, in the period of March 2006 until April 2017. The trends are presented as a proportional percentage of the decisions per application year with a power of 0.92. The median acceptance rate of the time period between 2006 and 2015 is 78%, ranging from 67% to 100%. The acceptance rate of submissions made from January 2015 until the 26$^{th}$ of June 2015 is 66,7% (2/3). From the 26$^{th}$ of June 2015 until the 31$^{st}$ of December 2015 the acceptance rate of the submissions is 0% (0/3). The percentage of accepted submissions is 50% in the year after the

introduction of the new ZIN guideline. The median acceptance rate from the 26th of June 2015 until 31st of December 2016 is 25%. The median acceptance rate of submissions declines by 53% after the introduction of the new ZIN guideline. The only submission in 2017 was declined. The number of submissions per year is included in appendix 2.

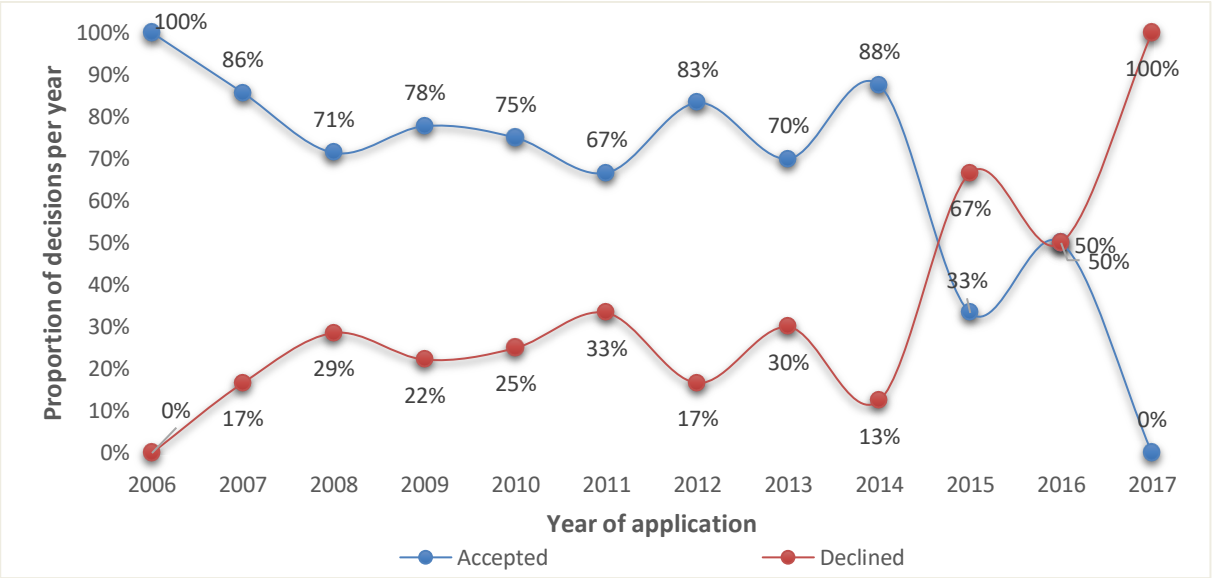


***Figure 1: Accepted and declined submissions from March 2006 until April of 2017 presented as a proportion percentage of decisions per year. A total of 82 submissions with a median percentage of 78% were made between 2006 and 2015.***

Figure 2 shows the percentages of accepted and declined submissions before and after the 26th of June 2015 (power 0.92). In total, 64 submissions were made before this period and 18 submissions after. Before 26th of June 2015, 78% (n=50) of all submissions were accepted by the ZIN to be taken into the medicine reimbursement system compared to 44% (n=8) after this time period (p=0.009, Pearson Chi-Square Test).

