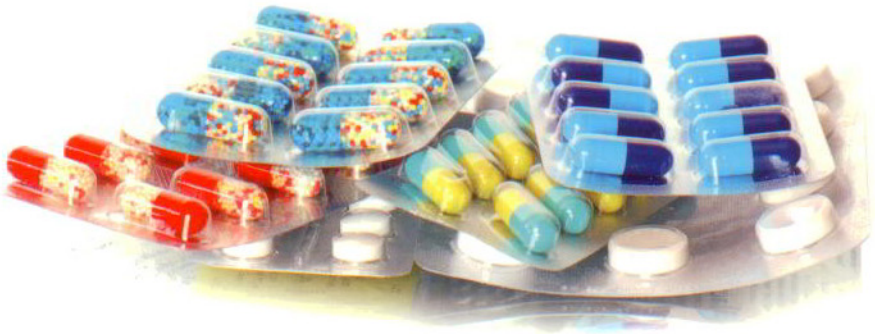
The Evaluation of Drug Regulation

Economic approaches into the valuation and evaluation of the drug regulatory framework



Jacoline Bouvy

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Evaluatie van geneesmiddelenregulering – Economische toepassingen in de waardering en evaluatie van het regulatoire geneesmiddelensysteem
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 23 januari 2013 des middags te 12.45 uur

door

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geboren op 27 maart 1985 te Rotterdam

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‘It is our choices, Harry, that show what we truly are, far more than our abilities.’

Albus Dumbledore (In J.K. Rowling’s *Harry Potter and the Chamber of Secrets*)

Glossary

ADR	Adverse drug reaction
CBG-MEB	Dutch Medicines Evaluation Board
CKD	Chronic Kidney Disease
DCE	Discrete Choice Experiment
DHPC	Direct Healthcare Professional Communication
ECG	Electrocardiograph
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
HRQL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
IAT	Intra-arterial thrombolysis
IVT	Intravenous thrombolysis
MAH	Market Authorization Holder
mRS	modified Rankin Scale
NMB	Net Monetary Benefit
PASS	Post-Authorization Safety Study
PRCA	Pure Red Cell Aplasia
PSA	Probabilistic sensitivity analysis
PSUR	Periodic Safety Update Report
QALY	Quality-adjusted life year
QTc	QT interval corrected for heart rate
R&D	Research and Development
rhBMP-2	recombinant human bone morphogenetic protein-2
RMP	Risk Management Plan
rTPA	recombinant plasminogen activator
SCD	Sudden cardiac death
sICH	Symptomatic intracranial hemorrhage
TdP	Torsade de pointes
TQT study	Thorough QT/QTc study
VF	Ventricular fibrillation
WTP	Willingness to pay

Contents

Chapter 1
General Introduction

Regulation of the pharmaceutical market

The pharmaceutical market in Europe is strictly regulated. A pharmaceutical product has to demonstrate sufficient levels of quality, safety, and efficacy before it is allowed to enter the European market. The safety profile of a pharmaceutical, however, is usually incomplete at market entry.[1] Therefore, a comprehensive pharmacovigilance system exists, intended to monitor a product's safety (and sometimes efficacy) throughout its life cycle. If new safety issues are identified through post-marketing surveillance, the benefit-risk profile of a product will be re-evaluated. Drug regulation has two aims: first, to *protect* public health by keeping low-quality, unsafe, or inefficacious products from entering the market, and second, to *promote* public health by ensuring needed drugs reach patients without unnecessary delay.[2] These aims, however, are potentially conflicting. If regulatory requirements are not strict and rigorous, dangerous products might not be recognized as such, enter the market, and harm patients. Conversely, if regulatory requirements are too stringent, potentially needed drugs might no longer reach the market. This occurs when the costs of compliance with regulatory requirements outweigh potential profits and thus create a disincentive to develop new drugs or when stringent regulatory requirements hinder efficacious drugs with acceptable or manageable risks from entering the market.

The development of new regulatory requirements is often prompted by the identification of novel safety issues. Thalidomide, which was highly used as a sleeping pill and morning-sickness treatment in pregnant women during the 1950s and 1960s, caused an estimated 10,000 birth defects worldwide[3] before it was removed from the market and directly resulted in the implementation of efficacy requirements for pharmaceuticals in 1962.[4] More recently, the 2006 TeGenero scandal, in which six healthy volunteers developed life-threatening symptoms during a first-in-man trial, led to adapted requirements for first-in-man trials.[5] Also, guidelines for mandatory pre-clinical and clinical testing of a drug's QT-prolonging potential were implemented in 2005, in a response to a series of post-marketing drug withdrawals due to QT-prolongation during the 1990s.[6] It seems, however, that although regulatory requirements are often *added* to the regulatory framework, they are hardly ever *removed*, even if removing certain requirements would not result in increased drug safety risks.[7]

Strict regulatory requirements have resulted in a drug development process that is both lengthier and more expensive than it was 30 years ago.[8,9] The usual patent life of a pharmaceutical molecule is 20 years. A lengthier drug development process therefore leaves a pharmaceutical company with a shorter time frame to earn back its investments before patent expiration and the subsequent market entry of generic competitors. It could be

argued, therefore, that adding regulatory requirements invokes additional development costs and ultimately increases drug prices. Whether this is a desirable situation (assuming it would result in safer and more effective drugs reaching the market) would be determined by (i) the value society places upon drug safety and efficacy, (ii) the safety and efficacy levels society is (un)willing to accept, and (iii) whether these regulatory requirements increase public health in a cost-effective manner.

There is very little empirical evidence supporting the drug regulatory framework. We do not know, either in general of for each drug separately, what level of drug safety is expected or required.[10] At the moment, there is no information available supporting the idea that pharmacovigilance activities improve public health in a cost-effective manner.[10] Even though a comprehensive regulatory framework intended to protect and promote public health is in place, we neither know its effectiveness nor its outcomes. Therefore, it needs to be determined whether the drug regulatory framework has a measurable impact on preventable drug harm in clinical practice.[10]

Health Technology Assessment

The rise in healthcare spending in most Western countries has urged governments to turn to various policies aimed at controlling healthcare expenditures. Determining an efficient allocation of scarce resources is becoming gradually more important, as every Euro a country spends on healthcare cannot be spent elsewhere. Health Technology Assessment (HTA) is used by governing bodies and decision-makers in several European countries to determine whether new medical interventions provide value for money. The cost-effectiveness of a new technology expresses the resources that are required to achieve increased public health (**Box 1**) and weighs both the incremental costs and benefits of a new technology against that for an existing therapeutic option. Cost-effectiveness analysis is mostly used to inform reimbursement decisions. The economic evaluation of medical technologies thus enables the assessment of an efficient allocation of scarce resources.

The development of methods for the assessment of the cost-effectiveness of medical technologies started in the 1970s.[11] Nowadays, HTA is predominantly used to assess the cost-effectiveness of healthcare interventions. The preferred measurement of health gains is through the quality-adjusted life year (QALY),[12] which combines the length of life lived with the experienced health-related quality of life. Hence, one QALY can be interpreted as one year of life lived in full health (**Box 1**). A particularly useful property of the QALY is that it captures both gains from reduced morbidity and gains from reduced mortality in one single, generic measure of health.[12] Consequently, it can be used as a measure in an economic

evaluation of any intervention aimed at increasing health, regardless of the disease or health issue in question, *including drug regulatory measures*.

Say a new drug is developed for the treatment of a certain disease. The current standard therapy for this disease costs €500 per year (per patient) and results in a life expectancy of 70 years and an average health-related quality of life of 0.6 for each patient with the disease. These patients fall ill, on average, at the age of 50.

The new drug will increase the length of life of these patients by one year and will improve the patients' health-related quality of life to 0.8. The annual treatment costs of the new drug are €10,000.

The incremental cost-effectiveness of the new drug is calculated as follows:

Incremental costs:
The incremental costs per patients are €10,000 – €500 = €9,500.

Incremental effects:
The expected quality-adjusted life years (QALYs) per patient:

With the standard therapy: (70 - 50) * 0.6 = 12 QALYs
With the new drug: (71 - 50) * 0.8 = 16.8 QALYs.

The incremental health effects therefore are 16.8 - 12 = **4.8 QALYs** per patients.

Incremental cost-effectiveness ratio (ICER):

The incremental cost-effectiveness ratio of the new drug versus the standard therapy is:

€9,500 / 4.8 = **€1,979 per QALY gained**.

The incremental cost-effectiveness ratio reflects the resources that are required to gain one QALY, if the new drug were to be reimbursed.

Box 1. Example of the calculation of the incremental cost-effectiveness of a medical technology

Drug safety regulations have several features that are similar to medical interventions, most notably, their aims being to increase public health. Furthermore, drug safety regulation will most likely invoke implementation costs and might *save* costs by preventing healthcare consumption and productivity losses through the prevention of adverse drug reactions. An important distinction between drug safety regulation and medical interventions, however, is the *mechanism* through which health gains are achieved. Medical interventions usually will increase public health by improving the health of individual patients, whereas drug safety regulation will increase health by preventing health losses due to adverse drug reactions in individual patients. The drug regulatory framework is not only extensive but also expanding, as illustrated by the implementation of a set of new pharmacovigilance legislations in Europe in 2012.[13] However, no evidence currently is available that the drug regulatory framework contributes to public health in a cost-effective manner, as the cost-effectiveness of drug safety regulatory measures, as opposed to medical interventions, has not been studied.

Objectives and scope of this thesis

Given the aims of the drug regulatory framework to protect and promote public health and the probable impact of stringent regulatory requirements on drug development costs, the objective of this thesis was the evaluation of the drug regulatory framework. The cost-effectiveness of two safety-related drug regulatory measures was assessed. As the application of HTA to the evaluation of drug regulation has never been systematically performed, a cost-effectiveness analysis of a medical technology (endovascular treatment for acute ischemic stroke) was performed to assess the similarities and differences between the economic evaluation of healthcare technologies and drug regulatory measures. Furthermore, to add to our understanding of how the weighing of benefits and safety risks of pharmaceuticals (i.e. benefit-risk assessment) is applied within the drug regulatory framework, a study that elicited benefit-risk preferences for pharmaceuticals was performed. The societal valuation in monetary terms of safety-related regulatory actions was also determined in a separate study.

Outline of this thesis

Chapter 2 of this thesis concerns the societal valuation of safety-related drug regulatory actions and aimed to determine what the general public and patients are willing to pay to reduce a specific drug safety risk. In **Chapter 3**, a discrete choice experiment regarding benefit-risk assessment of pharmaceuticals is reported. **Chapter 4** discusses the rationale for the use of HTA in the evaluation of the drug regulatory framework. **Chapter 5** is a cost-effectiveness analysis of a medical technology which reports the cost-effectiveness of endovascular treatment for acute ischemic stroke. **Chapter 6**[*] and **Chapter 7**[*] consist of two regulatory cost-effectiveness analyses, in which HTA methods, as demonstrated in **Chapter 5**, are applied to evaluate two different parts of the regulatory framework: the thorough QT/QTc study (**Chapter 6**) and Periodic Safety Update Reports (**Chapter 7**). **Chapter 8** is the last chapter of this thesis and contains a general discussion of this thesis' main findings.

[*] Chapter 6 and Chapter 7 have the following structure: Introduction, Results, Discussion, Methods due to Journal guidelines. The other chapters follow the standard structure (Introduction, Methods, Results, Discussion).

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Chapter 2

Willingness to pay for adverse drug event regulatory actions

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Summary

Background: Regulatory requirements for the pharmaceutical industry have become increasingly demanding with respect to the safety and effectiveness of drugs.

Objective: The objective of this study was to determine the willingness to pay (WTP), of both the Dutch general public and dialysis patients, for regulatory requirements related to reducing the risk of pure red cell aplasia (PRCA) associated with epoetin alpha use.

Methods: A survey was carried out in April 2009. The Dutch general public (n = 422) was approached through a survey sampling agency. Patients (n = 112) were included through several Dutch dialysis clinics because they are often treated with epoetin alpha and therefore were expected to have a higher WTP than the general public. The survey aimed to determine the WTP for reducing the risk of PRCA in epoetin alpha users from 4.5 to 0 per 10,000 patients per year, based on regulatory actions that have been taken by the European Medicines Agency (EMA). WTP was determined via a payment scale and an open-ended follow-up question. Patients were asked how much extra per year they would be willing to pay for their basic healthcare insurance. We used two censored regression models to test the association between WTP and a set of independent variables: a Tobit model with the stated WTP as the dependent variable and an interval regression model with the interval between the lower and upper bounds of the payment scale as the dependent variable.

Results: The patients' mean WTP was significantly higher (€46.52) than that of the general public (€24.40). The Tobit model showed significant associations (a = 0.05) with WTP for dialysis patients, risk perception and respondents' opinions on costs of healthcare. The interval regression model showed significant associations with WTP for the same variables as the Tobit model and for one additional variable (risk aversion). Income did not significantly affect WTP. A scenario with a 10-fold larger risk reduction did not increase WTP significantly.

Conclusion: This study is, as far as we know, one of the first attempts to analyse the WTP for drug regulation and should in future be used in studies of the societal costs of drug regulation for epoetin alpha use. Our results indicate that the Dutch general public, especially Dutch dialysis patients, are willing to pay limited amounts to reduce the risk of serious adverse events associated with drug use.

Introduction

Regulatory requirements for the pharmaceutical industry have become increasingly demanding with respect to the safety and efficacy of drugs.[1] They are aimed at both drugs under development and marketed drugs[2,3] and are intended to protect the general public against unsafe, ineffective and potentially harmful drugs. In a heavily regulated industry, with increasing drug development costs,[4] it is important to determine the public value of new regulatory requirements as a response to newly identified safety threats.

Regulatory requirements often lead to increased resource consumption in the drug development process and their effectiveness is not always evident. Within the Dutch healthcare system, these costs are eventually covered by citizens in the form of higher health insurance premiums. In the development and implementation of these regulatory requirements, cost effectiveness has thus far not been an issue. We performed a willingness to pay (WTP) study to evaluate the Dutch public's valuation of risk reduction measures. The WTP method has primarily been used in healthcare research to elicit preferences for individual treatment programmes and, to our knowledge, no WTP studies have focused on regulatory safety measures in healthcare. By determining people's valuation of a risk reduction in healthcare, we tried to establish whether people are willing to pay for regulatory safety measures. Furthermore, we wanted to analyse whether WTP is a feasible approach for the evaluation of drug risk reduction measures and what the public valuation of these measures is in monetary terms. A survey was designed to obtain the WTP for a drug risk reduction measure. We also measured several personal values and attitudes to test their relationship with WTP.

Methods

The drug risk reduction measure considered for this study reduces the risk of a serious adverse event known as pure red cell aplasia (PRCA), which has been associated with subcutaneous use of human recombinant erythropoietin alpha (epoetin alpha).[5] Epoetin alpha is often prescribed to patients with chronic kidney disease (CKD) who experience chronic renal insufficiency and who undergo dialysis treatment. PRCA is a rare condition defined as severe anaemia secondary to the virtual absence of red cell precursors in the bone marrow.[6] The implications of PRCA are severe: patients need blood transfusions to survive, and long-term blood transfusions also have major adverse effects.[7] Prior to 1998, hardly any cases of PRCA had been associated with epoetin alpha use. Between 1998 and 2002, the incidence of PRCA increased after a formulation change, reaching a maximum of

approximately 4.5 per 10,000 patients per year in Europe.[8,9] Regulatory safety measures were implemented to ensure appropriate storage, handling and administration (intravenous rather than subcutaneous injection was indicated for CKD patients) and PRCA incidence decreased to approximately baseline level after 2004 (0.02 per 10,000 per year).[6-8]

Dutch Healthcare System

The Dutch healthcare system is partially financed through mandatory health insurance premiums (about €1,100 per year per person aged >18 years).[10] Annual premiums differ slightly between health insurance providers, which are mandated to accept all people who wish to be insured by that provider, and premium differentiation among insurees is not allowed.[10] Furthermore, the healthcare system is financed through income taxes (maximum of 7.05% of income).[11] Individuals with low incomes receive an income-dependent healthcare allowance, which is capped at €735 per year for the lowest incomes.[11]

Survey

In April 2009, a survey was used to query two comparative populations: the general public and dialysis patients in the Netherlands. Dialysis patients are at higher risk of developing PRCA and are therefore expected to have a higher WTP. Not all dialysis patients use epoetin alpha and the drug is also prescribed to non-dialysis patients who are anaemic. However, most dialysis patients do use the drug and have experience with anaemia. Furthermore, dialysis patients are relatively easy to access as they visit a dialysis clinic approximately three times a week to undergo dialysis. Patients in five dialysis clinics in five different regions of the Netherlands were asked to complete the questionnaire during their attendance at the clinic or to hand in the survey at their next visit. Eligible participants were required to be sufficiently fluent in Dutch and mentally and physically able to complete the questionnaire as judged by the attending doctor or nurse. Approximately 50% of all patients (n = 396) were excluded. The remaining 199 patients approached resulted in 112 respondents (56% response rate). Patients dialyzing at home (n = 127) were sent a questionnaire by mail. The Dutch general public was reached through a survey sampling agency (Survey Sampling International [SSI], Rotterdam, the Netherlands) that randomly approached sample (n = 422) from their online survey population stratified for age and sex (response rate 100%).

Two pilot studies were conducted; the first involved 56 respondents from various educational levels and income classes – 19 of whom were patients. All comments were analysed and the survey was adjusted for clarity. In the second pilot study, the final WTP format was tested on an additional group of five people. The first pilot study showed that some respondents had difficulty understanding some questions and descriptions of risks so

we simplified the questions and descriptions. In particular, questions 17 and 18 – concerning risk aversion – were judged too difficult (**Appendix 2.A**). These were originally three questions, based on Barsky et al.,[12] about whether the respondent would accept a new, similar job with a 50% probability of a 2-fold increase in income if combined with a 50% probability of a loss in income of (i) one-third, (ii) 50% and (iii) 20%. Although this instrument has been tested several times,[12,13] the pilot study indicated that it was too complicated. We thus simplified the questions and limited the instrument to two questions.

Two versions of the questionnaire were allocated: the first presented an estimated risk reduction due to safety measures from 4.5 to 0 per 10,000 patients as based on the literature;[6,8,9] the second presented a 10-fold greater risk reduction (from 45 to 0 per 10,000 patients) to see whether the magnitude of risk reduction affected WTP.

No consensus exists on the best WTP format or the applicability of the contingent valuation method in healthcare. The four most widely used techniques are open-ended questions, bidding games, payment cards and closed-ended questions.[14] Building on the literature,[15,16] the format we used was a payment scale with an open follow-up question (**Appendix 2.A**). Respondents were first asked to indicate the highest amount per year they were definitely willing to pay and the lowest amount per year they were definitely not willing to pay in addition to their current health insurance premium. The subsequent open-ended question asked respondents to indicate their specific WTP. We used the minimum and maximum amounts specified to give respondents upper and lower reference points when indicating their specific WTP. Those indicating a WTP of €0 were asked to explain their response so we could differentiate between 'actual' and 'protest' responses. Respondents were also asked to indicate their confidence in their response. Indication of the confidence in response has been shown to increase the explanatory power of the determining variables.[17-19]

The first two questions introduced the respondents to the format of the WTP question and the valuation of risk reductions in general. They presented reduction scenarios for familiar risks such as motor vehicle accidents and influenza. The subject of the survey was then introduced. The scenario description consisted of the indication of the drug, the population at risk and the actual risk of the serious adverse event. To avoid information bias and cognitive overload,[20] the explanation of the risk and the risk reduction was kept to a minimum of relevant information and no scientific terms were used. The name of the drug was not mentioned.