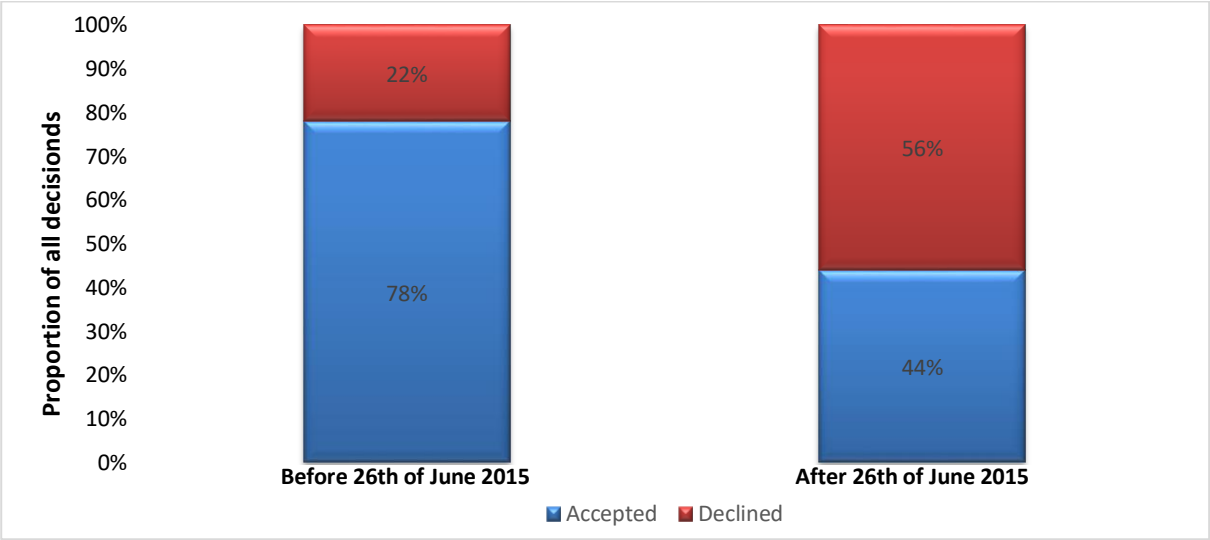


***Figure 2: Percentages of accepted and declined submissions before and after the introduction of the new ZIN guidelines in June of 2015. Before 26th of June 2015: Total number of 64 submissions with 78% (n= 50) acceptance and 22% (n=14) declined. After the 26th of June 2015: A total of 18 submissions with 44% (n= 8) acceptance and 56% (n=10) declined.***

## Trends in acceptance of cancer medicine

Figure 3 presents the submission of cancer medicine as a share of all submissions from March 2006 until April 2017. In total, 36 submissions were made of which 31 were submitted before the 26th of June 2015 and five were submitted after this time period. Before the 26th of June 2015, 81% (n=25) of the submissions were accepted by the ZIN to be taken into the medicine reimbursement system compared to 20% (n=1) after this time period (p=0.015, Pearson Chi-Square Test corrected with Fisher's Exact Test).