Several studies have stressed the importance of risk representation and the different forms thereof.[18,20,21] In our scheme, the incidence of the drug-associated PRCA was first presented, followed by the incidence of all types of PRCA per year in the Netherlands. In addition, a visual representation of the risk was used: a square field with 1999 yellow dots and one red

dot (nine red dots were used in the 10-fold risk representation). After the risk representation, we explained that the safety measures decreased the risk of the serious adverse event to zero and the serious adverse event was described as fatal if not treated. Subsequent questions asked respondents to relate the risk to more familiar ones such as traffic accidents. Respondents were also asked to indicate their respective interpretations of the magnitude of the risk and risk reduction not in relation to any other risk.

The respondents' health-related quality of life (HRQL) was measured using the EQ-5D and the Dutch general public's valuation was assigned to the self-reported HRQL-score.[22] Respondents in good health were expected to have a lower WTP because they will perceive the probability of having to use the drug as lower than those in worse health states.

Personal Values and Attitudes

Risk reduction of epoetin alpha-induced PRCA associated with the regulatory-issued formulation change is considered a public good because the drug risk reduction measures apply to all potential consumers of the drug and no consumer of the drug can be excluded from the measures. We hypothesized that WTP for a public good is at least partially based on values and attitudes and therefore investigated their influence in our study. Four sets of statements designed to measure values and attitudes were included: collectivism versus individualism (questions 11 and 12), uncertainty avoidance (questions 13 and 14), long-term orientation (questions 15 and 16) and risk aversion (questions 17 and 18) [**Appendix 2.A**]. The first three sets were based on the study by Hofstede and Hofstede[23] of cultural differences across 70 nations. Respondents were asked to indicate whether they disagreed or agreed with the statement using a five-point Likert scale. We expected a higher WTP in three types of respondents: the more collectively minded, the more uncertainty avoidant and the more long-term oriented.

Table I: Variable specifications

Variable name	Definition
PATIENT	1 = CKD patient , 0 = no CKD patient
RISK1	Risk averse; 1 = little risk averse , 0 = otherwise
RISK2	Risk averse; 1 = very risk averse , 0 = otherwise
HORISK	Respondent's risk perception; 1 = high/very high , 0 = very small/small/average
COSTS	Respondents opinion of costs of healthcare; 1 = high/very high , 0 = very low/low/good

Abbreviations: CKD Chronic kidney disease

The fourth set of statements was designed to measure the relationship between risk aversion and WTP.[24] Risk aversion refers to how people approach risk trade-offs. The difference between risk aversion and uncertainty avoidance is that a risk focuses on a specific event

(e.g. losing income) with an attached probability, while uncertainty is a diffuse feeling with no exact probability attached. The instrument developed by Barsky et al.[12] was used to measure risk aversion. As stated previously, the results of the pilot study led to a simplification of this instrument.

Respondents were asked for their opinions on the cost and quality of the Dutch healthcare system, as we expected those who perceived the quality of healthcare as good and the costs as low to have a higher WTP than respondents with more negative opinions on healthcare costs and quality. Respondents were asked if they or a next of kin had ever had a seriously debilitating disease, or if they had ever been an informal caregiver for a person with a seriously debilitating disease. They were also asked if they knew a person with anaemia or were anaemic themselves. We expected respondents with experience (either themselves or a next of kin) of such disease to have a different risk perception. Several socio-demographic questions on age, sex, working status, education, income and marital status were also included.

Analysis

The appropriate model to use for the analysis of WTP data elicited using an open-ended question format is the Tobit model as the ordinary least squares (OLS) does not always lead to consistent estimates in the case of non-negative dependent variables.[25] WTP data have a lower limit of €0 and often yield a considerable number of 'zero' responses; 15% (81 respondents) in our study. If a respondent indicates a WTP of €0 for reasons other than the true value of the subject at hand, it is considered a 'protest zero', a common problem in WTP studies. Protest zeros can lead to biased results and it is important to differentiate them from a true WTP of €0.

The Tobit model coefficients do not have a direct interpretation as effects of the co-variates on the dependent variable. Unlike the OLS model, the Tobit is a censored regression model and expresses the observed dependent variable *y* in terms of an underlying latent variable *y** (equations 1 and 2):[26]

$$If\ y^* = XB + e => 0\ , then\ y = XB + e \quad (1)$$

$$If\ y^* = XB + e =\leq 0\ , then\ y = 0 \quad (2)$$

where *XB* is a scalar of the values on *X* (the independent variables multiplied by the appropriate Tobit coefficient B) and *e* is the Normally distributed error term. Tobin's formula for the expected value of the dependent variable for all cases (*Ey*) is as shown in equation 3:

$$Ey = F \times \frac{XB}{\sigma} + \sigma \times f\ \frac{XB}{\sigma} \quad (3)$$

where *XB* is defined as in equation 1. *F(y)* is the cumulative Normal distribution function, *f(y)* is the Normal density function, and *σ* is the standard deviation of the error term.[24] In other words, the coefficients of the Tobit model are 'corrected' for the probability of being above the €0 limit, given *XB.* Deriving *Ey* for a set of independent variables using the formula in equation 3 is beyond the scope of this paper.

Furthermore, the payment scale data were analysed. Respondents may find it difficult to provide a specific value of their WTP.[27] Therefore, we also used an interval data regression model, another form of the censored regression model, which analyses the effect of independent variables on the dependent variable that is constructed by the lower and upper bounds of WTP, as measured by the payment scales (question 8, **Appendix 2.A**) preceding the specific WTP question.

The variables included in the regression analyses are listed in **Table I**. Being a patient, risk perception, opinion on the costs of healthcare and risk aversion were included as independent variables in all models. The software package Stata/IC 11 was used for all analyses.

Results

Respondents were allocated to complete a questionnaire with either a risk reduction of 4.5 to 0 per 10,000 patients per year (n = 289 [70 patients, 219 general public]) or of 45 to 0 per 10,000 patients per year (n = 245 [42 patients, 203 general public]). The total number of respondents was 534, comprising 112 CKD patients and 422 non-patients randomly selected from the Dutch general public.

To determine possible protest zeros, the 81 'zero' respondents were asked for their motivation; 46 gave a reason. We regarded "I cannot afford it" as a true zero response, and "it should be in the health insurance basket," "the government should pay" and "the health insurance company should pay" as protest zeros. The protest zeros were removed from the dataset because the respondents might actually have a WTP > €0. The data from those 35 'zero' respondents who did not give a reason were retained because we assumed that those who did not feel the need to explain their response were giving true WTP values of €0. Of the 46 explained zeros, 34 were protest zeros, eight of which were from CKD patients.

Incomplete questionnaires (36 patients) and protest zero responses (8 patients, 26 non-patients) reduced the sample for statistical analysis to 68 patients and 396 members of the general public. **Table II** shows the sample characteristics for all respondents included in the analysis.

The mean WTP for all respondents and for subgroups are shown in Table III. The reported WTP is the mean of the stated value respondents indicated as their WTP after specifying their upper and lower bounds on a payment scale. The overall sample WTP was €27.64 (n = 464). Patients were willing to pay considerably more than the general public: the mean WTP for patients was €46.52 as opposed to the general public's h24.40 (p = 0.00, Mann-Whitney test).

Table II: Sample characteristics

	Patients (N=68)	General Public (N=396)
Age*	62(1.79)	41(0.66)
Sex(male)**	60	50
quality of life(EQ-5D)*	0.74(0.03)	0.86(0.01)
Higher education**	30	41
Risk perception high/very high**	20	12
Risk adverse**	63	69
Quality of health care good/very good**	85	62
Costs of health care high/very high**	59	78
Income brackets (Euros per month)		
€0 - €1,500	19	14
€1,500 - €2,000	15	9
€2,000 - €2,500	12	8
€2,500 - €3,000	0	13
€3,000 - €3,500	18	9
€3,500 - €4,000	7	6
€4,000 - €4,500	4	3
€4,500 - €5,000	6	4
more than €5,000	6	7
Does not want to say income/other	13	27

* mean (standard error) ** percentage

True zero WTP values were given by 10% of the patients and 12% of the general public. The mean WTP for only the non-zero WTP observations was €31.21. The mean value of the lower WTP bound was €16.98 and the mean value of the upper WTP bound was €34.09. The standard deviation, median and 25th and 75th percentile for all WTP values are also reported in table III.

Tables IV and **V** show the results of the Tobit regression including marginal effects (the Tobit coefficients do not have a direct interpretation as effects on the dependent variable) (**Table IV**) and the interval data regression with the interval of the lower and upper bounds indicated by the respondents as the dependent variable (**Table V**). Initially, a large number of co-variates were included in both models. However, many of these variables did not reach significance (a = 0.05). All variables that did not reach significance in these unlimited models were excluded and the reported Tobit and interval data regression models only included those variables that reached significance in one of the unlimited models. However, a table with all definitions of the variables that were included in the unlimited models can be found in **Appendix 2.B**.

Table III: Willingness to pay estimates

	mean WTP	St. dev.	Med.	25-perc.	75-perc.	% WTP=0	P	N
all respondents	€27.64	45.89	€10.5	€5	€40	11	-	464
Only positive WTP	€31.21	47.61	€15	€4	€70	-	-	411
Patients	€46.52	48.51	€35	€0	€100	10	0.00*	68
Non-patients	€24.40	44.69	€10	€0	€60	12	0.00*	396
4.5 per 10,000[a]	€24.92	36.38	€10	€0	€60	13	0.1847**	247
45 per 10,000[b]	€30.74	54.67	€15	€1	€75	10	0.1847**	217
Payment scale lower bound	€16.98	23.04	€5	€0	€50	-	-	448[c]
Payment scale upper bound	€34.09	32.03	€20	€5	€100	-	-	394[d]

a. Risk in questionnaire: PRCA incidence 4.5 per 10,000 patients per year.
b. Risk in questionnaire: PRCA incidence 45 per 10,000 patients per year.
c. Lower than overall sample size due to missing values (not all respondents indicated minimum WTP)
d. Lower than overall sample size due to missing values (not all respondents indicated maximum WTP).
*Mann-Whitney test for difference in means of patients and non-patients
**Mann-Whitney test for difference in means of respondents with incidence of 4.5 per 10,000 patients per year and respondents with incidence 45 per 10,000 patients per year

In the Tobit model, being a patient was significantly associated with higher WTP (t-value = 2.65). Respondents who perceived the risk of PRCA as 'high' or 'very high' had a higher WTP than those perceiving the risk as 'very low' to 'average' (see HORISK variable, t-value = 4.01). Respondents who perceived the costs of Dutch healthcare as 'high' or 'very high' had a lower WTP than those perceiving otherwise (t-value=-3.46). The personal value and attitude variables did not explain respondents' WTP in this model; i.e. they were not significant and were therefore not included in the final Tobit model.

Table IV also reports the results of the marginal effects of the Tobit model. The Tobit model has three conditional means providing different marginal effects: (i) the marginal effect on the probability that the dependent variable is greater than zero; (ii) the marginal effect on the expected value (mean) of the dependent variable conditional on being greater than zero; and (iii) the marginal effect for the expected value of the dependent variable unconditional on being uncensored. The first marginal effects model (i) gives the marginal effects of each variable on the probability of being greater than zero, their standard errors and z-values. Being a dialysis patient resulted in a 12% higher probability of a WTP above zero. When the PRCA risk was perceived as high, the probability of a positive WTP increased by 17%. Conversely, when healthcare costs were perceived as high, the probability of a WTP of zero was increased by 13%.

The second marginal effects model (ii) provides the marginal effects for the WTP observations above zero, their standard errors and z-values. The marginal effects are all considerably smaller than the Tobit coefficients, as they result from scaling the coefficients by an adjustment factor between zero and one.[28] Furthermore, the marginal effects for all WTP observations (both zero and positive responses, marginal effects [iii]) are larger than the marginal effects for the positive-only WTP observations. The predicted mean WTP estimates for these models are larger than the mean WTP values reported in **Table III**.

The interval data regression model (Table V) included the same independent variables as the Tobit model but its dependent variable was the interval within which respondents indicated their WTP fell (payment scale). All variables that reached significance in the Tobit model (PATIENT, HORISK, COSTS) were also significantly associated with the dependent variable in the interval model. Two additional variables reach significance in the interval model: RISK1 (z-value=-1.99) and RISK2 (z-value=-3.07). These dummy variables (Table I) represent the respondents' risk aversion. However, the sign of the coefficients of RISK1 and RISK2 indicate that being more risk averse was associated with a lower WTP (see the Discussion section).

The predicted mean WTP value of the interval regression model was €27.48. This value was very close to the mean WTP value of the sample (€27.64). This indicates that analysis of the payment scale yields results similar to the sample mean of the stated WTP values.

We did not analyse the effect of subgroup-specific (subgroup defined by being a patient or not being a patient) variables we measured in the questionnaire. The patient sample was small for sub-analysis and we limited the analysis to one model including the entire sample.

Table IV: Tobit Model

				Marginal Effects[a]			Marginal Effects[b]			Marginal Effects[c]		
Variable	**Coef.**	**std. error**	**t-value**	**dy/dx**	**std. error**	**z-value**	**dy/dx**	**std. error**	**z-value**	**dy/dx**	**Std. error**	**z-value**
CONSTANT	41.96	7.52	5.58									
PATIENT	16.92	6.39	2.65	0.12	0.04	2.88	8.87	3.59	2.47	12.46	4.97	2.51
HORISK	26.20	6.53	4.01	0.17	0.04	4.67	14.31	3.97	3.60	19.88	5.34	3.72
COSTS	-18.04	5.21	-3.46	-0.13	0.03	-3.67	-9.30	2.84	-3.28	-13.10	3.94	-3.32
RISK1	-7.88	8.02	-0.98	-0.06	0.06	-0.96	-3.74	3.70	-1.01	-5.33	5.27	-1.01
RISK2	-13.02	6.71	-1.94	-0.09	0.05	-2.00	-6.55	3.47	-1.88	-9.26	4.88	-1.90
Sigma	47.32	1.67										
53 left-censored observations at truezeros<=0												
411 uncensored observations												
0 right-censored observations												
N	464											
LR chi2(11)	43.17											
Prob > chi2	0.00											
Log likelihood	-2215.20											
Pseudo R2	0.01											

Dependent variable: stated willingness to pay (WTP). Please see table I for definitions of variables.
Abbreviations: Dy/dx derivative of y; LR likelihood ratio
a. Marginal effect for the probability of being greater than zero: y = Probability WTP > 0 = 0.69
b. Marginal effect for the expected value of the dependent variable conditional on being uncensored: y = Expected(WTP) | WTP > 0 = €47.97
c. Marginal effect for the expected value of the dependent variable unconditional on being uncensored:
y = Expected(WTP) | 0 < WTP < maximum = €33.34

Table V: Interval Regression Model

Variable	Coefficient	Std. Error	z-value
CONSTANT	40.54	4.36	9.31
PATIENT	18.53	4.20	4.42
HORISK	9.40	3.78	2.49
COSTS	-9.40	2.99	-3.15
RISK1	-9.21	4.62	-1.99
RISK2	-11.77	3.83	-3.07
Sigma	24.39	0.95	
43 uncensored observations			
61 right-censored observations			
343 interval observations			
N	447		
LR chi2(11)	54.27		
Prob > chi2	0.00		
Log likelihood	-936.94		

Dependent variable: interval payment scale willingness to pay (upper bound - lower bound). Please see table I for variable specifications. Abbreviations: LR log-likelihood.

Discussion

This study was designed to measure the WTP of the Dutch general public and Dutch CKD patients for the PRCA-related drug risk reduction regulatory requirement regarding epoetin alpha. The mean WTP was €27.64. CKD patients were willing to pay considerably more than the general public: €46.52 versus €24.40. Two censored regression models indicated that being a patient, the perception of the risk presented to the respondent, the respondent's opinion on costs of healthcare and risk aversion were significantly associated with WTP. Personal values and attitudes (individualism, collectivism, uncertainty avoidance and long- and short-term orientation) were not significant in explaining WTP. Our results indicate that WTP in this study was influenced by the respondent's risk perception, but not by the actual magnitude of the risk presented to them. This result is consistent with other research: WTP has often been found to be under-sensitive to the magnitude of the benefit[29,30] and people tend to have difficulties distinguishing between small probabilities or risks.[31] Furthermore, the relationship between the magnitude of the risk reduction and the WTP is not always proportional.[18] In sum, there is evidence of reasonable construct validity of our findings compared with other studies.

The variables RISK1 and RISK2, intended to measure risk aversion, were significant (a = 0.05) in the interval regression model. However, the sign of the coefficient for these two variables

was negative (see **Table I** for specification of variables). This is contradictory to economic theory as it implies that more risk averse respondents in our study have a lower WTP or indicate a lower interval for their WTP. We hypothesized that respondents who were more risk averse would be willing to pay more to reduce the risk. There are several possible explanations for this finding. We simplified the instrument we included in our questionnaire intended to measure risk aversion according to feedback from the pilot study: respondents found the original three questions too difficult. It is possible that, despite limiting the instrument to two questions, it was still misunderstood by respondents. The instrument we used to measure risk aversion consisted of an income lottery. It is possible that risk aversion as measured by an income lottery is not identical to risk attitudes towards health and drug-related risks. Furthermore, the risk presented to respondents in the income lottery is much larger than the risk that was the subject of the risk reduction measures. For risk averse respondents, the disutility of a very small risk might be so low it does not yet start to affect their WTP. Future WTP studies wishing to study the determinants of WTP might want to look at other instruments measuring risk aversion.

As far as we know, this study is the first to investigate WTP for drug risk reduction measures. A study by Werner and Vered[32] used the contingent valuation method to evaluate WTP for a regulatory framework. However, the regulatory framework they studied concerned the introduction of public funding for osteoporosis drugs in Israel. This makes it difficult to compare their findings to our valuation of safety regulation.

Our results suggest that both patients at risk of a drug-induced serious adverse event and members of the general public are willing to pay for measures to lower the risk of serious adverse events from drugs. Only 12% of the general public were not willing to pay anything, which indicates the mean WTP for these measures is higher than zero. However, we were surprised by the relatively high mean WTP in members of the general public (€24.40) as most of them will never have to use the drug at which the risk reduction measures were aimed. We used the standard methodology: asking the WTP for one scenario. However, we suggest that future WTP studies of drug risk reduction regulatory measures should explore more scenarios (different types of regulation aimed at risk reduction) simultaneously, combined with a budget restriction. This approach might more closely resemble realistic choice situations and might reduce hypothetical bias.

The explanatory power of models in WTP studies in general is limited and therefore we included additional variables intended to measure respondents' personal values and attitudes. However, none of these variables were statistically significant at the a = 0.05 level and the overall explanatory power of our models remains rather low. This suggests that a person's WTP depends on (i) other (socioeconomic) factors that we did not measure; and/or

(ii) a random factor. We feel that, because the explanatory power of WTP studies is usually quite low, factors other than demographic variables, such as income, age and sex, should be studied.

We used the Tobit regression model to analyse the relationship between WTP and the independent variables included in our study. There is no consensus on the proper model that should be used for the analysis of contingent valuation WTP data. However, a considerable proportion (11%) of our data consisted of zero responses, even after removing protest zeros. Therefore, an OLS model would have led to biased results and our use of the Tobit model was appropriate. Furthermore, we analysed not only the specific WTP answers of our respondents but also the lower and upper bounds of their WTP, which we asked them to indicate using a payment scale. Both models produced similar results.

Income was not significantly associated with WTP in our model, which is consistent with other research.[33,34] Several other studies, however, did not find this result.[24,35-39] There are several possible explanations: the mean WTP (€27.64) is low compared with both the annual health insurance premium (around €1,100 per person) and total household income. Additionally, the income-dependent healthcare allowance (a low income implies a higher allowance) could subdue the income effect. Finally, this study concerns the valuation of a public good in a contingent setting. Free-rider behaviour, protest answers and altruistic answers can occur in any income class, distorting the relationship between income and WTP.

We found the perception of healthcare costs in the Netherlands to be associated with WTP: respondents who perceived the costs of healthcare (COSTS) as 'high' or 'very high' were willing to pay less for the risk reduction. Upon testing for whether COSTS correlated with income, we found that the relationship was very low (correlation coefficient=-0.03), suggesting that the 'true income effect' is not measured by the COSTS variable.

We hypothesized that WTP would be influenced by the respondent's HR-QOL as others have found such a relationship.[33] The average HR-QOL of patients in our study was relatively high (0.74) compared with the average HR-QOL of the general public (0.86), which could explain the absence of an association between WTP and HR-QOL. The high HR-QOL of patients in our study indicates that they were in relatively good health. However, since the variable PATIENT was associated with higher WTP, it could potentially pick up the influence of health on WTP.

Risk perception was significantly associated with WTP in our study. This result is consistent with other WTP studies.[24,38] Respondents are expected to show rational decision making (i.e. a higher valuation of a higher risk reduction). However, the ability to show rational decision making depends on a correct interpretation of the risk and the risk reduction. In our case, the actual risks and risk reductions were interpreted differently between respondents.

The correlation between these variables was 0.11, which indicates either no relation or a mixed relation between the variables. The risk they were presented with (4.5 or 45 per 10 000 patients per year) did not significantly influence their WTP. However, the respondents' risk perception influenced how much they were willing to pay for the risk reduction. Respondents were still behaving rationally; their interpretation of the risk rather than the actual risk magnitude determined their WTP.

We intended to use a sample size of at least 600 (400 members of the general public and 200 patients). However, it was difficult to collect enough patient questionnaires: we originally approached 396 patients. Their eligibility to participate had to be assessed by either a doctor or a nurse. We used questionnaires that patients had to complete on paper. Incomplete questionnaires eventually led to a total of 76 patient observations. Due to protest zeros we were able to use 68 patient observations in our analyses. Ideally, studies using a sample from a patient population as well as the general public should try to collect a sufficient sample size.

We designed the questionnaire to prevent several forms of bias but the contingent valuation method is known to be subject to some that are impossible to eliminate when performing a WTP study. We could not eliminate hypothetical bias, despite the emphasis that was put on the scenario description and the risk representation.[40-42] Selection bias might have occurred as a result of using a survey sampling agency. While the agency specializes in providing samples representative of the Dutch population, its population is limited to internet users. The patients' eligibility was assessed by the attending doctor or nurse and those judged to be unable did not participate in the study. Approximately 50% of all patients at the clinics were excluded for this reason. Because patients in worse health states might have had a higher WTP for the risk reduction, eliminating this cohort from the study could have biased the results. That notwithstanding, our results indicated that patients have a higher WTP than the general public.

We asked respondents to indicate their confidence in their response after they had stated their WTP (question 9, **Appendix 2.A**). There was no relationship between WTP and confidence in response (correlation coefficient 0.01). However, confidence in response was correlated with a WTP of €0 (correlation coefficient 0.41). This indicates respondents who have a WTP of €0 are more confident about their WTP, which is consistent with results found by others.[43,44]

Future research should focus on the representation and perception of risks. We have shown that, even though the risk is represented in different ways, respondents interpret risks differently. Our results show that the respondent's perception of the risk determines their WTP more than the actual risk presented to them. Having the risk perception approach the actual risk would lead to a more reliable WTP estimate and could prevent hypothetical bias.

An instrument that is able to make respondents better understand and perceive risks should be developed.

Our study provides some indication of the existence of altruistic values in the case of drug adverse event risk reduction measures. Altruistic values in healthcare can be compared to existence values found in the environmental sciences (values for the existence rather than the use of an environmental resource),[45] which have been shown to influence WTP.[46] Individuals may derive utility from seeing another person receiving healthcare[47,48] or, in our study, a person might derive utility from knowing that others are protected against a risk they themselves most likely will never face. The number of zero responses, even when 'protest zeros' are included, was only 15%, meaning that most members of the general public are willing to pay to have the risk of PRCA in epoetin alpha users reduced to zero, even though they are unlikely to be ever faced with this risk. Altruism in healthcare has been described by others.[45,49-51] When evaluating drug risk reduction measures, researchers should take into account that altruistic values might influence WTP.

Conclusion

Our study is, as far as we know, the first study to provide empirical evidence for the public valuation of drug adverse event regulatory actions intended to improve the safety of drugs. People are willing to pay for these measures but the amount they are willing to pay is limited. Therefore, the results of our study should be confronted with the societal costs of risk reduction regulatory actions.

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Appendix 2.A: Willingness to pay questionnaire

Risk reduction in health care

This research project is conducted by the institute of Health and Policy Management at the Erasmus Medical Centre in Rotterdam. Measures are being taken to make drugs as safe as possible. These measures are expensive and society will account for these costs. Therefore, for every measure it has to be determined whether the measure offers value for money. There always is a risk of a serious adverse event when using drugs. The goal of this study is to determine how much money Dutch citizens are willing to pay to lower the risk of a serious adverse event. Filling out this questionnaire will take approximately 15 minutes. The questionnaire is anonymous. At the end of the questionnaire you will find additional information about this study. This information is not necessary to answer the questions.
You can hand in the completed questionnaire at the dialysis clinic or mail it free of charge using the return envelope.

The aim of these first two questions is to introduce you to these types of questions.

Every year approximately 8,000 pedestrians and cyclists are admitted to a hospital due to an accident with a car involved. Approximately 300 of these 8,000 victims do not survive the accident. By making an adjustment to cars, the number of casualties can be reduced to 200. While answering this question please assume that you have a car.

1. If you take into account your household income, what is the maximum amount of money you would be willing to pay to adjust your car? This is a one-off payment.

Below, mark the amount you are definitely willing to pay with a V. Mark the amount you are definitely unwilling to pay with an X.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
€ 0	€ 5	€ 10	€ 20	€ 30	€ 40	€ 50	€ 60	€ 70	€ 80	€ 90	€ 100	More

What is the exact amount you are willing to pay? This amount lies between the V and the X you marked above. €…….

Only answer the following question when you answered € 0.

Why did you answer € 0?

☐ It is not worth more

☐ I do not want to pay

☐ Other:……
……

Each year approximately 280,000 people in The Netherlands get influenza. Approximately 200 people die due to complications as a result of influenza. A new vaccine becomes available that reduces the number of casualties to 75 people per year. This vaccine could be added to the basic insurance package.

2. If you take into account your household income, what is the **maximum** amount of money you would be willing to pay **extra per year** for your basic health insurance to have this vaccine added to the basic insurance package? This amount adds to the cost of the basic health insurance premium. The basic health care insurance premium is approximately € 1100 per year.

Below, mark the amount you are definitely **willing to pay** with a V. Mark the amount you are definitely **unwilling to pay** with an X.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
€ 0	€ 5	€ 10	€ 20	€ 30	€ 40	€ 50	€ 60	€ 70	€ 80	€ 90	€ 100	More

What is the exact amount you are willing to pay? This amount lies between the V and the X you marked above. €……

Only answer the following question when you answered € 0.

Why did you answer € 0?

☐ It is not worth more

☐ I do not want to pay

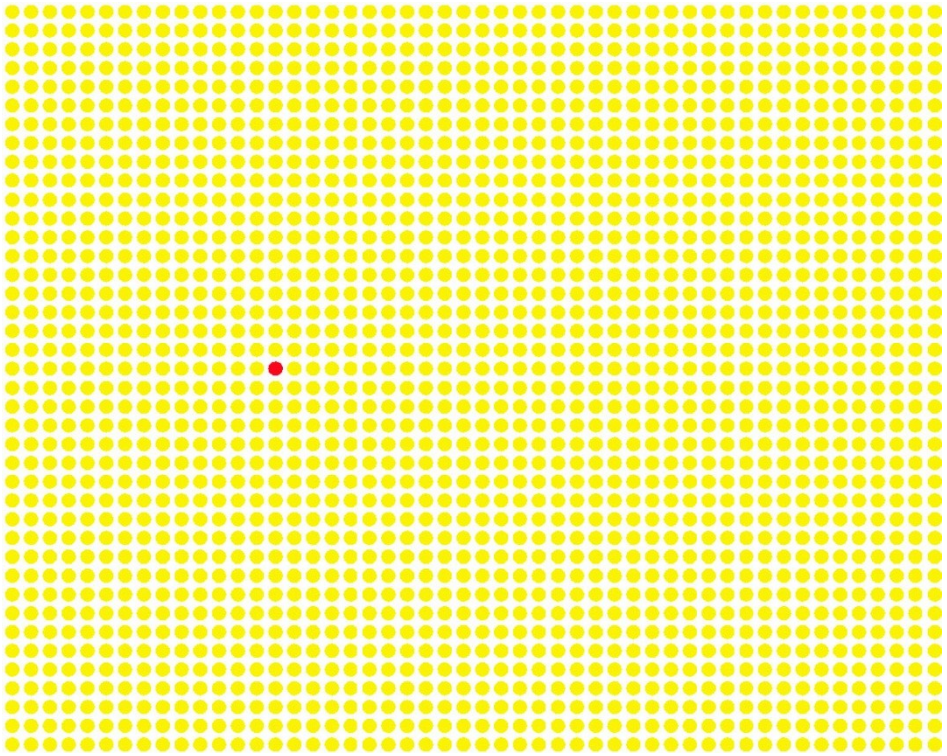
☐

Other:……
……..

The following questions are about the subject of this study.
Approximately 40,000 people in The Netherlands have ill functioning kidneys. 13,000 people are treated for this condition. A part of these patients use a drug to treat anemia. Some years ago it appeared that this drug could cause a serious adverse event. Without instant hospitalization this adverse event was fatal. Several measures were being taking when this issue happened. These measures have reduced the risk of the serious adverse event to 0. Nowadays there is no longer a safety issue with this drug.

Before the risk of the serious adverse event was reduced to 0, the risk of the serious adverse event was approximately 4.5 per 10,000 patients per year. Approximately 15,000 patients in The Netherlands use this drug against anemia. This means that every year 6 or 7 patients in The Netherlands develop the serious adverse event.

This can be depicted as follows:



The yellow dots represent the patients receiving the drug. The red dot represents the 1 patient that would develop the serious adverse event.
The next questions are about the risk of the serious adverse event before measures were taken to reduce the risk of the serious adverse event. You should therefore imagine that the risk of the serious adverse event is still present.

3. What do you think of the risk of the serious adverse event?

☐ Very small ☐ Small ☐ Average ☐ Large ☐ Very large

4. Do you think that your risk of ever developing the serious adverse event is bigger or smaller than the risk that you will ever die in a plane crash? Assume you fly once a year.

☐ Much smaller ☐ Smaller ☐ Similar ☐ Larger ☐ Much larger

5. Do you think that your risk of ever developing the serious adverse event is bigger or smaller than the risk that you are will ever die in a car crash? Assume you drive one hour per day.

☐ Much smaller ☐ Smaller ☐ Similar ☐ Larger ☐ Much larger

6. Do you think that your risk of ever developing the serious adverse event is bigger or smaller than the risk that you will ever die in a train accident? Assume you travel by train one hour per day

☐ Much smaller ☐ Smaller ☐ Similar ☐ Larger ☐ Much larger

As mentioned before, measures were taken that have reduced the risk of the serious adverse event to 0.

7. What do you think of the reduction of the risk?

☐ Very small ☐ Small ☐ Average ☐ Large ☐ Very large

The basic health care insurance premium is approximately € 1100, - per year. This is without the health care allowance or additional health insurance. The drug against anemia for kidney disease patients is being covered by the basic health care insurance package.

Imagine that the measures that reduced the risk of the serious adverse event to 0 had not been taken yet. So you should imagine that the risk of the serious adverse event is still present.

8. If you take your household income into account, what is the maximum amount of money you would be willing to pay extra per year for your basic health care insurance to lower the risk of the adverse event to 0? This amount adds to the cost of the basic health care insurance premium.

Below, mark the amount you are definitely willing to pay with a V. Mark the amount you are definitely unwilling to pay with an X.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
€ 0	€ 5	€ 10	€ 20	€ 30	€ 40	€ 50	€ 60	€ 70	€ 80	€ 90	€ 100	More

What is the exact amount you are willing to pay? This amount lies between the V and the X you marked above. €…….

Only answer the following question when you answered € 0.

Why did you answer € 0?

☐ It is not worth more

☐ I do not want to pay

☐ Other:……
……

9. How confident are you that you would definitely pay this amount?

☐ Not at all confident ☐ Not confident ☐ In between ☐ Confident ☐ Very confident

With the following statements we will determine how you value your own health.

10. By placing a tick in one box in each Group below, please indicate which statements best describe your own health state today.

Mobility

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

Self-care

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

Pain/discomfort

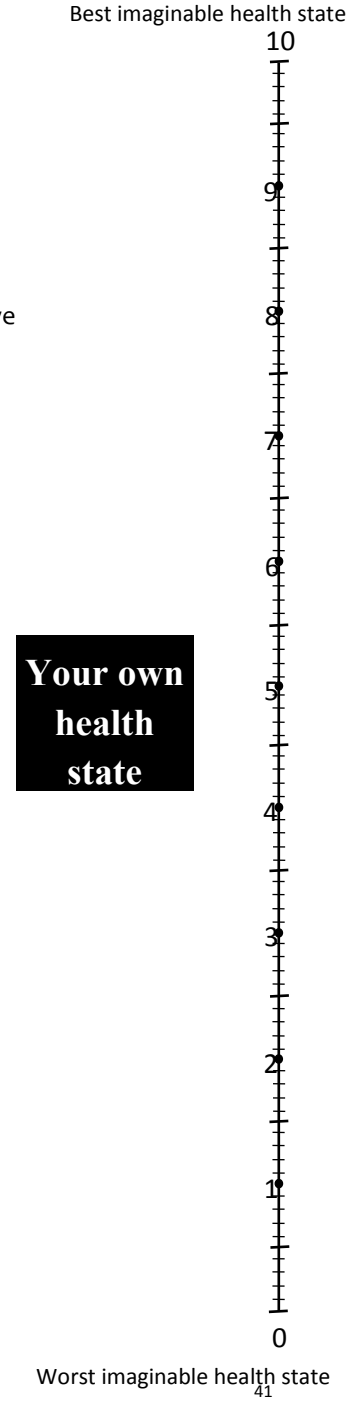
- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

Anxiety/depression

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

To help people indicate how good or bad a health state is, we created a scale (rather like a thermometer) on which the best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today.
Please do this by drawing a line from the box below to the point on the scale that indicates how good or bad your health is today.



Please indicate to what extent you agree or disagree with the following statements:

11. Society should focus on taking care of the more vulnerable, not on opportunities for the stronger

☐ Disagree ☐ Slightly disagree ☐ Neither ☐ Slightly agree ☐ Agree

12. I am responsible for my own well-being, society should not have to take care of my well-being.

☐ Disagree ☐ Slightly disagree ☐ Neither ☐ Slightly agree ☐ Agree

13. Uncertainty is a normal feature of my life and I live from day to day.

☐ Disagree ☐ Slightly disagree ☐ Neither ☐ Slightly agree ☐ Agree

14. I try to avoid risks and unclear situations as much as I can.

☐ Disagree ☐ Slightly disagree ☐ Neither ☐ Slightly agree ☐ Agree

15. I save as much money as possible and work hard now for later in life.

☐ Disagree ☐ Slightly disagree ☐ Neither ☐ Slightly agree ☐ Agree

16. I do not think about the long term in my daily operations and decisions.

☐ Disagree ☐ Slightly disagree ☐ Neither ☐ Slightly agree ☐ Agree

Imagine that you are the sole provider in your family. Your current job guarantees you your current income for the rest of your life.

17. Would you accept a similar job when there is a 50% chance that your income doubles, or decreases with 30%?

☐ Yes ☐ No

18. Would you accept a similar job when there is a 50% chance that your income doubles, or decreases with 50%?

☐ Yes ☐ No

19. How do you experience the quality of healthcare in The Netherlands?

☐ Very bad ☐ Bad ☐ No opinion ☐ Good ☐ Very good

20. What do you think of the costs of the basic insurance premium for healthcare?

☐ Very low ☐ Low ☐ Good ☐ High ☐ Very high ☐ No opinion

Finally, we would also like to ask you some personal questions.

21. What is your year of birth?

……

22. What is your gender?

☐ Male ☐ Female

23. Which of the following descriptions best describes your daily activities?

☐ Paid job or entrepreneur
☐ Retired
☐ Household work
☐ Student
☐ Volunteer
☐ (long term) Sick leave
☐ Unemployed

24. What is the highest level of education you completed?

☐ None
☐ Elementary (primary) school
☐ Middle school
☐ High (secondary) school
☐ Vocational/technical institution
☐ College
☐ University

25. What is your household income (you and your (possible) partner combined)?

☐ €0-€1,500 per month
☐ €1,500-€2,000
☐ €2,000-€2,500
☐ €3,000-€3,500
☐ €3,500-€4,000

☐ €4,000-€4,500
☐ €4,500-€5,000
☐ More than €5,000
☐ Do not want to say/other

26. Are you:

☐ Married?
☐ Living together?
☐ Single?
☐ Do not want to say/other

Do you have any remarks?

……
……
……
……
……
……
……
……

If you have any questions about the questionnaire or this study, you can send an email to: *(e-mail address researcher)*

Thank you very much for your time and participating in this study

You can hand in the completed questionnaire at the dialysis clinic or mail it free of charge using the return envelope.

The research project

In The Netherlands and Europe measures are taken to make and keep drugs as safe as possible. These measures are often precautionary measures that reduce the risk of serious adverse events. This could be compared to the Dutch national vaccination program where children are vaccinated to reduce the risk of certain diseases like measles, mumps and rubella.

Measures are also taken when afterwards (after a drug/treatment has been made available for patients) it shows that a drug/treatment is not as safe as was initially thought. This could happen when, for example, a certain serious adverse event is linked to a drug/treatment after a longer period of time. Or, when a change in the production process of a drug is made or the treatment process changed. Some measures have only a limited positive effect resulting in the possibility of questions being raised about the societal support for such a measure. In the end, it is the general public that pays for these measures through their health insurance premiums or taxes.

The aim of this research is to determine whether it is possible to attach a financial value to the general public's societal support. In other words, we want to know how much the Dutch general public is willing to pay for a risk reduction of a serious adverse event of a drug. In this questionnaire we are trying to determine, using the example of a real drug and an associated serious adverse event, how much you are really willing to pay for a reduction of the risk of a serious adverse event.

A second goal of this research project is to determine what factors influence people's willingness to pay for a risk reduction. We made assumptions (hypotheses) about what we think could influence the willingness to pay. Income, for example, will most probably be of direct influence on someone's willingness to pay. Whether this is true will show from the results. This is also the reason why certain questions have been incorporated in the questionnaire that might appear to have no relation to the subject, but might be related to the willingness to pay.

Questions are also asked about how you approach risks. We are trying to determine whether your attitude towards risks is related to your willingness to pay for the risk reduction of drug use associated serious adverse events.