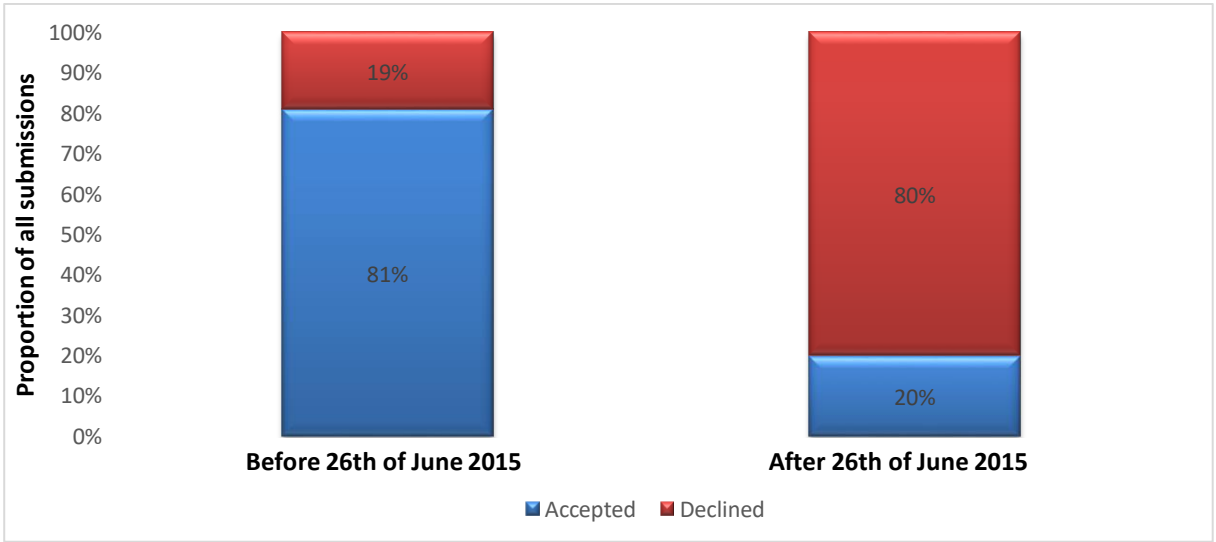


***Figure 3: Percentages of accepted and declined submissions of cancer medicine before and after the introduction of the new ZIN guidelines. Before 26th of June 2015: Total number of 31 submissions with 81% (n=25) acceptance and 19% (n=6) declined. After 26th of June 2015: A total of 5 submissions were made with 20% (n= 1) acceptance and 80% (n=4) declined.***

## Cost-effectiveness in relation to disease burden

Table 1 presents an overview of the total number of cases accepted and declined by the ZIN. The disease burdens are presented with their equivalent maximum reference costs per QALY. Figure 4 shows the relation between accepted and declined cases are ordered according to the maximum additional cost per QALY and plotted as a proportion of all decisions. The highest acceptance within the range of its reference value is 80% (n=8) at a maximum cost below €50,000/QALY. The highest acceptance of submissions greater than its reference value is at 43% (n=19), exceeding the maximum reference cost of €80,000/QALY.

**Table 1: Cost-effectiveness in relation to disease burden**

| Disease burden[2,5] | Max additional cost/QALY[2,5] | Total cases | Cases accepted under max cost/QALY | Cases accepted exceeding max cost/QALY | Cases declined under max cost/QALY | Cases declined exceeding max cost/QALY |
|---|---|---|---|---|---|---|
| 0.10 – 0.40 | €20,000 | 28 | 8 | 11 | 5 | 4 |
| 0.41 – 0.70 | €50,000 | 10 | 8 | 0 | 2 | 0 |
| 0.71 – 1.00 | €80,000 | 44 | 12 | 19 | 4 | 9 |

**Disease burden 0.10 - 0.40**

A total of 11 out of 28 cases (39%) were accepted by the ZIN to be taken into the reimbursement system at a higher price than the maximum additional cost of €20,000 per QALY. All of these cases were submitted before the introduction of the new ZIN guideline on the 26th of June 2015. In five out of 28 cases (18%), the submissions were declined when offered under the maximum additional cost of €20,000 per QALY. Four of these medical interventions were submitted before the introduction of the new ZIN guideline and 1 intervention was submitted after this time period. These submissions were declined because the research outcomes on cost-effectiveness were insufficiently supported (n=4) or because reimbursement could be considered in the future after price negotiations (n=1). In all five cases, efficacy and pharmacotherapy of the submitted drugs was found to be sufficient.

**Disease burden 0.41– 0.70**

The ZIN declined two out of ten submissions (20%) that were offered for reimbursement at a price lower than the reference value of €50,000/QALY. The ZIN stated that the added therapeutic value of both drugs was sufficiently supported, but that the cost-effectiveness research was insufficiently substantiated. Both submissions were made before the introduction of the new ZIN guideline.

**Disease burden 0.71 - 1.00**

In total, 19 submissions out of 44 (43%) were accepted by the ZIN to be taken into the reimbursement system at a price exceeding the maximum cost of €80,000/QALY. In all of these cases the submissions were taken into the list of orphan drugs or add-on medicine, because the submissions were either made for indications with no available pharmaco-therapeutic treatment or presented as a last resort for treatment to enhance quality of life and/or life expectancy. Furthermore, 4 cases (1%) were declined to be taken into the reimbursement system when offered at a price lower than €80,000/QALY. All these cases were offered for reimbursement before the introduction of the new ZIN guideline and were declined because the efficacy, added therapeutic value, costs and/or cost-effectiveness were insufficiently supported.