Appendix 2.B Variable specifications

Table 2.B: Variable specifications of all variables included in original analysis

Variable name	Definition
SEX	Sex of respondent; 1=female . 0=male
RISK	Risk reduction; 1=45 per 10,000 , 0=4.5 per 10,000
PATIENT	1=CKD patient , 0=no CKD patient
AGE	Age of respondent in years
QOL	Quality of life of respondent
EDUC	Level of education: 1=college/university , 0=otherwise
INCOME1	Income; 1=2000-4000 Euros , 0=otherwise
INCOME2	Income; 1=4000 Euros and higher , 0=otherwise
RISK1	Risk averse; 1= little risk averse , 0=otherwise
RISK2	Risk averse; 1=very risk averse , 0=otherwise
HORIS	Respondent's risk perception; 1=high/very high , 0=very small/small/average
RISKREDUC	Respondent's opinion on risk reduction; 1=big/very big , 0=very small/small/average
QUALITY	Respondents opinion of quality of HC; 1=good/very good , 0=very bad/bad/no opinion
COSTS	Respondents opinion of costs of HC; 1=high/very high , 0=very low/low/good
TAKINGCARE1	Question 11; 1=neutral , 0=otherwise
TAKINGCARE2	Question 11; 1=agree , 0=otherwise
WELLBEING1	Question 12; 1=neutral , 0=otherwise
WELLBEING2	Question 12; 1=agree , 0=otherwise
UNCERTAINTY1	Question 13; 1=neutral , 0=otherwise
UNCERTAINTY2	Question 13; 1=agree , 0=otherwise
AVOIDRISK1	Question 14; 1=neutral , 0=otherwise
AVOIDRISK2	Question 14; 1=agree , 0=otherwise
SAVEMONEY1	Question 15; 1=neutral , 0=otherwise
SAVEMONEY2	Question 15; 1=agree , 0=otherwise
LONGTERM1	Question 16; 1=neutral , 0=otherwise
LONGTERM2	Question 16; 1=agree , 0=otherwise

Abbreviations: CKD chronic kidney disease; HC healthcare.

Chapter 3

Trading off benefits and risks: Eliciting preferences for pharmaceuticals using a discrete choice experiment

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Submitted

Summary

Background: Benefit-risk assessment is used by regulatory agencies to weigh a pharmaceutical's benefits against its safety risks. This is the first discrete choice experiment (DCE) that elicited benefit-risk preferences from four groups of stakeholders in benefit-risk assessment, including Dutch regulators.

Methods: A stated choice survey was created, consisting of 20 choice sets each containing two alternatives (Drug A and Drug B). An efficient, unlabeled design was used with five attributes: target population, health status without any treatment, health status with treatment, seriousness of adverse drug reaction (ADR), frequency of ADR, and alternative treatments available. Data was analysed using a nested logit model to enable the comparison of the relative utility functions of the groups.

Results: A sample of 26 regulators and 19 pharmacologists were found to have largely similar preferences regarding benefit-risk profiles of pharmaceuticals but some differences were observed. Both regulators as pharmacologists did not weigh health gains (benefits) and health losses (risks) equally and regulators were found to exhibit more loss aversion, as they were less willing to trade off large health gains for large ADR risk than the pharmacologists group.

Conclusions: Although this study was exploratory and suffers from low sample size, we established the feasibility of using the DCE format to investigate benefit-risk assessment. Preferences for drugs with favorable benefit-risk profiles (large health gains, non-severe and infrequent ADRs) were confirmed, although several preferential differences between regulators and academics were found. Our results stipulate the need for more explicit and transparent benefit-risk assessment, which could identify important factors (e.g. loss aversion, fatality gap) that affect regulatory decision-making.

Introduction

Pharmaceuticals contribute substantially to public health by producing therapeutic benefits in patients. All pharmaceutical products, however, also cause harm through adverse drug reactions (ADRs). Regulatory benefit-risk assessment is the cornerstone of the scientific evaluation of a pharmaceutical's market application and concerns the weighing of a product's expected beneficial health effects against its safety risks.[1] Benefit-risk assessment is applied throughout a product's life-cycle[2] and aims to determine whether sufficient levels of quality, efficacy, and safety of a new product are demonstrated.[3] A pharmaceutical product will only be granted a market license when the product is determined to have a positive benefit-risk profile, which means that the expected benefits of the drug have to outweigh its expected harms in a specific patient population.[1] 'Intuitive expert judgment' is the basis of benefit-risk assessment for the authorization of pharmaceuticals in Europe.[3]

During the last years, both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the US have recognized the need to improve the methodology, consistency, transparency, and communication of benefit-risk assessment.[3,4] Notwithstanding, currently hardly any evidence exists regarding the *explicit* preferences of regulatory agencies regarding benefits, risks, and benefit-risk trade-offs of pharmaceuticals. Furthermore, it is unclear to what extent regulatory decision-making reflects societal preferences of both patients and the general public. The aim of this study therefore was to study how trade-offs in benefit-risk assessment are made by (i) regulatory agencies, (ii) pharmaceutical companies, (iii) academics (pharmacologists/pharmacoepidemiologists), and (iv) hospital pharmacists.

We used a discrete choice experiment (DCE) to elicit benefit-risk preferences for pharmaceuticals. DCEs are based on the notion that people's preferences for products are determined not by the product itself, but by the product's *characteristics*. The attractiveness of a pharmaceutical product, therefore, is assumed to be a function of its characteristics. DCEs have been applied before to elicit benefit-risk preferences for pharmaceuticals, but so far have only studied specific patient populations.[5-8] We used a study design that presented benefits and risks in a general format, in order to study preferences regarding benefit-risk assessment for all pharmaceuticals.

Methods

Design

A DCE measures preferences by presenting respondents with a number of choice sets consisting of two or more alternatives. DCEs are based on random utility theory which assumes individuals always will choose the alternative from a choice set that they prefer most, or in economic terms, that will generate the highest utility. For each choice set, respondents are asked to indicate which of the alternatives (in our study, Drug A and Drug B) they prefer. The utility of a product is determined by an observable component V_i (the characteristics of the product) and an unobservable component ε_i. An individual's utility for an alternative can be expressed as follows:

$$U_i = V_i + \varepsilon_i \quad (1)$$

A DCE therefore enables the estimation of a relative utility function. The relative utility function examines the extent to which the different characteristics contribute to the respondents' preferences for a drug. In this study, we developed an unlabeled, experimental design, which consisted of 20 choice sets of two alternatives (Drug A and Drug B). The scientific literature, EMA documents on benefit-risk assessment, and expert opinion were used to identify all attributes of pharmaceuticals that needed to be included (i.e., all observable components of utility V_i).

Table I: Attributes and levels

Attributes		Levels	Expected sign
Target population	**1**	Adults	-
	2	Children	+
Health status without any treatment	**1**	Patient experiences: Death	+
	2	Patient experiences: some problems in walking about inability to wash or dress him/herself inability to perform usual activities moderate pain or discomfort no anxiety/depression	+
	3	Patient experiences: no problems in walking about no problems washing or dressing him/herself some problems performing usual activities no pain/discomfort extreme anxiety/depression	(ref.)

Table I continued			
Health status with treatment	**1**	Patient experiences: no problems in walking about. some problems washing or dressing him/herself inability to perform usual activities. no pain/discomfort no anxiety/depression	- -
	2	Patient experiences: some problems in walking about no problems washing or dressing him/herself ability to perform usual activities no pain/discomfort no anxiety/depression	-
	3	Patient experiences: Full health	(ref.)
Seriousness adverse drug reaction	**1**	GRADE 2: Moderate Mild to moderate limitation in activity No or minimal medical intervention needed	+
	2	GRADE 3: Severe Marked limitation in activity, medical intervention required	+
	3	GRADE 4: Life-threatening Extreme limitation in activity, Significant medical intervention required, hospitalization/hospice probable	(ref.)
Frequency adverse drug reaction	**1**	1 in 10,000 patients	+
	2	1 in 1,000 patients	+
	3	1 in 100 patients	+
	4	1 in 10 patients	(ref.)
Alternative treatment available	**1**	Yes, three other treatments with: somewhat lower effectiveness than drug A/B milder adverse drug reactions than drug A /B	-
	2	Yes, one other treatment with: somewhat lower effectiveness than drug A/B milder adverse drug reactions than drug A/B	-
	3	Yes, one other treatment with: somewhat lower effectiveness than drug A/B similar but less frequent adverse drug reactions than drug A/B	-
	4	No	(ref.)

All attributes were dummy coded. The last level of each attribute was chosen as the reference level. For all other levels, the expected sign of the coefficient (that was used for generating the design) is indicated. A plus sign indicates an expected increase in the relative utility of an alternative including the attribute level (relative to the reference level).

The design was piloted among a group of seven pharmacologists working in academia and subsequently revised. The final design included the following attributes (**Table I**): 'target

population', 'health status without any treatment' (as an indicator for the disease severity), 'health status with treatment', 'seriousness of adverse drug reaction' (ADR), 'frequency of ADR', and 'alternative treatments available'. We described all health-state levels with EQ-5D health states. The EQ-5D is a validated instrument used to measure and value health-related quality of life[9] which allowed us to use a non-disease specific description of the attributes 'health status without any treatment' and the attribute 'health status with treatment'. For the ADR severity attribute, we used the World Health Organization's grading system of ADR severity (*moderate*, *severe*, and *life-threatening*). We included four levels for the attribute 'alternative treatments available' as the pilot study revealed this as an important attribute.

We used an efficient multinomial logit (MNL) design with Bayesian priors that was generated with NGene (Choice Metrics, Pty Ltd). The efficiency of the design was determined by the D-error. A D-efficient design is generated by specifying the expected relative utility function for the alternatives and it minimizes the variance-covariance matrix of the attributes included in the design.[10] As argued by Bliemer and Rose (2006), an efficient design is preferred when *some* information about the expected relative utility function is available, even if merely the expected sign of the coefficient.[11] The assumed expected signs (negative or positive) are indicated in **Table I**. The design was generated by giving uniform distributions for all priors, ranging from -1.5 to 0 in case of a negative expected sign and from 0 to 1.5 in case of a positive expected sign. The design was generated for an MNL model.

The electronic questionnaire started with an introduction screen, explaining the purpose and subject of the questionnaire to the respondents. The questionnaire format was subsequently introduced by means of an example question (where all attribute levels of drug A were set to the hypothesized least preferred levels and all attribute levels of drug B were set to the hypothesized most preferred levels). Each choice set was introduced as follows: *'Both Drug A and Drug B have been on the market in the European Union for several years. Below, you see the characteristics of both drugs. When you take all characteristics into account, which drug do you think has a better overall benefit-risk profile?'* An example of a choice set is shown in **Table II**. With the introduction question, respondents were instructed to answers all questions, even if they felt both drugs had an equally positive or negative benefit-risk profile. In such a case, they were asked to indicate which drug they considered better or less bad. No opt-out option was included.

Table II: Example of a choice set

	Drug A	Drug B
Target Population	Adults	Adults
Health status without any treatment	Patient experiences: **some** problems in walking about **inability** to wash or dress him/herself **inability** to perform usual activities **moderate** pain or discomfort **no** anxiety/depression	Patient experiences: **no** problems in walking about. **no** problems washing or dressing him/herself. **some** problems performing usual activities. **no** pain/discomfort. **extreme** anxiety/depression
Health status with treatment	Patient experiences: **no** problems in walking about. **some** problems washing or dressing him/herself **inability** to perform usual activities. **no** pain/discomfort **no** anxiety/depression	Patient experiences: **some** problems in walking about **no** problems washing or dressing him/herself **ability** to perform usual activities **no** pain/discomfort **no** anxiety/depression
Seriousness adverse drug reaction	GRADE 2: **Moderate** Mild to moderate limitation in activity No or minimal medical intervention needed	GRADE 4: **Life-threatening** Extreme limitation in activity Significant medical intervention required Hospitalization or hospice care probable
Frequency adverse drug reaction	1 in 100 patients.	1 in 10,000 patients.
Alternative treatment available?	No.	Yes, **one** other treatment with: somewhat lower effectiveness than drug B similar but less frequent adverse drug reactions than drug B

Respondents were asked to indicate which alternative (Drug A or Drug B) they felt had a better overall benefit-risk profile

Data collection

An electronic version of the questionnaire was sent out to all assessors (pre-clinical, clinical, and pharmacovigilance) at the Medicines Evaluation Board in the Netherlands (N=135), originally in November 2011, after an instruction was given at an assessors meeting. Reminders were sent in January and February 2012. Another instruction was given at a meeting in April 2012 and this time, questionnaires were handed out to all assessors on the spot. In total, this resulted in 26 completed questionnaires (response rate: 19.3%).

Originally, we had planned to include a patient group in our study as well. However, given the nature of our experiment and the types of attributes included, we doubted whether lay people would be able to trade-off the drug attributes we included. Therefore we approached a sample of academics (at the division of Pharmacoepidemiology and Clinical Pharmacology (N=114), Utrecht University, the Netherlands, and at Groningen University, the Netherlands). We assumed this group of academics would have sufficient knowledge of pharmaceuticals to participate in the experiment but would not necessarily have preferences similar to assessors, and therefore could be viewed as a proxy for patients/the general public. We

approached this sample through e-mail in February 2012, resulting in 19 completed questionnaires (response rate 16.7%).

Furthermore, we included a sample of persons (N=200) working in Regulatory Affairs of a large European pharmaceutical company by e-mail after an instruction was given during a seminar at the company in May 2012. After two reminders were sent out, this resulted in 10 completed questionnaires (response rate 5%). Last, we approached a sample of hospital pharmacists through the Dutch Association of Hospital Pharmacists by e-mail (N=522). This resulted in a total of 7 responses (response rate 1.3%).

Analysis

A commonly used model for the analysis of stated choice data is the MNL model. It is problematic, however, to directly compare the coefficients of the MNL functions of different groups[12,13] as the scale parameters in the MNL model are correlated with the coefficients. Therefore, observed differences in MNL functions between groups cannot be assumed to be reflecting true preferential differences but could be caused by differences in unobserved variance between groups. (see **Appendix 3.A** for a more detailed explanation). Therefore, we used a nested logit (NL) model to estimate the relative utility functions of the four groups. The NL model enables the comparison of coefficients of the relative utility function of different groups and therefore was the appropriate model to use.[14] The observed choice variable (a preference for either Drug A or Drug B in each choice set) is the dependent variable. All attribute levels were dummy coded and added as explanatory variables. One coefficient was treated as generic among subgroups,[15] resulting in 13 coefficients per utility function (see **Appendix 3.A** for the utility functions). After testing for significance, no constant was included as the design was unlabeled and a constant therefore does not convey any behavioral information related to the alternative. We tested significant differences between the coefficients of the relative utility functions of the different groups with the test for equality of maximum likelihood regression coefficients described by Brame et al. (1998).[16] All analyses were performed with Limdep NLOGIT 4.0 (Econometric Software, Inc.)

Results

NL model

The final sample consisted of 26 regulators, 19 academics (pharmacologists and pharmaco-epidemiologists), 10 pharmaceutical company employees, and 7 hospital pharmacists (**Table III**).

Table III: Sample characteristics

Sample characteristics	Regulators	Pharmacologists	Company	Hospital pharmacists
N	26	19	10	7
Age (mean)	44	43	31	46
Years of experience (mean)	8.2	n/a	3.4	17.7
Preclinical	4%			
Safety	23%			
Efficacy	27%			
Pharmacovigilance	35%			
CNS	31%			
Cardiovascular/Diabetes	15%			
Oncology	12%			
Infectious diseases	12%			

Abbreviations: CNS central nervous system.

The average age of the regulator group was 44 years and average number of years they worked at the regulatory agency was 8.2. All coefficients of the NL model (**Table IV**) had the expected sign (although not all were significant): a drug was more preferred when it was intended to treat an otherwise fatal disease, if it had infrequent and non-severe ADRs, and when no therapeutic alternatives were available. The attribute 'target population' was not significant for any of the subgroups, indicating that a drug's benefit-risk profile is not significantly influenced by the target population being adults or children. The model fit was particularly high with a McFadden pseudo-R^2 of 0.74. Yet this was not surprising, as the significance of the scale parameters (see **Appendix 3.A**) showed there were differences in the unobserved variance of the different groups. Given the small number of observations for the company group (N = 10) and the hospital pharmacists group (N = 7), we limit the reporting of the DCE results to the regulator and pharmacologists group.

Three coefficients in the utility functions (corresponding to the attribute levels for 'health status without any treatment' is death, ADR severity of moderate, and ADR severity of severe) significantly (α=0.10) differed between the regulators and pharmacologists (**Table IV**). These differences indicate that the regulators more strongly preferred the benefit-risk profile of a drug intended either for a fatal disease or with a low ADR severity than the pharmacologists.

Scenarios 1, 2, and 3: trading off benefits versus risks

In order to examine the preferential differences we identified, we simulated several choice scenarios. The simulation was performed by calculation the predicted choice variables for a given choice set. The estimated relative utility functions for all the groups (**Table IV**, **Appendix 3.B**) were used to calculate the predicted choice probabilities for different choice

scenarios. The first scenario (**Table V**) entailed a trade-off between health gains and risks. A choice between Drug A and Drug B was simulated, where Drug A concerned a drug with minimal health gains but also minimal ADR risks, whereas Drug B concerned a drug with maximum health gains but also maximum ADR risks. In this scenario, 66% of the regulators preferred the benefit-risk profile of Drug A over Drug B, whereas 52% of the pharmacologists preferred Drug A over Drug B. indicating that the regulator group was less willing to trade off a higher ADR risk for more health gains than the pharmacologists group.

In scenario 2, we only changed (as compared to scenario 1) the ADR frequency attribute of Drug B (1 in 10,000 patients in scenario 2, whereas it was 1 in 10 patients under scenario 1). Now, 43% of the regulators and 30% of the pharmacologists preferred Drug A over Drug B. In this scenario, more respondents from both groups (23% increase of regulators and 23% increase of pharmacologists as compared to scenario 1) are willing to trade off a severe ADR (*life-threatening, 1 in 10,000 patients*) for maximum health gains, demonstrating that the benefit-risk profile of a drug is considered more favorable when the risk of an ADR is infrequent.

The ADR severity of Drug B in scenario 3 was changed from life-threatening to severe (as compared to scenario 1). The preferences of the two groups now became much more equal: 43% of the regulators and 37% of the pharmacologists preferred the benefit-risk profile of Drug A over Drug B, indicating that for both groups, more respondents are willing to trade off the risk of a *severe* ADR for maximum health gains, than they are willing to trade off a *life-threatening* ADR for maximum health gains.

Scenarios 4 and 5

We changed the health status without any treatment of Drug B to the second level (patient experiencing some problems in walking about, inability to wash/dress him/herself and to perform usual activities, moderate pain/discomfort, no anxiety/depression) in scenario 4 (**Table VI**), while all other attribute levels of Drug A and Drug B remained identical to scenario 1. This scenario demonstrates the major impact of a patient's health status before treatment and the total health gains on the willingness of both groups to trade off maximum health risks for maximum benefit, as now 87% of the regulators and 79% of the pharmacologists preferred the benefit-risk profile of Drug A over the benefit-risk profile of Drug B.

In scenario 5 (**Table VI**), the 'alternative treatments available' level of Drug A and the ADR severity of Drug B were changed (as compared to scenario 1). This scenario indicates that the benefit-risk profile of a drug substantially decreases when several therapeutic alternatives are available, as now only 26% of the regulators and 13% of the pharmacologists preferred Drug A over Drug B.

Table IV: Nested logit results

Attributes:		Regulators			Pharmacologists			Pharmaceutical Company			Hospital Pharmacists		
	Levels:	Coef.	St.Er.	p	Coef.	St.Er.	p	Coef.	St.Er.	p	Coef.	St.Er.	p
Target Population		-0.09	0.13	0.47	0.05	0.09	0.59	-0.07	0.17	0.69	0.02	0.15	0.89
Health status no treatment:													
1	Patient experiences: death	**1.32**	**0.18**	**0.00**	**0.92****	**0.14**	**0.00**	**1.22**	**0.27**	**0.00**	**0.73***	**0.22**	**0.00**
2	Patient experiences: some problems in walking about inability to wash or dress him/herself inability to perform usual activities moderate pain or discomfort no anxiety/depression	0.06	0.16	0.68	0.16	0.12	0.20	0.37	0.25	0.14	-0.01	0.20	0.95
Health status with treatment:													
1	Patient experiences: no problems in walking about some problems washing or dressing him/herself inability to perform usual activities no pain/discomfort no anxiety/depression	**-0.59**	**0.20**	**0.00**	**-0.55**	**0.16**	**0.00**	**-0.83**	**0.30**	**0.01**	**-0.86**	**0.25**	**0.00**
2	Patient experiences: some problems in walking about no problems washing or dressing him/herself ability to perform usual activities no pain/discomfort no anxiety/depression	-0.14	0.17	0.40	-0.35	0.13	0.01	0.09	0.25	0.73	-0.08	0.19	0.66
Seriousness ADR:													
1	moderate	**1.62**	**0.22**	**0.00**	**0.92***	**0.16**	**0.00**	**1.46**	**0.31**	**0.00**	**1.24**	**0.28**	**0.00**
2	severe	**0.93**	**0.17**	**0.00**	**0.39***	**0.12**	**0.00**	**0.75**	**0.24**	**0.00**	**0.67**	**0.22**	**0.00**

Table IV continued

Frequency:													
1	1 in 10,000 patients	**0.95**	**0.26**	**0.00**	**0.61**	**0.19**	**0.00**	**0.72**	**0.35**	**0.04**	**1.05**	**0.32**	**0.00**
2	1 in 1,000 patients	**0.48**	**0.21**	**0.02**	**0.50**	**0.16**	**0.00**	0.39	0.32	0.22	0.49	0.26	0.06
3	1 in 100 patients	**0.58**	**0.18**	**0.00**	**0.24**	**0.12**	**0.05**	**0.83**	**0.26**	**0.00**	**0.54**	**0.21**	**0.01**
Alternative treatments available:													
1	Yes, three other treatments with milder ADRs	**-0.77**	**0.19**	**0.00**	**-0.88**	**0.15**	**0.00**	**-1.11**	**0.31**	**0.00**	**-0.62**	**0.23**	**0.01**
2	Yes, one other treatment with milder ADRs	**-0.72**	**0.10**	**0.00**	**-0.72**	**0.10**	**0.00**	**-0.72**	**0.10**	**0.00**	**-0.72**	**0.10**	**0.00**
3	Yes, one other treatment with similar but less frequent ADRs	**-0.47**	**0.17**	**0.01**	**-0.56**	**0.14**	**0.00**	**-0.48**	**0.23**	**0.04**	**-0.40**	**0.20**	**0.04**
IV parameter		**1.00**			**0.64**			**0.83**			**0.54**		
Scale		**1**			**1.57**			**1.21**			**1.84**		
McFadden pseudo-squared:		0.74											

Abbreviations: ADR adverse drug reaction; Coef. Coefficient; st.er. standard error; p p-value.

*These coefficients significantly differ from the regulators coefficients at α=0.05

**These coefficients significantly differ from the regulators coefficients at α=0.10

this parameter was held constant across models for estimation purposes

Table V: Scenario analyses Benefits versus risks

Scenario 1: Trading off maximum benefits and maximum risks.	**Drug A**	**Drug B**
Target population	Adults	Adults
Health status without and with treatment	Minimum health gains	Maximum health gains
Seriousness ADR	Moderate	Life-threatening
Frequency ADR	1 in 10,000 patients	1 in 10 patients
Alternative treatments available	No.	No.
Regulators:	66%	
Pharmacologists:	52%	
Scenario 2: Trading off maximum benefits for high ADR severity.	**Drug A (identical to scenario 1)**	**Drug B**
Target population	Adults	Adults
Health status without and with treatment	Minimum health gains	Maximum health gains
Seriousness ADR	Moderate	Life-threatening
Frequency ADR	1 in 10,000 patients	1 in 10,000 patients
Alternative treatment available	No.	No.
Regulators:	43%	
Pharmacologists:	30%	
Scenario 3: Trading off maximum benefits for severe risk.	**Drug A (identical to scenario 1)**	**Drug B**
Target population	Adults	Adults
Health status without and with treatment	Minimum health gains	Maximum health gains
Seriousness ADR	Moderate	Severe
Frequency ADR	1 in 10,000 patients	1 in 10 patients
Alternative treatments available	No.	No.
Regulators:	43%	
Pharmacologists:	37%	

Table VI: Scenario analyses 2

Scenario 4: Impact of disease severity	**Drug A (identical to scenario 1)**	**Drug B**
Target population	Adults	Adults
Health status without treatment	Minimum health gains	Patient experiences: **some** problems in walking about **inability** to wash or dress him/herself **inability** to perform usual activities **moderate** pain or discomfort **no** anxiety/depression
Health status with treatment		Patient experiences: Full health
Seriousness ADR	Moderate	Life-threatening
Frequency ADR	1 in 10,000 patients	1 in 10 patients
Alternative treatments available	No.	No.
Regulators: 87% Pharmacologists: 79%		
Scenario 5: impact of alternative treatments available.	**Drug A**	**Drug B**
Target population	Adults	Adults
Health status without and with treatment	Minimum health gains	Maximum health gains
Seriousness ADR	Moderate	Severe
Frequency ADR	1 in 10,000 patients	1 in 10 patients
Alternative treatments available	Yes, **three** other treatments with: somewhat lower effectiveness than drug A milder adverse drug reactions than drug A	No
Regulators: 26% Pharmacologists: 13%		

Discussion

This study demonstrated that regulators and pharmacologists in the Netherlands prefer pharmaceutical products that are indicated for patients with an unfavorable health status before treatment (i.e., high disease severity), pharmaceuticals with large health gains, with non-severe and infrequent ADRs, and that have no therapeutic alternatives. Furthermore, this study established the feasibility of stated choice surveys in the measurement of benefit-risk preferences for pharmaceuticals. Preferences of regulators and pharmacologists were largely similar, yet some differences were identified, most notably, that regulators are less willing to trade-off large ADR risks for substantial health gains than pharmacologists.

We found that in benefit-risk assessment of pharmaceuticals, *health gains* (due to treatment) and *health losses* (due to ADRs) are not valued equally. In scenario 1 (**Table V**), the expected health gains for Drug B were higher (9 out of 10 patients would regain full health after treatment whereas they would have died without treatment) than the expected health losses (1 out of 10 patients would experience a substantial health loss) of Drug B, whereas the expected net health gains for Drug A were much more modest. Yet, the choice probabilities for this particular scenario (66% of the regulators and 52% of the pharmacologists preferred Drug A over Drug B) indicate that substantial proportions of both groups prefer the benefit-risk profile of a drug with minimum health gains and minimum ADR over a drug (Drug A) with maximum health gains and maximum ADR risks (Drug B). According to prospect theory[17] people tend be more sensitive to losses than to gains (loss aversion), meaning that '*the disappointment due to a loss is more extreme than the joy due to an equally-sized gain*'.[18] Our results suggest that loss aversion is a component in benefit-risk assessment as well. Furthermore, the observed differences in preferences (**Table V** and **Table VI**) between the regulators and the pharmacologists suggest that regulators might exhibit *more* loss aversion than pharmacologists.

The benefit-risk profile of a drug was strongly influenced by the health status before treatment. In scenario 4, where the 'health status without any treatment' level was no longer *death* (as it was under scenario 1), 88% of the regulators preferred Drug A over Drug B, whereas under scenario 1, 66% of regulators preferred Drug A over Drug B. This substantial preferential shift could be explained by the 'rule of rescue',[19] which is often observed in reimbursement decisions for life-saving interventions and states that when interventions are life-saving, strict utilitarian rationality is often disregarded.[19] Our results indicate that in benefit-risk assessment, a similar effect could exist: high safety risks are much more acceptable when treatments are life-saving. There might be a substantial benefit-risk 'fatality

gap': the safety risks of pharmaceuticals indicated for severe but non-fatal indications are much less acceptable than similar safety risks of pharmaceuticals indicated for fatal diseases.

Our results are consistent with studies regarding benefit-risk preferences of patients. Crohn's disease patients were found to be willing to trade off higher ADR risks for more benefits.[7,20] Johnson et al. (2007) found that Crohn's disease patients were willing to accept an annual risk of progressive multifocal leukoencephalopathy (PML), an infection of the central nervous system which is often fatal, of 0.7% if they would move from a severe health state to remission, but the maximum acceptable risk was 0.19% if accompanied with minimum health gains.[7] A DCE performed to elicit benefit-risk preferences of psoriasis patients found that patients were willing to trade off time to achieve treatment improvement for lower risks of serious ADRs.[6] Furthermore, people at risk of developing Alzheimer's disease are willing to accept a substantial risk of treatment-related death in exchange for the benefits of a treatment for Alzheimer's disease.[8] Our sample consisted of regulators and pharmacologists, and even though regulators evaluate the benefit-risk profile of drugs on behalf of patients, it is not to be said that their preferences are similar to those of patients. A discussion into whose values should be reflected in regulatory benefit-risk assessment is beyond the scope of this paper.

Our study has several limitations. First, we had a small sample size. We suspect the low response rate might have been due to the length of the questionnaire and the electronic format, which did not allow respondents to submit their filled-out questionnaire without having completed all twenty choice sets. Second, our experiment was of hypothetical nature. DCEs are based on random utility theory, which assumes that individuals strive to maximize utility and will have normative preferences within a choice context.[21] In reality, however, not all people will have clear and well-ordered preferences ready, but many respondents will construct their preferences during a complex elicitation process, and preferences usually are context-specific.[22] We forced respondents to choose between two hypothetical drugs, which is not how 'real-life' benefit-risk assessment is performed, as decisions are usually made evaluating one product as opposed to a set of alternatives, and more factors than the included attributes have to be taken into account.[3] Therefore, our results cannot directly be translated into implications for actual pharmaceutical products. Furthermore, the used attribute levels for 'health status without any treatment' and 'health status with treatment' might have been difficult for respondents to interpret as they were quite extensive descriptions of health states, which could have resulted in the non-significance of the middle levels for both attributes. Another explanation might be that the valuation of the different health states differed little to respondents and therefore the levels did not greatly impact preferences.

For the regulators, the coefficient of the ADR-frequency level of 1 in 1,000 patients was 0.48, whereas this coefficient was 0.58 for the 1 in 100 patients level. Both coefficients were significant at the α=0.05 level. The difference between the two coefficients was not significant, suggesting that an ADR frequency level of 1 in 1,000 patients had an identical impact on the relative utility of an alternative as an ADR frequency level of 1 in 100 patients. This could imply scale invariance for the regulators: an ADR risk of 1 in 100 patients was perceived to be virtually equal to an ADR risk of 1 in 1,000 patients. If scale invariance would exist in regulators, this could result in subjective regulatory decision-making.

Our study should be seen as exploratory, and interpretations of our results should be made with caution due to the low sample size. Notwithstanding, we established that the DCE is feasible approach in studying regulatory benefit-risk assessment. Our study suggests that regulatory decision-making in benefit-risk assessment is influenced by several factors that result in a deviation from 'rational' decision-making – although it has long been recognized that the view of a rational utilitarian decision maker does not reflect reality very well.[17] We found evidence for loss aversion, possible scale invariance, and several differences between regulators and pharmacologists. These results therefore stipulate the need for more explicit regulatory benefit-risk assessment. A transparent, standardized, and more coherent benefit-risk framework, as opposed 'intuitive expert judgment', would facilitate the assessment of preferences and trade-offs that are actually made by regulators. Such a framework should not be used to scrutinize regulators, but it would enable us to assess whether regulatory benefit-risk assessment is in line with societal preferences regarding the acceptability and unacceptability of benefits and risks. As we included the pharmacologist group as a 'proxy' for the general public and identified several preferential differences, this might imply that regulator preferences do not necessarily reflect societal preferences - even though it is not clear whose preferences should 'count' regarding benefit-risk assessment. An explicit benefit-risk assessment framework would enable the identification of relevant factors influencing regulatory decision-making, which would improve the communication of regulatory decision-making to the general public and the pharmaceutical industry. Furthermore, it would increase the social accountability of regulatory decision-making regarding benefit-risk assessment.

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Appendix 3.A: Using the right discrete choice model

A problematic feature of the MNL model is the correlation of the error variance with the parameters (through a scale parameter λ). In the MNL model, the scale parameter is arbitrarily set to one (assuming that the error variances of all choice sets in the sample are equal). The scale parameter hinders the comparison of coefficients of the relative utility functions between groups when there are differences in the error variances, i.e., the unobserved heterogeneity, between groups. As the scale parameter is inversely related to the error variances (Hensher et al. 2005), this means that MNL coefficients of subgroups cannot be directly compared. Therefore, when comparing different groups, differences in coefficients of the relative utility functions can be caused either by a true difference in preferences, sampling error, or a difference in error variance between the groups through the scale parameter (Swait and Louviere 1993). As we surveyed four different groups of respondents, whom cannot be assumed to be identical to each other (and we were interested in possible differences in preferences among the groups), it would not be appropriate to use an MNL model to compare the relative utility function coefficients.

The nested logit trick (Hensher 2012) is mostly used to pool sources of stated preferences and revealed preferences data, but can be applied to pool different groups of stated preferences data as well. The NL model is an extension of the MNL model, in which the assumption of independence of irrelevant alternatives (i.e. all choice sets in the sample have an identical error variance) is relaxed. Therefore, we used an NL model with a two level structure. The NL model enables the estimation of the scale parameters as the inclusive value (IV) parameters are estimated. It was shown (Hensher et al. 2005) that the scale parameter is equal to the IV parameter at level 2 divided by the scale parameter at level 1. By normalizing the IV parameters at level 2 (Random Utility Model 2 (RU2)), the IV parameters at level 1 are freely estimated and the coefficients estimated for the utility functions of the subgroups can subsequently be compared. We treated one coefficient (alternative treatments attribute level two) as generic across all alternatives to ensure consistency with utility maximization (Hensher & Greene 2002) and set the IV parameter for the regulator group to one as well, to estimate the coefficients of the subgroups relative to those of the regulator group.

The utility functions of the different subgroups are specified as follows:

$$U_{Regulator} = \beta_{TP} TP + \beta_{HS\ no\ treatment} HS\ no\ treatment + \beta_{HS\ treatment} HS\ treatment + \beta_{seriousness\ ADR} Seriousness\ ADR + \beta_{frequency\ ADR} Frequency\ ADR + \beta_{Alt\ treatments} Alt\ treatments + \varepsilon_{Regulator}$$

$$U_{Pharmacologist} = \beta_{TP}TP + \beta_{HS\ no\ treatment}HS\ no\ treatment + \beta_{HS\ treatment}HS\ treatment + \beta_{seriousness\ ADR}Seriousness\ ADR + \beta_{frequency\ ADR}Frequency\ ADR + \beta_{Alt\ treatments}Alt\ treatments + \varepsilon_{Pharmacologist}$$

$$U_{Company} = \beta_{TP}TP + \beta_{HS\ no\ treatment}HS\ no\ treatment + \beta_{HS\ treatment}HS\ treatment + \beta_{seriousness\ ADR}Seriousness\ ADR + \beta_{frequency\ ADR}Frequency\ ADR + \beta_{Alt\ treatments}Alt\ treatments + \varepsilon_{Company}$$

$$U_{Pharmacist} = \beta_{TP}TP + \beta_{HS\ no\ treatment}HS\ no\ treatment + \beta_{HS\ treatment}HS\ treatment + \beta_{seriousness\ ADR}Seriousness\ ADR + \beta_{frequency\ ADR}Frequency\ ADR + \beta_{Alt\ treatments}Alt\ treatments + \varepsilon_{Pharmacist}$$

Where the variables in the utility functions are:

TP = target population (two levels, dummy coded)
HS no treatment = Health status without any treatment (three levels, dummy coded)
HS with treatment = Health status with treatment (three levels, dummy coded)
Seriousness ADR = seriousness of adverse drug reaction (three levels, dummy coded)
Frequency ADR = frequency of adverse drug reaction (four levels, dummy coded)
Alt treatments = alternative treatments available (four levels, dummy coded)

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Appendix 3.B: Multinomial Logit (MNL) models for all subgroups

In **Table 3.B1**, all MNL models are reported that were estimated for the separate datasets for all groups. We tested adding a constant to the utility functions for all groups but none were significant. If a constant would be significant this could indicate left-right bias. In an unlabeled choice experiment, there should be no significant preference for either the left or right alternative in each choice set. A significant constant therefore would imply that respondents have a preference for either the right or left alternative. As none of the constants were significant, this indicates no left-right bias.

Attributes:		Regulators			Pharmacologists			Pharmaceutical Company			Hospital Pharmacists		
	Levels:	Coef.	St.Er.	p	Coef.	St.Er.	p	Coef.	St.Er.	p	Coef.	St.Er.	p
Target Population		-0.09	0.13	0.47	0.08	0.14	0.59	-0.08	0.21	0.70	0.04	0.27	0.89
Health status no treatment:													
1	Patient experiences: death	1.32	0.19	0.00	1.46	0.23	0.00	1.47	0.35	0.00	1.34	0.44	0.00
2	Patient experiences: some problems in walking about inability to wash or dress him/herself inability to perform usual activities moderate pain or discomfort no anxiety/depression	0.06	0.16	0.68	0.24	0.19	0.20	0.45	0.31	0.15	-0.02	0.38	0.95
Health status with treatment:													
1	Patient experiences: no problems in walking about some problems washing or dressing him/herself inability to perform usual activities no pain/discomfort no anxiety/depression	-0.59	0.21	0.00	-0.86	0.25	0.00	-1.00	0.39	0.01	-1.58	0.51	0.00
2	Patient experiences: some problems in walking about no problems washing or dressing him/herself ability to perform usual activities no pain/discomfort no anxiety/depression	-0.14	0.17	0.42	-0.56	0.21	0.01	0.11	0.32	0.74	-0.16	0.37	0.67
Seriousness ADR:													
1	moderate	1.62	0.23	0.00	1.45	0.26	0.00	1.77	0.40	0.00	2.28	0.57	0.00
2	severe	0.93	0.17	0.00	0.62	0.20	0.00	0.91	0.31	0.00	1.23	0.47	0.01
Frequency:													
1	1 in 10,000 patients	0.95	0.26	0.00	0.96	0.30	0.00	0.87	0.44	0.05	1.94	0.63	0.00
2	1 in 1,000 patients	0.48	0.22	0.03	0.78	0.26	0.00	0.47	0.39	0.24	0.89	0.49	0.07

3	1 in 100 patients	0.58	0.18	0.00	0.38	0.20	0.05	1.00	0.32	0.00	0.99	0.40	0.01
Alternative treatments available:													
1	Yes, three other treatments with milder ADRs	-0.77	0.22	0.00	-1.39	0.27	0.00	-1.34	0.45	0.00	-1.15	0.51	0.02
2	Yes, one other treatment with milder ADRs	-0.72	0.19	0.00	-1.13	0.23	0.00	-0.87	0.34	0.01	-1.32	0.47	0.01
3	Yes, one other treatment with similar but less frequent ADRs	-0.47	0.21	0.02	-0.88	0.25	0.00	-0.58	0.33	0.08	-0.74	0.47	0.11

Table 3.B1: Multinomial logit models estimated separately for all subgroups. Abbreviations: Coef. Coefficient; St.Er. standard error; p p-value; ADR adverse drug reaction.

Chapter 4

Value for money of drug regulation

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Introduction

Three keystones of pharmaceutical market authorization are quality, safety and efficacy. The required standards for market authorization are set out by regulatory authorities, such as the US FDA and the EMA in Europe. The objective of drug regulation is to protect and promote public health. Drug regulation protects public health by keeping low quality, unsafe and inefficacious drugs from entering the market, and promotes public health through facilitating needed drugs to enter the market without unnecessary delay[1]. These objectives are reached through hundreds of guidelines that structure both drug development and post marketing surveillance.