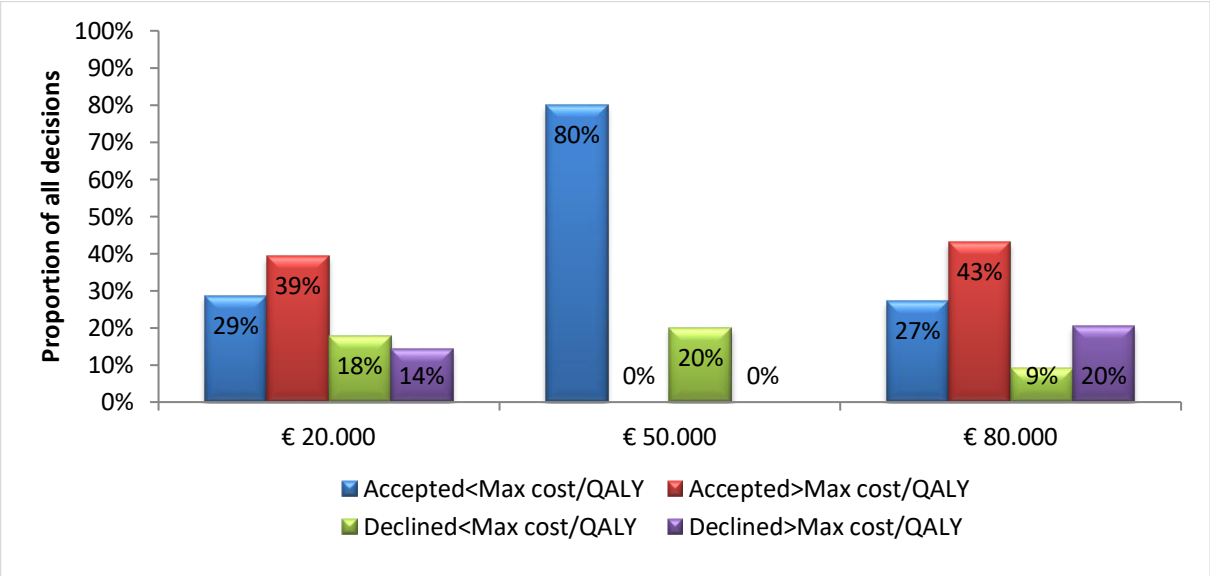


***Figure 4: Decisions on acceptance and rejections made by the ZIN when comparing the maximum additional cost per QALY in relation to the disease burden. The outcome of the decisions are ordered per QALY reference (€ 20,000, €50,000 and €80,000) and plotted as a proportion percentage of all decisions.***

**Used models**

Figure 5 presents the models that were used to provide the pharmaco-economic data to analyze the cost-effectiveness of the medicines. In 76% (n=62) of the cases, the Markov model was used to provide the economic analysis. The acceptance rate of submissions using the Markov model is 69% (n=43) from the period March 2006 until April 2017. In 4% (n=3) of the submissions, no description of economic model was provided. The acceptance rate of the submissions without description of an economic model is 0%. The total amount of cases per model and their relations to acceptance is included in appendix 4.