However, the pharmaceutical industry is struggling. It takes pharmaceutical companies many years to discover and develop new products and to generate all the required data for market authorization. Moreover, the costs of pharmaceutical R&D have been increasing exponentially during the last four decades[2], and the costs of pharmaceutical R&D are directly related to compliance with regulatory requirements. The drug regulatory framework may have contributed substantially to public health. However, drug regulation could also hinder public health by setting unnecessary hurdles for much-needed drugs entering the market through ineffective and costly regulatory requirements. Until now, the potential negative impact that drug regulation might have on the costs and output of pharmaceutical R&D has received relatively little attention in the literature, even though the need for an efficient and effective drug regulatory framework has been stipulated before[1]. If regulatory requirements do not result in promoting health by ensuring that more safe and efficacious drugs reach the market, but do yield substantial costs, they should be revoked from the drug regulatory framework.

The WHO's 2002 report 'Effective Drug Regulation' provided an elegant framework for evaluating the efficiency and effectiveness of drug regulation by identifying all relevant parts of drug regulation that should be examined, but concluded that "*ideally, an assessment of drug regulation should begin by studying regulatory outcomes to judge overall performance and identify problem areas…* [yet] *outcomes are often not readily measurable*"[1]. We believe that it is not only possible but also essential to measure drug regulatory outcomes, as drug regulation serves a societal objective and therefore should be subjected to social scrutiny. Health technology assessment (HTA), a method that enables assessment of the cost–effectiveness of any intervention aimed at increasing health, should be used to determine the value of drug regulation.

Drug regulation

The 'cautious regulator' problem has been named as one of the four main causes of increasing R&D costs and declining R&D efficiency.[3] Often, the regulatory ratchet is tightened after incidents that ignite the development of new regulatory requirements so as to prevent a similar incident from occurring in the future. A well-known example is the instigation of modern-day drug regulation after the thalidomide disaster in the 1960s. More recent examples include the rofecoxib (Vioxx; Merck) withdrawal (owing to an increased risk of heart attack and stroke) in 2004, which has been named a 'wake-up call' for regulatory authorities[4] and created a greater public and regulatory awareness of drug safety. TeGenero's infamous 2006 TGN1412 clinical trial, in which six healthy volunteers developed life-threatening complications after administration of the compound, resulted in adapted regulatory requirements for first-in-man trials.[5] In addition, a Phase I clinical trial devoted to studying a compound's QT interval-prolonging abilities (the 'thorough QT/QTc study') has been a mandatory part of drug development since 2005, after the QT-prolonging and torsadogenic potential of several pharmaceuticals was the most common cause of drug withdrawal during the 1990s.[6] New requirements are frequently added to the regulatory framework but requirements are rarely removed, even if removing the regulatory requirement would not result in a significant risk to drug safety.[3] A risk averse society might prefer such a 'better safe than sorry' regulatory approach. However, if this risk-averse approach significantly increases R&D costs without resulting in meaningful promotion of public health, a new view on the drug regulatory framework is warranted, especially if by revoking pointless regulatory requirements from the regulatory framework, savings could be achieved without health losses.

HTA & the value of drug regulation

Drug regulation serves a societal function. Society pays for it through consumption of medicines, through taxes that are used to finance regulatory authorities and medical expenses, and through health insurance to cover the costs of medicines. Consequently, if drug regulation is not cost effective, this will result in substantial opportunity costs for society. HTA assesses the added value of health interventions by weighing incremental effects against incremental costs. Although predominantly used to assess the cost–effectiveness of medical interventions, any policy aimed at increasing public health, including drug regulation, can be subjected to a cost–effectiveness analysis. Furthermore, if all

regulatory requirements were cost effective, drug regulation would be highly efficient in producing good health outcomes at acceptable costs.

The structures and processes that are in place in the drug regulatory framework produce regulation outcomes that can be assessed by the availability of safe, effective and good-quality drugs, rational prescribing and appropriate dispensing.[1] However, drug regulation outcomes should also produce actual health outcomes, in the form of better treatment of illness, increased prevention of disease and decreased morbidity and mortality.[1] Cost–effectiveness analysis could identify whether the costs of drug regulations produce acceptable returns in the form of increased public health.

We have performed a cost–effectiveness analysis of the guideline requiring a thorough QT/QTc study to assess a product's QT-prolonging ability during clinical development, which was adapted by the regulatory authorities of the USA, Europe and Japan in 2005. This guideline intends to increase patient safety by minimizing the risk of products that could cause drug-induced sudden cardiac deaths from entering the market. Our results show that it is very unlikely that this regulation is cost effective.[7] Health gains achieved through its implementation result in incremental cost–effectiveness far beyond what is considered acceptable for medical interventions. If this guideline is withdrawn as a clinical development requirement, total R&D costs would decrease (a thorough QT/QTc study costs between €1 and 5 million) and a modest reduction in clinical development times could be achieved.

Society seems to value safety-related regulatory actions. In a recent willingness-to-pay (WTP) study, we found that the general public was willing to accept a small increase of their annual health insurance premium (median WTP of €10, total annual premium of ±€1,100) in order to protect epoetin users from the risk of pure red cell aplasia.[8] However, our study also shows that WTP for regulatory actions is not unlimited. Therefore, it is important to also determine the cost–effectiveness of safety-related regulatory requirements post approval.

Cost–effectiveness analysis of drug regulation is not without challenges. In particular, when using quality-adjusted life years in a study, patient-specific life expectancy and health-related quality-of-life estimates based on published sources will have to be used. However, a paradox that has been encountered in the cost–effectiveness analysis of drug regulation is of greater concern. Drug regulation should, directly or indirectly, protect or promote public health, as is also stated by regulatory authorities. Nevertheless, identifying the actual mechanism through which health gains from a regulatory requirement are to be achieved proves to be daunting in reality. This mechanism is often indirect, nonexistent or unclear, but is essential in assessing a regulatory requirement's cost–effectiveness. Therefore, regulators developing new guidelines should define directly how the guideline will contribute to public health. Such a definition is needed for an ex-post evaluation of a guideline after implementation.

The impact of drug regulation on the current crisis in the pharmaceutical industry has long been overlooked. Therefore, the assessment of the effects of drug regulation on the development of innovative drugs is necessary. Systematically evaluating the cost–effectiveness of drug regulation in order to determine whether adding a requirement to the development process offers value for money would be an essential step toward a more sustainable system of drug development.

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Chapter 5

The cost-effectiveness of two endovascular treatment strategies versus intravenous thrombolysis

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Summary

Objective: To assess the cost-effectiveness of endovascular treatment against intravenous thrombolysis (IVT) when varying assumptions concerning its effectiveness.

Methods: We developed a health economic model including a hypothetical population consisting of patients with ischemic stroke, admitted within 4.5 hours from onset, without contra-indications for IVT or IAT. A decision tree and life-table were used to assess 6 month- and lifetime costs (in Euros) and effects in quality-adjusted life years (QALY) treatment with IVT alone, IAT alone, and IVT followed by IAT if the patient did not respond to treatment. Several analyses were performed to explore the impact of considerable uncertainty concerning the clinical effectiveness of endovascular treatment.

Results: Probabilistic sensitivity analysis demonstrated a 54% probability of positive incremental lifetime effectiveness of IVT-IAT versus IVT alone. Sensitivity analyses showed significant variation in outcomes and cost-effectiveness of the included treatment strategies at different model assumptions.

Conclusions: Acceptable cost-effectiveness of IVT-IAT compared to IVT will only be possible if recanalization rates are sufficiently high (>50%), treatment costs of IVT-IAT do not increase, and complication rates remain similar to those reported in the few randomized studies published to date. Large randomized studies are needed to reduce the uncertainty concerning the effects of endovascular treatment.

Introduction

Thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA) significantly improves clinical outcome in patients with acute ischemic stroke when administered within 4.5 hours after symptom onset.[1-3] However, the effectiveness of intravenous thrombolysis (IVT) is limited in patients with large intracranial occlusions.[4] Only a few randomized controlled trials have tested the safety and efficacy of intra-arterial treatment (IAT) for acute ischemic stroke caused by proximal intracranial arterial occlusion.[5-8] These studies suggest IAT might be beneficial if treatment is started within 6 hours from onset of stroke symptoms - compared to conservative treatment[6] or even IVT.[8]

Several other endovascular interventions have emerged in the last decade: mechanical clot removal by means of aspiration and retraction devices,[9,10] IVT followed by IAT if recanalization is not achieved and the use of a retrievable stent.[4] However, these studies only provide limited evidence of safety and efficacy as they consist of selected and non-randomized patient groups.[11,12]

As endovascular treatment remains an experimental treatment to date, the cost-effectiveness against IVT has not been established, but is crucial if endovascular treatment is introduced as a standard therapy in clinical practice. Therefore, we created a health economic model that combines available published evidence to assess the cost-effectiveness of endovascular treatment against IVT. Furthermore, we report cost-effectiveness at different levels of key parameters determining the potential cost-effectiveness of endovascular treatment against IVT: successful recanalization, the complication rate, and total treatment costs of endovascular treatment.

Methods

Overview

We included four treatment strategies for acute ischemic stroke patients eligible for endovascular treatment in our model: (1) conservative treatment for all, (2) IVT for all, (3) direct IAT for those with an intracranial arterial occlusion and IVT for all others, and (4) IVT-IAT (IVT for all, followed by IAT for those with an intracranial arterial occlusion that has not yet recanalized).

A health economic model was created in the program TreeAge Pro 2009 Healthcare Module (TreeAge Software Inc., Williamstown, Mass.) as a decision tree to model costs in 2010 Euros

and effects in quality-adjusted life years (QALYs) up to 6 months after initial stroke. A multistate life-table originally created for analyzing the cost-effectiveness of stroke services[13] was adapted for use in this study to model the lifetime costs and effects of the treatment strategies. The life-table was written in Microsoft Excel (Microsoft Office 2010). The outcome distribution in modified Rankin Scale (mRS) of the decision tree at six months was input for the life-table. The decision model (**Figure 1**) provided the partial effects of different clinical mechanisms (arterial occlusion, recanalization and symptomatic intracranial hemorrhage (sICH)) that combined, lead to the overall treatment effect of IVT and/or IAT.

Patient characteristics

In patients with a clinical diagnosis of ischemic stroke a CT scan is performed to rule out intracerebral hemorrhage. In patients who may be candidates for intra-arterial treatment, CTA or MRA is used to diagnose a relevant intracranial arterial occlusion. Patients who can be treated within 4.5 hours from symptoms onset are included. The usual contra-indications for IVT apply[14] and patient characteristics were assumed to be similar to those reported in the NINDS trial.[15,16] Therefore the model calculated expected health outcomes (in QALYs) and costs (in 2010 Euros) for an average patient eligible for IVT treatment.

Interventions

In the conservative treatment strategy, patients undergo CT scan and receive best medical care including antiplatelet therapy, but no thrombolytics. The reported risk of symptomatic intracranial hemorrhages in these conservatively treated patients varies between trials from 0% to 1%, depending on definitions and co-medication; we used a point value of 0.1%[2] (**Table I**). The rate of recanalization of occluded vessels (TICI 2 or 3) without further treatment was 0. Even though spontaneous recanalization has been observed,[23,24] it was not included separately as it is difficult to accurately quantify. The probability of conservatively treated patients with no recanalization of occluded vessels to have a good outcome (mRS of 0-1 or 2-3) was 50%, allowing for favourable outcome after conservative treatment. Conservatively treated patients with no visible occlusion had a probability of good outcome of 60%.

In the model, effectiveness of different treatment strategies was achieved through the recanalization rate of the treatment strategies. The relationship between recanalization and good clinical outcome has not been well established in the literature, due to differences in timing of the interventions, assessment of vessel recanalization, and exact definitions of revascularization in different studies. The most comprehensive overview of recanalization rates and good clinical outcome is reported by Rha and Saver (2007).

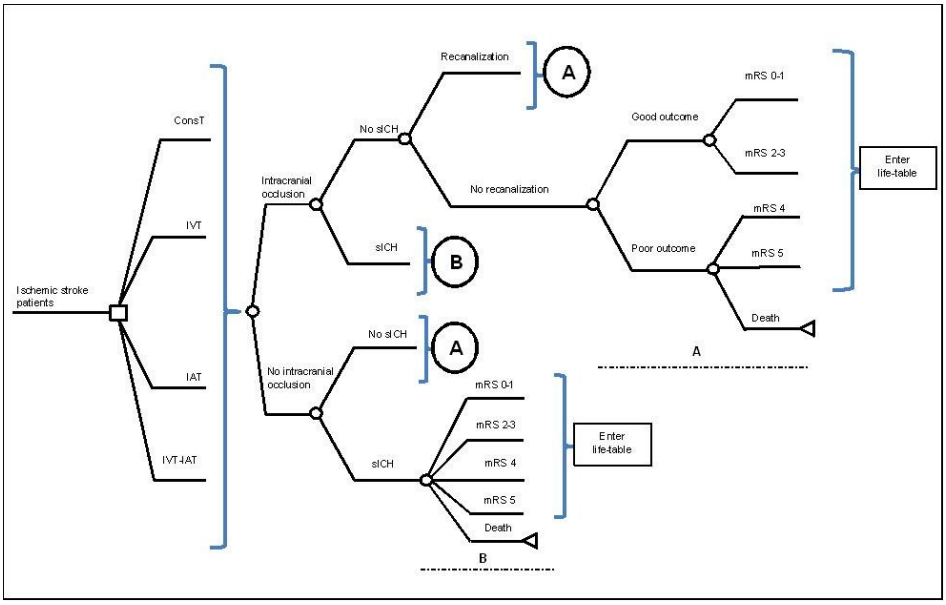

Figure 1: Outline of decision tree 0-6 months

They reported good outcome in recanalized patients of 58.1%, versus 24.8% in nonrecanalized patients.[20] We used an estimated probability of 80% of good outcome after recanalization in patients. Our estimate is higher as we define good outcome as mRS of 0-3 where Rha and Saver define good outcome as either a mRS of 0-2, or whichever other definition of good outcome was used in the studies they included. To validate the estimated relationship between recanalization and good outcome, we included conservative treatment in our model to check whether the model predicts a valid difference in mRS distribution at 6 months after initial stroke between conservative treatment and IVT. The difference in clinical outcome between conservative treatment and IVT has been well reported[1] and is similar to the difference in clinical outcomes calculated by the model for conservative treatment and IVT (**Appendix 5.B**). Although recanalization is not the only predictor of clinical outcome,[25] for modeling purposes we only included recanalization and the occurrence of sICH as determinants of clinical outcome in our model.

Patients in the IVT treatment strategy undergo CT scan and receive alteplase, 10% as bolus, and remaining 90% as 1-hour infusion. Recanalization of occluded vessels after IVT is assumed to be 30% in patients with a visible occlusion. Patients in the IAT treatment strategy undergo CT and CTA scan. The proportion of patients with a proximal intracranial arterial occlusion was estimated at 25%.[17] These patients will be treated with 0.3 mg/kg rtPA or an equivalent dose of urokinase administered at-around the lesion within 1 hour from diagnosis using a microcatheter. A retrievable stent is used in 50% of patients, based on clinical experience in a

Dutch University hospital. It was assumed that 70% of patients would achieve recanalization after IAT[19,26] (**Appendix 5.A**). Patients who enter the IVT-IAT treatment strategy undergo CT and CTA scan and will be treated with standard dose IV alteplase. Patients with an intracranial occlusion will subsequently receive intra-arterial treatment as described above. Estimates of the rate of recanalization (85% of patients that undergo IVT-IAT) were based on published data from randomized and non-randomized studies (**Appendix 5.A**).

It is important to note that even in the IAT and IVT-IAT treatment strategies, 75% of patients were treated with IVT only. The overall difference in clinical outcomes between the treatment strategies is driven by the 25% of patients that would have a visible intracranial occlusion at CTA/MRA <4.5 hours of symptom onset and subsequently would receive IAT or IVT-IAT. Consequently, the probabilities for the actual IVT-IAT treatment group differ (and are less favourable) to the overall treatment strategy probabilities: the proportion of patients with a visible occlusion, with good outcome after IVT-IAT is 67%, and mortality risk at three months for this subgroup is 22.4%.

Endpoints

The intermediary endpoints of the model were mRS scores six months after initial stroke.[27] We assumed that the mRS and corresponding health utility as a result of the initial stroke did not change after six months. To convert functional outcome as measured by mRS at six months into a health utility measure, we used data from the PRACTISE trial.[16] We used the Dutch general public's valuation of EQ-5D health states[28] to assign utility values to the different mRS categories in this study and used these in the model. A score on the mRS of 0-1 was assigned a utility of 0.90, mRS of 2-3 was assigned 0.66, mRS of 4 0.43 and a mRS score of 5 was assigned a utility of 0.18 (**Table 1**).

Multistate Life-table

To calculate lifetime costs and effects we used a life-table with five transition states: mRS 0-1, 2-3, 4, 5, and death (**Figure 1**). Patient flows between these states were based on epidemiological estimates from the Netherlands and have been described elsewhere.[13] All transitions were assumed to take place at the end of a six-month cycle. Entry into the life-table was based on functional outcome at six months after initial stroke, as provided by the decision tree. The life table calculated lifetime QALYs and healthcare costs for each treatment strategy. Transition probabilities in the life table were differentiated for stroke severity, patient sex and age and are consecutively weighted by age- and sex-specific stroke incidence rates from the Netherlands.[29] Death (by stroke recurrence, complications, other cardiovascular events, or other cause mortality) was the only absorbing state.

Costs

Cost data from the EDISSE trial and PRACTISE trial, converted to 2010 Euros, were used for cost estimates in the model. Details of these studies have been published elsewhere.[13,16,22] The basic cost estimates (similar for all treatment strategies) were measured in the EDISSE trial and represented averages of patient-level cost data for hospital care, rehabilitation, nursing home, and home care costs, differentiated by functional outcome at six months (**Table I**). These costs include personnel, overhead, and housing costs. We used cost-data from the EDISSE trial intervention region (Delft) as nowadays all stroke care is provided through stroke units and services in the Netherlands.[30] We collected additional cost data from a University hospital in the Netherlands (Erasmus University Medical Center, Rotterdam), providing additional costs components for IVT and IAT treatment: rt-PA, additional nurse and physician time, catheters, vascular closure device, mechanical thrombectomy device, retrievable stent, and radiology personnel. Additional treatment costs were €971 for IVT, €3,847 for IAT, and €4,171 for IVT-IAT per patient (**Table I**). The life-table distinguished between costs 0-6 months after stroke, 7-12 months after stroke, and half-yearly costs after the first year per disability state. Costs and effects were discounted at 3% annually.[31]

Sensitivity analyses

The sICH rate, recanalization rate after IVT-IAT, good outcome after recanalization, IVT-IAT treatment costs, and percentage of visible occlusions were varied in a sensitivity analysis. We performed probabilistic sensitivity analysis (PSA) using Monte Carlo simulation for the 6-month and lifetime cost-effectiveness. We used standard distributions[32] for all parameters (indicated in **Table I**) in the model in the PSA after six months. We performed the lifetime PSA by using a distribution (**Appendix 5.B**) for the mRS scores at 6-months that are entered into the life-table. We used a threshold willingness to pay of €50,000 per QALY to determine what percentage of the simulations resulted in cost-effective outcomes.