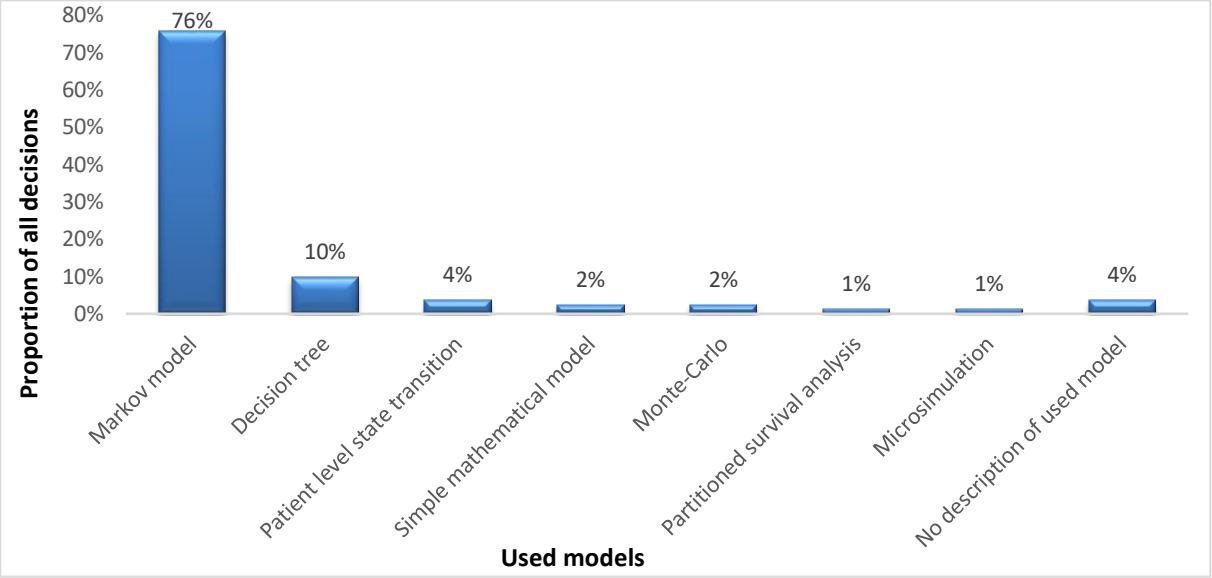


***Figure 5: Proportion percentages of all decisions ordered by per model used to provide the pharmaco-economic data.***

Figure 6 illustrates the acceptance rates of cases where the Markov model is used to present the pharmaco-economic data. The acceptance rate declines by 19% after the introduction of the new ZIN guideline on the 26$^{th}$ of June 2015.

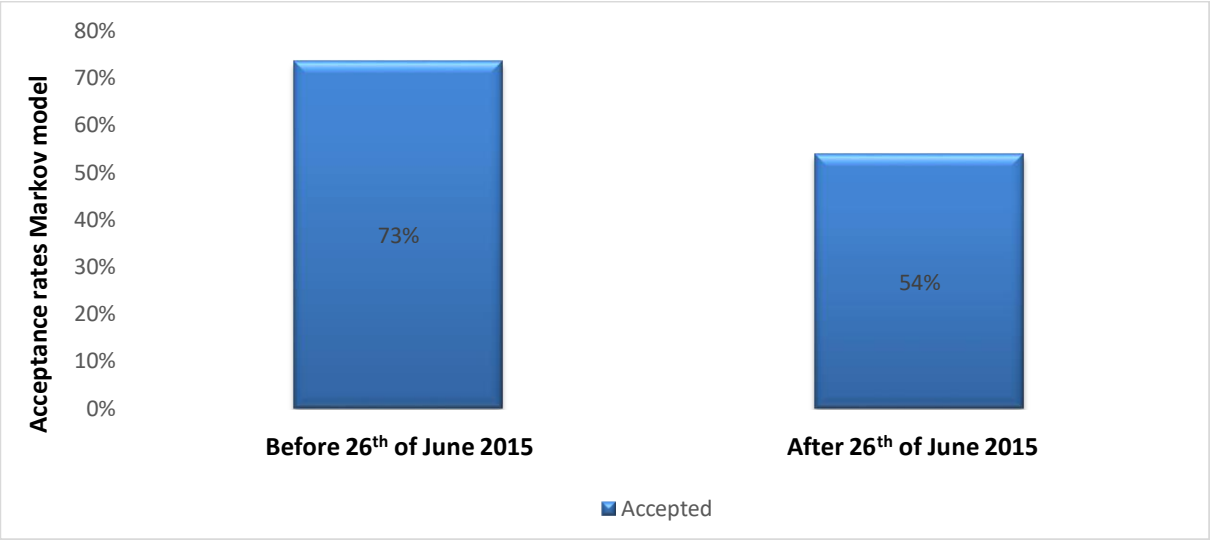


***Figure 6: Acceptance rates of the Markov model ordered by time period: Before the introduction of the new ZIN guideline (2006 until the 26th of June 2015) and after (26th of June 2015 until the 11th of April 2017).***