Table I: Parameters in decision tree and life table

Parameter	Base case	Range	Distribution	Reference
Visible occlusion	0.25	0.20 – 0.30	Beta	[17]
sICH - conservative treatment	0.01	-		[3]
sICH - IVT	0.06	-		[18]
sICH - IAT	0.1	0.06 – 0.14	Beta	[5]
sICH - IVT-IAT	0.11	0.06 – 0.17	Beta	[6,19]
Recanalization after visible occlusion -ConsT	0	-		Expert opinion
Recanalization after visible occlusion - IVT	0.3	0.20 – 0.40	Beta	
Recanalization after visible occlusion - IAT	0.7	0.60 – 0.80	Beta	
Recanalization after visible occlusion - IVT-IAT	0.85	0.75 – 0.95	Beta	[6]
Good outcome after recanalization	0.8	0.70 – 0.90	Beta	[20], expert opinion
Good outcome after no recanalization	0.5	0.40 – 0.60	Beta	[20]), expert opinion
Good outcome with no visible occlusion - ConsT	0.6	0.50 – 0.70	Beta	[20], expert opinion
Good outcome with no visible occlusion - IVT	0.7	0.60 – 0.80	Beta	[20], expert opinion
mRs 0-1 after good outcome	0.6	0.50 – 0.70	Beta	Expert opinion
mRs 2-3 after good outcome	0.4	0.30 – 0.50	Beta	Expert opinion
mRs 4 after poor outcome	0.4	0.30 – 0.50	Beta	Expert opinion
mRs 5 after poor outcome	0.2	0.10 – 0.30	Beta	Expert opinion
Death after poor outcome	0.4	0.30 – 0.50	Beta	Expert opinion
mRs 0-1 after sICH	0.01	0 - 0.10	Beta	[21]
mRs 2-3 after sICH	0.09	0.01 - 0.20	Beta	[21]
mRs 4 after sICH	0.2	0.10 – 0.30	Beta	[21]
mRs 5 after sICH	0.2	0.10 – 0.30	Beta	[21]
Death after sICH	0.5	0.40 – 0.60	Beta	[21]
mRs 0-1 utility index	0.9	0.89 – 0.91	Normal	[16]

Table I continued				
mRs 2-3 utility index	0.66	0.65 – 0.67	Normal	[16]
mRs 4 utility index	0.43	0.42 – 0.44	Normal	[16]
mRs 5 utility index	0.18	0.17 – 0.19	Normal	[16]
Death utility index	0	-		[16]
mRs 0-1 total costs 6 months - ConsT	€2.769	± 20%	Gamma	[13,22]
mRs 2-3 total costs 6 months - ConsT	€10.508	± 20%	Gamma	[13,22]
mRs 4 total costs 6 months - ConsT	€32.947	± 20%	Gamma	[13,22]
mRs 5 total costs 6 months - ConsT	€29.775	± 20%	Gamma	[13,22]
Death total costs 6 months - ConsT	€6.403	± 20%	Gamma	[13,22]
Additional costs 6 months IVT	€971	± 20%	Gamma	2010 prices
Additional costs 6 months IAT	€3.847	± 20%	Gamma	2010 prices
Additional costs 6 months IVT-IAT	€4.171	± 20%	Gamma	2010 prices

Additional costs IVT: additional physician time, additional nurse time, tPA. Additional costs IAT and IVT-IAT: additional physician time, additional nurse time, tPA, radiologist time, retrievable stent (costs per stent €4,000 used in 50% of patients), catheter, Angio seal. All parameters were included in the PSA (apart from sICH after conservative and intravenous thrombolysis, as they is little uncertainty regarding these estimates, as well as the utility for health state death, as there is no uncertainty regarding this value either). The used distributions and corresponding plausible ranges are provided.
Abbreviations: sICH symptomatic intracranial hemorrhage; IVT intravenous thrombolysis; IAT intra-arterial thrombolysis; mRs modified Rankin score; ConsT conservative treatment.

Results

Base-case

The incremental cost-effectiveness ratio (ICER) of IVT-IAT compared to IVT was €31,687 at six months and €1,922 at the lifetime horizon (**Table II**; see **Appendix 5.C** for an explanation of the calculation of the ICERS). However, as our base-case estimates were surrounded by considerable uncertainty concerning the treatment effect of IVT-IAT, sensitivity analysis was undertaken to investigate the impact of varying effect assumptions on the ICER.

Table II: Base-case results

Strategy	6 months Costs	Lifetime Costs	6 months Effects (QALYs[a])	Lifetime Effects (QALYs)	6 months ICER[b]	Lifetime ICER
Cons. T.	€ 12,617	€ 34,182	0.274	3.39	-	-
IVT	€ 12,360	€ 32,113	0.292	3.61	Reference strategy	Reference strategy
IAT	€ 12,695	€ 32,199	0.298	3.67	Dominated[d]	Dominant[d]
IVT-IAT	€ 12,633	€ 32,335	0.300	3.72	€ 31,687[d]	€ 1,922[e]

a Quality-adjusted Life Years b Incremental cost-effectiveness ratio; c ICER compared to conservative treatment; d ICER compared to IV thrombolysis; e ICER compared to IA thrombolysis. Dominant indicates the strategy has higher health gains and lower costs than the comparator strategy and thus is preferred. Dominated indicates the strategy has lower health gains and higher costs than the comparator strategy and thus is not preferred.

Table III: Sensitivity Analysis.

Symptomatic intracranial hemorrhage after IVT-IAT	ICER IVT-IAT versus IVT 6 months	ICER IVT-IAT versus IVT lifetime
5%	€ 13,911	Dominant
10%	€ 27,783	€ 726
15%	€ 54,567	€ 3,223
20%	€ 127,725	€ 10,990
25%	€ 1.1 million	€ 139,472

Abbreviations: ICER incremental cost-effectiveness ratio; IVT intravenous thrombolysis; IAT intra-arterial thrombolysis.

Sensitivity analysis

We performed a sensitivity analysis (**Table III**) for the symptomatic haemorrhage parameter in the IVT-IAT treatment strategies, illustrating that the symptomatic haemorrhage rate should remain as low as possible: the lower the sICH rate, the more favourable the 6-month and lifetime ICERs become. At a sICH rate of 26% or higher the expected health outcomes after IVT-IAT will be lower than after IVT alone. We also performed a set of sensitivity analyses depicted in figure 2. The net monetary benefit (NMB) was calculated for a low and high value for each parameter to depict the impact of varying the parameters. The NMB was calculated with a threshold of €50,000 per QALY gained using the formula:

$$NMB = 50{,}000 * \Delta Costs - \Delta Effects \quad (1)$$

A positive NMB therefore indicates an ICER below the threshold whereas a negative NMB indicates an ICER above the threshold. The tornado diagram (**Figure 2**) demonstrates that results are most sensitive to the probability of good outcome after recanalization and the probability of recanalization after IVT-IAT. Results become more favorable at lower sICH rates after IVT-IAT.

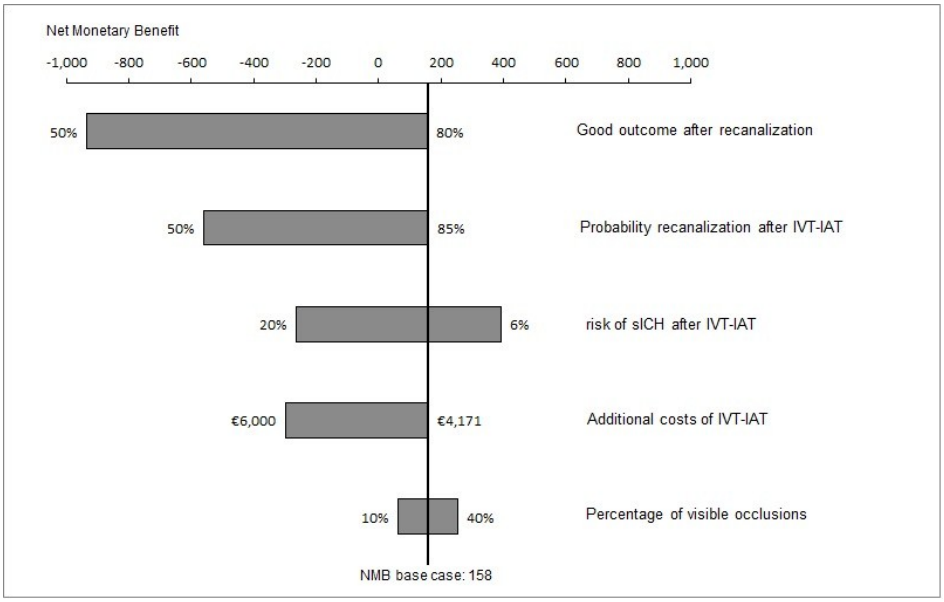

Figure 2: Tornado diagram. The impact of varying one parameter on the results is shown in this figure. The net monetary benefit was calculated with a threshold willingness to pay of €50,000 per QALY gained. A positive NMB indicates an incremental cost-effectiveness ratio below this threshold, whereas a negative NMB indicates an ICER higher than the threshold. This tornado diagram shows that the results are most sensitive to the probability of good outcome after recanalization.

Probabilistic sensitivity analysis

We performed a PSA for both the results (IVT-IAT versus IVT) at six months and lifetime. At a willingness to pay threshold of €50,000 per QALY, the probability of six-month cost-effectiveness was 54.6% and the probability of lifetime cost-effectiveness was 67.3% (**Figure 3**). The PSA illustrated that there is substantial uncertainty whether IVT-IAT versus IVT alone will produce positive incremental health effects and acceptable cost-effectiveness.

Discussion

Our model indicates that in only 54% of simulations of the lifetime PSA, IVT-IAT yielded higher effectiveness for ischemic stroke patients compared to IVT alone, although the point

estimate for the lifetime ICER was €1,922 per QALY gained. This demonstrates the high uncertainty regarding the clinical effectiveness of IVT-IAT versus IVT alone. If recanalization (TICI 2 or 3) in 50% of all large vessel occlusion patients is achieved, IVT-IAT could be cost-effective (considering a societal maximum willingness to pay per QALY of €50,000). Furthermore, sensitivity analyses demonstrated that the rate of symptomatic intracerebral haemorrhage following endovascular treatment needs to remain lower than 20% in order to result in acceptable cost-effectiveness.

Our study has several limitations. First, there is substantial uncertainty concerning the effectiveness of various endovascular treatment strategies. Therefore our study should be seen as exploratory and our aim was not to estimate the cost-utility of IVT-IAT, but to explore at what levels of effectiveness of IVT-IAT would be considered cost-effective. These levels could be used as relevant targets for controlled trials of endovascular treatment. Second, we combined data from different sources and trials not specifically designed for measuring costs and effects of IVT and/or IAT. Studies investigating the clinical effectiveness of different endovascular treatment strategies therefore ideally should also measure the costs of different treatment strategies in clinical practice, especially since endovascular treatment is more expensive than IVT treatment. Furthermore, our model is a simplified depiction of endovascular treatment: recanalization may not necessarily result in nutritive reperfusion of the target bed and sICH is not the only predictor of poor outcome. Additionally, time-to-treatment is quite heterogeneous in the literature but we did not include a time-dependent treatment effect. Hospitals managing to reduce the "door-to-groin" time may have better results than we estimated.

The costs and effects our model calculates for the conservative and IVT treatment strategies are similar to those reported by others.[33,34] The distribution of patients in the disability states at six months for conservative treatment and IVT (**Appendix 5.B**) are quite similar to those reported by a meta-analysis of several IVT trials reporting the distribution of the control group patients and IVT.[1] We believe this supports the reliability of the predicted values produced by our model.

We used a 'lean' intervention cost estimate: a retrievable stent or mechanical clot removal device is only used in 50% of patients, no additional intensive care is needed, and additional specialist time is limited. Therefore our estimated treatment costs of IVT-IAT might be lower than in clinical practice. If actual treatment costs would be considerably higher than we estimated, which could be the case when more stents or other costly materials are used, this would negatively affect our results (**Figure 2**).

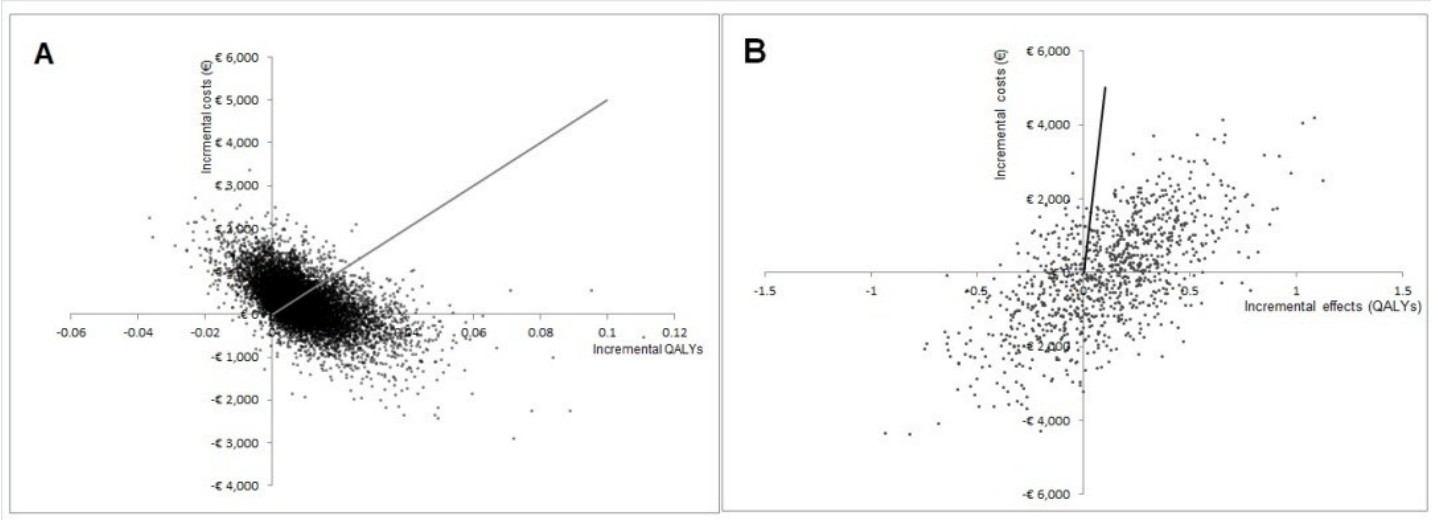

Figure 3: Probabilistic sensitivity analysis. A: Cost-effectiveness plane at 6 months, IVT-IAT versus IVT alone. Each dot represents one iteration (Monte Carlo simulation, 10,000 iterations). B: Cost-effectiveness plane at lifetime, IVT-IAT versus IVT alone. Each dot represents one iteration (Monte Carlo simulation, 1,000 iterations). The line indicates a maximum willingness to pay per QALY of €50,000. At six months, 51.2% of all iterations resulting in both positive incremental costs and effects are below the threshold. At lifetime, 99% of all iterations with both positive incremental costs and effects are below the threshold.

Differences in expected costs and effects of the intervention strategies we included in the model are small. Only patients with an intracranial occlusion (25%) are eligible for endovascular treatment. Subsequently, 75% of patients in the model will only receive IVT, regardless of the intervention strategy deployed. The model thus calculates expected costs and effects of implementing IVT-IAT as an available treatment strategy for all acute ischemic stroke patients eligible for IVT reaching the hospital within 4.5 hours of onset. Consequently our results should be interpreted at the aggregated level of all ischemic stroke patients, regardless of the presence of a visible intracranial occlusion.

Three cost-utility analyses of endovascular treatment strategies have been performed to date[35-37] that all found evidence of reasonable cost-effectiveness of mechanical thrombectomy as compared to conservative treatment. However, all three studies only included hypothetical patients presenting with large vessel occlusion. As only approximately 25% of all acute ischemic stroke patients presenting within 4.5 hours after symptom onset will have a visible occlusion, our results cannot be directly compared to the published studies. All studies report more favourable ICERs and less uncertainty surrounding their results than our study. However, the differences in hypothetical patient cohorts between our study and the three currently published might well account for this difference. Kim et al. (2011)[37] report a threshold recanalization rate of 52%, which is quite similar to our results. Nevertheless, regional cost differences hinder a direct comparison, and all articles only report incremental costs for base case scenarios, which makes it impossible to compare our total expected lifetime costs and effects to those reported.

Empirical evidence is warranted before more general statements about the cost-effectiveness of endovascular treatment for acute ischemic stroke can be made. Therefore more randomized controlled studies investigating the effectiveness of intra-arterial treatment for acute ischemic stroke are evidently needed to reduce the current uncertainty concerning the effect of endovascular treatment on functional outcome of stroke patients. Furthermore, the costs of these highly expensive treatment strategies should also be assessed.

We tested the validity of our model by assessing its calculations of functional outcome for conservatively and IVT – treated patients and performed extensive sensitivity analyses exploring the substantial uncertainty concerning the actual treatment effect and costs of endovascular treatment. Concluding, we believe that if endovascular treatment is ever to make its way into clinical practice and become an accepted treatment option for acute ischemic stroke patients, three conditions will have to be met: (1) endovascular treatment costs should not increase beyond our base-case scenario estimated costs, (2) fair recanalization rates and improved functional outcome have to be confirmed by randomized

controlled studies, and (3) the rate of symptomatic haemorrhage following treatment should not exceed rates reported by the few randomized controlled studies published to date.[5-8]

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Appendix 5.A: Overview of recanalization rates in randomized controlled trials and observational studies

Study	N	Mean OTN	TIMI 2-3	TIMI 3	NIHSS‡
No thrombolysis					
PRO-ACT II[2]	50	306 min	18%	2%	17 (4-28)
PRO-ACT I[1]	14	330 min	14.3%	-	19*
Iv alteplase					
CLOTBUST[3]	63	130 min	-	13%	16 *
RECANALISE	107	163 min	52%	46%	16 (11-19)
IA alteplase or (pro) urokinase					
PRO-ACT II[2]	108	280 min	66%	19%	17 (5-27)
PRO-ACT I[1]	26	330 min	58%	19%	17 *
MELT[4]	57	200 min	74%	5%	14 *
EMS[7]	10	180 min	50%	10%	11 (9-16)
Mattle et al[6]	55	240 min	71%	16%	16.7 (±5.1)
IV+IA alteplase					
EMS[7]	11	220 min	82%	55%	16 (9-21)
IMS I[8]	62	210 min	56%	11%	18 *
IMS II[9]	55	180 min	60%	4%	19 *
Shaltoni et al[10]	69	285 min	72%	-	18 (6-39)
IA alteplase /urokinase followed by mechanical thrombectomy if deemed necessary					
MERCI –II[11]	141	<8hrs	48%	24%	20.1(± 6.6)
Multi MERCI final[12]	164	270 min	68%	-	19 (15-23)
Devlin[13]	25	< 8 hrs	56%	-	18 *
Kim[14]	24	177 min	50%	25%	21 (11-30)
Bose[15]	21	< 8 hrs	100%	52%	21
McDougall[16]	125	260 min	82%	27.2%	17.6 (± 5.2)
RECANALISE[5]	53	132 min	87%	77%	14 (10-18)

Table 5.A Recanalization rates. ‡ Data are mean (SD) or median*(IQR). † OTN=Onset to needle time

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Appendix 5.B Outcome distributions at six months for all treatment strategies

	mRS[a] 0-1	mRS 2-3	mRS 4	mRS 5	Death
Conservative treatment	34%	23%	17%	9%	17%
IVT[b] *Range for PSA[c]*	38% *(26%-52%)*	26% *(18%-37%)*	14% *(11%-17%)*	7% *(0.04%-0.11%)*	15% *(-)*
IAT[d] alone	39%	27%	12%	7%	15%
IVT-IAT *Range for PSA*	40% *(30%-49%)*	27% *(18%-37%)*	12% *(9%-15%)*	7% *(4%-10%)*	14% *(-)*

Table 5.B Outcome distributions. a mRS modified Rankin Score; b IVT intravenous thrombolysis; c Range for probabilistic sensitivity analysis at lifetime costs and effects. All probabilities are assumed to follow a beta distribution. No range is reported for 'death' as patients who are deceased at six months never enter the multi-state life table. d IAT intra-arterial thrombolysis

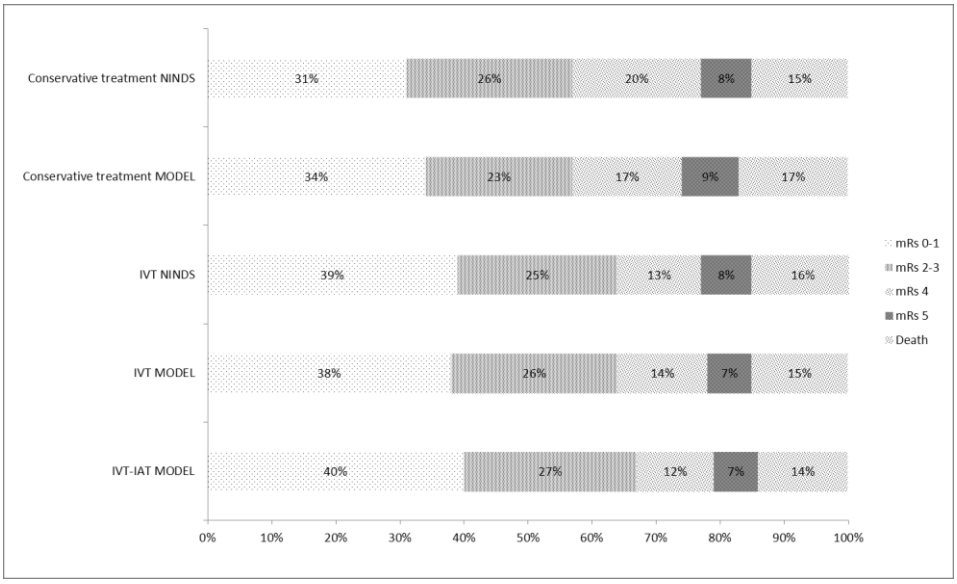

Figure 5.B Outcome distributions of the model at six months for conservative treatment and intravenous thrombolysis and reported distributions of NINDS trial

Appendix 5.C Additional information Results

Results – Base Case

At six months after initial stroke, the expected health outcome for a patient is 0.274 QALYs after conservative treatment, 0.292 QALYs after IVT, 0.298 QALYs after IAT and 0.300 QALYs after IVT-IAT. The expected costs per patient are €12,617 after conservative treatment, €12,800 after IVT, €13,003 after IAT, and €12,941 after IVT-IAT treatment.