# Discussion

**Trends in acceptance of medicine before and after application of the new ZIN guideline**

The ZIN received a total of 82 full submissions, of which four were re-submissions, that included a pharmaco-economic analyses, from March 2006 until April 2017. The overall trend in acceptance before the introduction of the new ZIN guideline, between 2006 and 2015, was more pronounced between 70% and 80% with a median of 78%. The median acceptance rate after the implementation of the new ZIN guideline, between the 26th of June 2015 and the 31st of December 2016, was 25%. In 2017, only one medicine with a cost-utility analysis was submitted between January and April. The effect of one submission in a time period of four months is not a representative for a whole year and was therefore excluded when drawing conclusions. This is also a limitation of this study.

The median acceptance rate declined by 53% after the implementation of the new ZIN guideline (p=0.009 and power =0.92). Figures 2 and 3 confirm the decrease in acceptance rates after the introduction of the new ZIN guideline. Figure 2 illustrates a statistical significant decrease in acceptance rate of 34% for all submissions (p=0.009) and figure 3 shows a decline of 61% in the acceptance of all submitted cancer medicine (p=0.015). This difference could be explained by the implementation of the new ZIN guideline. Before the introduction of the new ZIN guideline, the pharmaco-economic assessment of submitted medicine was performed using three different guidelines that did not always correlate and in which cost-effectiveness

as criterion was considered to be inadequate.[2,3] The new guideline consists of one directive in which the cost-effectiveness of a medical intervention is emphasized. This possibly provides the ZIN with more clarity to judge a medicine offered for reimbursement. The new ZIN guideline also contains additional criteria on cost-effectiveness, which makes it more challenging to obtain reimbursement for a medical intervention.[3] However, it is important to acknowledge the effect of comparing nine years prior to the introduction of the new ZIN guideline with 1.5 years after the implementation of this guideline. Therefore, to optimize the trends in acceptance rates, more data is needed in the future to compare the outcomes prior to the introduction of the new ZIN with the period following that.

## Cost-effectiveness in relation to disease burden

### Disease burden 0.10 - 0.40

In total 28 cases with a disease burden between 0.10-0.40 and a maximal additional cost of €20,000 per QALY were presented. In ten of these cases the ZIN accepted the medicine to be taken into the reimbursement system at a higher cost than the maximal additional cost per QALY that was set for the disease burden. It is noteworthy that the acceptance of all these cases occurred before the introduction of the new ZIN guideline. This could also be explained by the implementation of the new ZIN guideline in which cost-effectiveness is of great importance and in which it provides more clarity on criteria for medicine offered for reimbursement.[2,3] The ZIN however did not accept five medicines to be taken into the reimbursement system when offered under the maximal additional cost of €20,000 per QALY. The main argument for rejection was that the cost-effectiveness reports of the medicine under consideration were insufficiently supported, while the efficacy and pharmacotherapy of all submissions was founded to be sufficient. This could mean that the cost-effectiveness criteria outweigh the efficacy and pharmacotherapy of an intervention when offered for reimbursement. The new ZIN guideline however does not state that the cost-effectiveness as criterion outweighs other criteria, when assessing a medical intervention for reimbursement, such as effectiveness, practicability and necessity.[2,3]

**Disease burden 0.41 - 0.70**

A total of ten submissions were made within the disease burden of 0.41-0.70 coupled with a maximal additional cost of €50,000 per QALY. In two cases the ZIN did not accept the medicine under consideration to be taken into the reimbursement system when offered under the maximal cost of €50,000 per QALY. In both cases, the ZIN stated that the provided cost-effectiveness analysis was insufficient for the medicine to be taken into the reimbursement system, while the added therapeutic value was considered to be sufficient. This empowers the statement that the cost-effectiveness as criterion is of great importance.[2,3]

**Disease burden 0.71 - 1.00**

In total, 44 cases were offered for reimbursement with a disease burden between 0.71-1.0 and a maximal additional cost of €80,000 per QALY. In 19 of these cases the ZIN accepted the medicine to be taken into the reimbursement system at a higher cost than €80,000 per QALY. In all of these cases the medicines were taken into the list of orphan drugs or add-on medicine. These medical interventions were all supported with arguments to accept a higher cost per QALY, as mentioned in the new ZIN guideline.[2] The ZIN stated that these submissions were made for indications with no available pharmaco-therapeutic treatment or presented as a last resort for treatment to enhance the quality of life and/or the life expectancy. In these cases necessity as criterion seems to outweigh cost-effectiveness as criterion.

In four cases the ZIN did not accept the medicine under consideration to be taken into the reimbursement system when offered under the maximal cost set per QALY of €80.000. These medical interventions were declined to be taken into the reimbursement system because the efficacy, added therapeutic value, costs and/or cost-effectiveness were insufficiently supported.

**Used models**

The Markov model is the most frequently applied model (76%) to provide pharmaco-economic analysis of the cost-effectiveness of medicines. The acceptance rate of all submissions with a Markov model was 69% (n=43). The decision tree was used in 10% (n=8) of all the submissions with an acceptance rate of 100%. In the case that no description of the used model was presented, the ZIN declined the submissions according to the new guideline.[2] Furthermore, the difference in accepted submissions when observing the used models (figure 6), empowers the trend in acceptance before and after implementing the new guideline. The acceptance rates of submissions using the Markov model, to provide the economic data as required by the ZIN for reimbursement[2], declined by 19% (from 73% to 54%) after the introduction of the new guideline.

# Conclusion

The acceptance rates of medicine taken into the Dutch reimbursement system after the introduction of the new ZIN guideline on the 26$^{th}$ of June 2015 have declined significantly. This is supported by declined acceptance rates for all medicine with a median of 53% (p=0.009), for cancer medicine particularly with 61% (p=0.015), for all submissions before and after the 26$^{th}$ of June 2015 with 34% (p=0.009) and for submissions made using the Markov model with 19% (p=0.009).

The declined acceptance rates could be explained by the implementation of the new ZIN guideline. This guideline contains one directive in which cost-effectiveness is emphasized and therefore provides more clarity to asses a medicine offered for reimbursement. This directive also contains additional criteria on cost-effectiveness, which makes it more challenging to obtain reimbursement.

The new ZIN Guideline offers room for exceptions on cost-effectiveness as major criterion for reimbursement. This study found that the ZIN accepts a higher cost per QALY for orphan drugs and add-on medicine than is indicated by their disease burden. The ZIN stated that these medicines were accepted because they were offered for reimbursement for indications with no available pharmaco-therapeutic treatment or are presented as a last resort for treatment to enhance the quality of life and/or the life expectancy. In these cases, necessity as criterion seems to outweigh cost-effectiveness.

This study also found that the new guideline does not state that, cost-effectiveness as major criterion, outweighs other criteria combined when assessing a medical intervention offered for reimbursement such as effectiveness, practicability and necessity. This study however presents cases in which medicine offered for reimbursement were rejected because of the cost-effectiveness, while the efficacy and pharmacotherapy were described as sufficiently supported according to the ZIN.

# Appendix

## Appendix 1: Variables list

| |
|---|
| ATC code |
| Generic name |
| Brand name |
| Company |
| Medicine on the market |
| Group of medicines |
| Disease area |
| Indication |
| Indication for medicine reimbursement |
| Medicine taken into the reimbursement system |
| Model used for analysis |
| Date ZIN letter to VWS |
| Verdict ZIN |
| Disease burden |
| Reference QALY threshold |
| Mean ICER/QALY |
| Mean ICER/LYF |
| Drug costs |
| Incremental QALY |
| Total LYG |
| Incremental LYG |
| Direct costs |
| Indirect costs |
| Incremental costs |
| Drug costs |
| Dosage form |
| Drug cost per doses-dosage form |
| SPC dosage |
| Comparator |
| Number of patients in the Netherlands |
| Number of patients on treatment |
| Total costs per patient |
| Market penetration |

## Appendix 2: Total number of submissions per year from March 2006 until April 2017

| Year | Number of submissions |
|---|---|
| 2006 | 4 |
| 2007 | 7 |
| 2008 | 7 |
| 2009 | 9 |
| 2010 | 4 |
| 2011 | 6 |
| 2012 | 6 |
| 2013 | 10 |
| 2014 | 8 |
| 2015<br>(2015: January-26th of June 2015)<br>(2015: 26th of June-December) | 6<br>(3)<br>(3) |
| 2016 | 14 |
| 2017 | 1 |

## Appendix 3: Cost-effectiveness in relation to disease burden

| Disease burden[2,5] | Max additional cost per QALY[2,5] | Total cases | Cases accepted <max cost per QALY | Cases accepted >max cost per QALY | Cases declined <max cost per QALY | Cases declined >max QALY |
|---|---|---|---|---|---|---|
| 0.1 – 0.4 | €20,000 | 28 | 8 | 11 | 5 | 4 |
| 0.41 – 0.7 | €50,000 | 10 | 8 | 0 | 2 | 0 |
| 0.71 – 1.0 | €80,000 | 44 | 12 | 19 | 4 | 9 |

## Appendix 4: Models used for analysis and their relation to acceptance.

| Model | Total cases | Accepted | Declined |
|---|---|---|---|
| Markov model | 62 | 43 | 20 |
| Decision tree | 8 | 8 | 0 |
| Patient level state transition model | 3 | 2 | 1 |
| Simple mathematical model | 2 | 2 | 0 |
| Monte-Carlo method | 2 | 2 | 0 |
| Micro-simulation | 1 | 1 | 0 |
| Partitioned survival analysis | 1 | 1 | 0 |
| No description of used model | 3 | 0 | 3 |

# Literature


1. Statistics Netherlands. *Health, Lifestyle, Health Care Use and Supply, Causes of Death; Key Figures.* CBS Statline, 12 July 2019. Retrieved from: https://opendata.cbs.nl/statline/#/CBS/en/dataset/81628eng/table?ts=1563187947216

2. Moerkamp, A. *Kosteneffectiviteit in de praktijk, 26 June 2015.* Retrieved from: https://www.zorginstituutnederland.nl/publicaties/rapport/2015/06/26/kosteneffectiviteit-in-de-praktijk

3. Zorginstituut Nederland. *Guideline for economic evaluations in healthcare, 16 June 2016.* Retrieved from: https://tools.ispor.org/PEguidelines/source/Netherlands_Guideline_for_economic_evaluations_in_healthcare.pdf

4. O'Neill, P., and B. Zamora. Assessing *Trends in SMC Advice Decisions, October 2009 - September 2015.* EconPapers, Pzizer, 1 Feb. 2016, econpapers.repec.org/paper/oheconrep/001688.htm

5. World Health organization. *Global burden disease 2004 update: Disability weights for disease and conditions*. Retrieved from: https://www.who.int/healthinfo/global_burden_disease/GBD2004_DisabilityWeights.pdf?ua=1

6. Wan X, Wang W, Liu J, Tong T. *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range*. BMC Med Res Methodol. 2014;14:135.

7. Bernard Rosner. *Fundementals of Biostatistics. Hypothesis Testing: Two-Sample inference – estimation of sample size and power for comparing two means, 2011.*

8. Nayak BK. *Understanding the relevance of sample size calculation, 2010*. Indian J Ophthalmol. 58(6):469-70.

9. Moher D, Dulberg CS, Wells GA. *Statistical power, sample size, and their reporting in randomized controlled trials, 1994*. JAMA. 272:122–4.