The expected health outcome during the remaining lifetime of a patient after initial stroke is 3.39 QALYs after conservative treatment, 3.61 QALYs after IVT, 3.67 QALYs after IAT and 3.72 QALYs after IVT-IAT. The expected lifetime costs per patient are €34,182 for conservative treatment, €32,113 for IVT, €32,199 for IAT and €32,335 for IVT-IAT.

Results – Incremental cost-effectiveness ratios

We calculated all ICERs by dividing the incremental costs of IVT-IAT by the incremental QALYs of IVT-IAT compared to IVT alone. At six months, the expected health outcomes of IVT-IAT are highest, but the expected costs of IAT are highest of all strategies. When comparing both endovascular treatment strategies to the current standard treatment of IVT, we can conclude that IAT alone is dominated by IVT-IAT as the expected outcomes are higher and expected costs are lower (Table 3). The ICER of IVT-IAT versus IVT is €31,687 per QALY gained, implying that if IVT-IAT would become an available treatment for all acute ischemic stroke patients, €31,687 would have to be spent to gain one QALY after six months.

The expected lifetime costs of IAT and IVT-IAT are both lower than the expected lifetime costs of IVT and both endovascular treatment strategies have higher expected lifetime QALYs than IVT. However, IAT is not dominated by IVT-IAT as the expected costs are no longer highest for IAT but for IVT-IAT. Therefore, first the ICER of IAT versus IVT was calculated. As the expected costs of IAT are lower than the expected costs of IVT but the expected health outcomes are higher, IAT is dominant over IVT (implicating that for each QALY gained, money is saved when the new treatment is implemented). Subsequently the ICER of IVT-IAT versus IAT was calculated: €1,922 per QALY gained. Therefore, when taking a lifetime perspective IVT-IAT is the preferred treatment strategy as it produces the highest expected lifetime QALYs at acceptable costs: €1,922 will have to be spent for every QALY gained if IVT-IAT would be implemented as a standard treatment for acute ischemic stroke patients.

Chapter 6

The cost-effectiveness of drug regulation: The example of thorough QT/QTc studies

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Summary

We analyzed the cost-effectiveness of the International Conference on Harmonisation (ICH) E14 guideline that requires a thorough QT/QTc (TQT) study for all drugs under development. We compared two pharmacoeconomic scenarios: the health effects and costs resulting from implementing ICH E14 ("regulation" scenario) vs. not implementing ICH E14 ("no regulation" scenario). We used a dynamic population model to calculate the cost-effectiveness of ICH E14 for a prototype QT-prolonging antipsychotic drug entering the US and European markets. The incremental cost-effectiveness ratios of regulation vs. no regulation were ~€2.4 million per sudden cardiac death prevented and ~€187,000 per quality-adjusted life year (QALY) gained in users of antipsychotic drugs. The main driver of cost was the requirement for electrocardiogram (ECG) monitoring of users of QTc-prolonging drugs. Even when several of the assumptions in the model were varied, there were no results in favor of regulation. Our study shows that cost-effectiveness analysis of drug regulatory measures is feasible and should be considered before developing such measures.

Introduction

The pharmaceutical industry is one of the world's most intensively regulated industries. The average time between discovery and approval for a new drug is 10 to 13 years,[1] during which the quality, safety, and efficacy of the product must be demonstrated as required by all major regulatory agencies. The costs of developing and bringing a new drug to the market are high and continue to rise, although the exact costs remain disputed.[1,2] As these rising costs threaten to make the development of new drugs increasingly unaffordable, Rawlins (2004) has called for efforts to address this problem, recommending that all aspects of the drug discovery and development process be examined for potential cost savings.[3]

Restricted health-care budgets have forced governments worldwide to carefully scrutinize the cost-effectiveness of novel interventions, including drugs. A standard approach to evaluating the cost-effectiveness of health-care interventions is the quantification of health gains in terms of quality-adjusted life years (QALYs). Regulatory measures implemented to promote drug safety legitimately fall within the scope of such interventions. The costs of drug development are an integral part of the cost-effectiveness of a drug and are directly related to compliance with regulatory requirements. Therefore, regulatory measures that are not themselves cost-effective could ultimately have an adverse effect on the cost-effectiveness of new drugs. Currently, there is hardly any evidence regarding the cost-effectiveness of regulatory requirements.[4,5]

Prolongation of the QT interval in the surface electrocardiogram (ECG), which could result in potentially fatal ventricular tachyarrhythmias, most commonly torsade de pointes (TdP), was a leading cause for drug withdrawals during 1988–2001.[6] The QT interval represents the duration from the beginning of ventricular depolarization to the end of its repolarization. Drugs are a common cause of QT prolongation, but the extent of drug-induced QT interval prolongation is an imperfect marker of the proarrhythmic risk it poses clinically. However, a heart-rate corrected QTc interval of ≥500 ms is widely accepted as representing an increased risk of TdP, which could degenerate into ventricular fibrillation and result in sudden cardiac death.[7]

In 2005, the International Conference on Harmonisation (ICH) promulgated a guideline (ICH E14) aimed at characterizing the QT liability of a drug during its development. ICH E14, which calls for a "thorough QT/QTc" (TQT) study for all new drugs before approval, has been adopted by the US Food and Drug Administration, the European Medicines Agency, and the Japanese Pharmaceutical and Medical Devices Agency. ICH E14 requires the design of a TQT study to be rigorous enough to quantify the magnitude of drug-induced QT prolongation but does not necessarily imply that a QT-prolonging drug is proarrhythmic.[8]

The aim of this study was to determine, from a societal perspective, the cost-effectiveness and cost utility of ICH E14 as applied to antipsychotic drugs, including all medical costs plus drug development costs and health effects resulting from the regulation. We compared two scenarios: regulation (ICH E14 implemented) and no regulation (ICH E14 not implemented). This way, the incremental cost-effectiveness ratio (ICER) of regulation vs. no regulation could be estimated, yielding the amount society would have to pay to achieve the health gains envisaged by ICH E14.

The frequency and intensity of drug-induced QT prolongation vary between drugs. However, as a class, antipsychotic agents are particularly known to be associated with QT prolongation.[9,10] Consequently, antipsychotic drugs that enter the market are more likely to be those with a QT liability, and it is in this therapeutic class that ICH E14 can be expected to have maximum benefits in terms of cost-effectiveness. Therefore, we limit our calculation only to the effects of the regulation on the health of users of antipsychotic drugs. We also briefly comment on the implications of our findings for other therapeutic classes that include QT-prolonging drugs.

Results

Base case

On the basis of the discount rate in the Netherlands, the total discounted costs of 20 years of regulation were €715 million: 21% from TQT studies (€150 million) and 79% from ECG monitoring (€565 million). The total discounted health-care costs of no regulation (i.e., the health-care costs of sudden cardiac deaths) were €513,000. Regulation prevented 296 (discounted) sudden cardiac deaths and gained 5,317 life years and 3,819 QALYs during 20 years. The ICERs of regulation as compared to no regulation were approximately €134,000 per life year gained, €2.4 million per sudden cardiac death prevented, and €187,000 per QALY gained (**Table I**). Therefore, ICH E14 costs society €187,000 to gain one QALY and €2.4 million to prevent one drug-induced sudden cardiac death. The use of US discount rates for the calculation yielded values of approximately €169,000 ($246,000) per life year gained, €3 ($4.4) million per sudden cardiac death prevented, and €235,000 ($343,000) per QALY gained (exchange rate 1.4617; April 26, 2011). A more detailed description of the calculations used to derive these results can be found in **Appendix 6.A**.

Table I: Results

Regulatory scenario	Total costs (mil€)	SCDs prev.	LYs gained	QALYs gained	Incr costs per LY gained	Incr costs per SCD prevented	ICER
Regulation (*discount rate: costs 4%, health effects 1.5%)*	€715	296	5,317	3,819	€134,418	€2,412,749	€187,175
Costs of TQT studies	€150						
Costs of ECG monitoring	€565						
No regulation (*discount rate: costs 4%, health effects 1.5%*)	€0.6	0	0	0	-	-	-
Costs of SCDs	€0.6	0	0	0	-	-	-
Regulation (*US discount rate: costs 5%, health effects 5%)*	€673	222	3,993	2,867	€168,516	€3,024,781	€234,655
Costs of TQT studies	€150						
Costs of ECG monitoring	€523						
No regulation (*US discount rate: costs 5%, health effects 5%)*	€0.5	0	0	0			
Costs of SCDs	€0.5	0	0	0			

The incremental cost-effectiveness ratios (ICERs) of regulation compared to no regulation are reported in Euros per health effect gained. The ICER can be interpreted as the amount society will have to pay in order to gain one life year, prevent one sudden cardiac death, or gain one QALY when moving from an unregulated scenario to a regulated scenario. All total costs are discounted and summed over 20 years: e.g., the total costs of 20 years of ECG monitoring of new users are €565 million. All health effects and costs reported in this table are discounted, except the costs of TQT studies as they occur in year 0. Equation 1 was used to calculate all costs, health effects, and ICERs. Also see Supplementary Data online for explanation of the calculations. ECG, electrocardiograph; LY, life year; QALY, quality-adjusted life year; SCD, sudden cardiac death; TQT, thorough QT/QTc.

Sensitivity analyses

We performed several sensitivity analyses to determine the extent to which variations in the parameters would impact the results (**Table II**). Increasing proarrhythmic QTc prolongation to 2% resulted in lowering the ICER to €93,510 per QALY gained. Setting the number of TQT studies to 1 decreased the ICER to €148,157 per QALY gained. Decreasing the number of annual new users to 100,000 and setting the number of TQT studies to 1 changed the ICER to €150,514 per QALY gained, thereby identifying ECG monitoring as the main cost driver. We also analyzed two assumed outcomes of a virtual scenario in which compliance with ECG

monitoring is lowered by 70%: (i) health gains also decrease by 70% (ICER: €278,830 per QALY gained), and (ii) health gains decrease by only 20% (ICER: €104,464 per QALY gained). The latter outcome, corresponding to a situation in which the use of ECG monitoring is effectively restricted to individuals with risk factors for proarrhythmic QTc prolongation, would lead to preventing 80% of health losses.

Probabilistic sensitivity analysis

We performed a probabilistic sensitivity analysis to address the uncertainty surrounding various model parameters. The cost-effectiveness plane (**Figure 1**) shows the cost-effectiveness ratio for 10,000 iterations. Of these, 6.3% of ICERs were <€80,000 and 13.1% were <€100,000. Also, 28.9% of the ICERs were >€250,000 and 7.7% were >€400,000. The probabilistic sensitivity analysis shows the results to be robust to parameter uncertainty. Furthermore, the probabilistic sensitivity analysis indicates that there is an 86.9% possibility that the regulation requires society to pay more than €100,000 to gain one QALY (see **Appendix 6.A**).

Discussion

Our results indicate that the regulatory requirement for TQT studies during the clinical development of proarrhythmic drugs costs approximately €187,000 per QALY gained, a substantially higher sum than society is at present willing to pay per QALY gained for health-care programs in Europe (€20,000-80,000 per QALY).[11,12] In the United States, a threshold of $50,000– $100,000 per QALY gained is commonly cited.[13] In users of antipsychotic drugs, the health gains resulting from evaluating all drugs for their QT-prolonging properties do not outweigh the costs associated with the regulation.

We altered several parameters to demonstrate variation in the results under different assumptions in the model. None of these changes resulted in more favorable results for cost-effectiveness of the regulatory requirements, showing that although under our assumptions the model calculated maximum possible health gains for a prototype antipsychotic, changing assumptions about the regulatory scenarios is unlikely to produce favorable results.

It seems paradoxical that, although the purpose of ICH E14 is to promote drug safety and prevent drug-induced sudden cardiac deaths, if users of QT-prolonging drugs are not routinely monitored by ECG recordings, fewer sudden cardiac deaths will be prevented in clinical practice. However, our results indicate that, even for the current QTc-prolonging antipsychotics on the market, routine ECG monitoring of all new users in clinical practice is

not cost-effective: when only the costs of one TQT study and ECG monitoring are included in the analysis, the ICER for the regulation scenario remains at €148,000 per QALY gained.

Table II: Sensitivity Analysis

Parameter, base-case value	Costs per LY gained	Costs per SCD avoided	Costs per QALY gained
Base-case analysis	€ 134,418	€ 2,4 million	€ 187,175
Incidence of proarrhythmic QTc prolongation 1%			
Low estimate 0.5%	€ 268,948	€ 4,827,500	€ 374,506
High estimate 2%	€ 71,591	€ 1,205,374	€ 93,510
Costs of TQT study 1 million Euros			
Low estimate 500,000 Euros	€ 120,314	€ 2,159,580	€ 167,535
High estimate 2 million Euros	€ 162,627	€ 2,919,087	€ 226,456
Costs of ECG 20 Euros			
Low estimate 10 Euros	€ 81,258	€ 1,458,543	€ 113,150
High estimate 50 Euros	€ 293,900	€ 5,275,369	€ 409,251
3 ECGs per users	€ 187,579	€ 3,366,956	€ 261,201
Number of TQT studies performed N=150			
Low estimate N=1	€ 106,397	€ 1,909,787	€ 148,157
High estimate N=300	€ 162,627	€ 2,919,087	€ 226,456
Costs of SCD 2,500 Euros			
10-fold increase: costs 25,000 Euros	€ 133,415	€ 2,394,734	€ 185,778
Multivariate sensitivity analysis:			
New users + number of TQT studies			
Low estimate 100,000 , number of TQT studies =1	€ 108,090	€ 1,940,167	€ 150,514
30% of users 2 ECGs, 30% of SCDs avoided	€ 200,239	€ 3,594,204	€ 278,830
30% of users 2 ECGs, 80% of SCDs avoided	€ 75,020	€ 1,346,576	€ 104,464

For each sensitivity analysis, one (or two) parameters in the model were varied while all other parameters were held constant, demonstrating the impact on the incremental cost-effectiveness ratios. The base-case results (first row) are also included. ECG, electrocardiograph; LY, life year; QALY, quality-adjusted life year; SCD, sudden cardiac death; TQT, thorough QT/QTc.

It may be argued that a TQT study effectively prevents proarrhythmic drugs from ever entering the market, thereby justifying the current regulation. We did not consider potential health gains resulting from this scenario. In practice, it might be questionable whether a drug would fail to reach the market solely because of QT prolongation: it is a poor surrogate of a risk that can be managed by appropriate labeling and compliance, and the benefit/risk of a drug encompasses more than just the drug's QT-prolonging potential, as evidenced by the fact that several antipsychotics remain on the market despite their intense QT-prolonging potential.

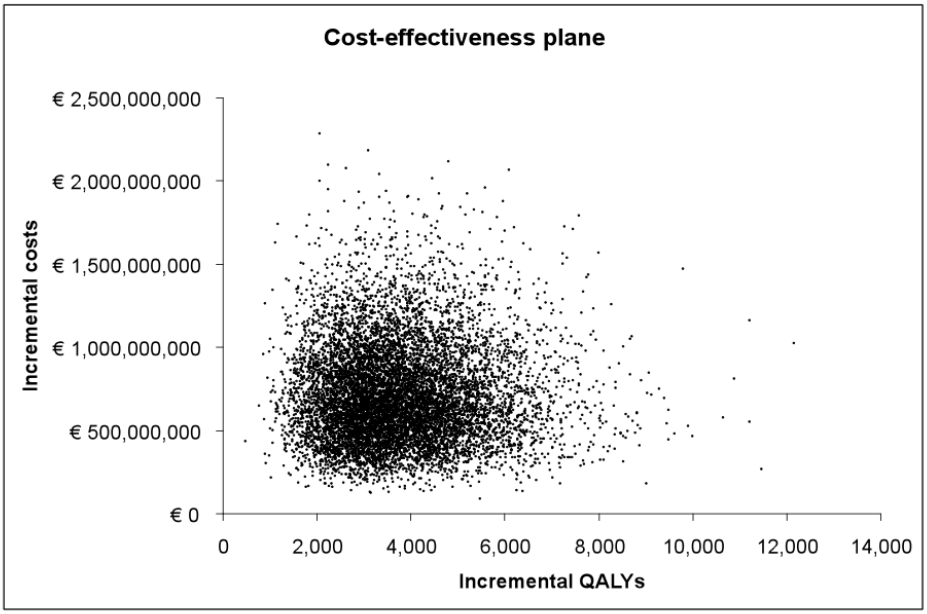

Figure 1: Cost-effectiveness plane. All iterations (10,000) are plotted in this graph. Each dot represents one ICER corresponding to one iteration. Of all ICERs, 6.3% are <€80,000 per QALY gained, 13.1% of all ICERs are <€100,000 per QALY gained. Further, 28.9% of all ICERS are >€250,000 per QALY gained and 7.7% of ICERs are >€400,000 per QALY gained. The probabilistic sensitivity analysis indicates that there is an 86.9% possibility that application of International Conference on Harmonisation (ICH) E14 will result in costs >€100,000 per QALY gained, as compared to a scenario in which ICH E14 is not applied. Abbreviations: ICER,incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The first drug to be withdrawn from the market because of its QT prolongation potential was prenylamine in 1988; this was followed by lidoflazine in 1989.[14] Between 1990 and 2006, an additional seven drugs were withdrawn from various markets because of their torsadogenic potential, as distinct from their QT-prolonging potential.[6] These drugs were developed during a period when no well-established nonclinical strategy existed to identify QT liability early and routine ECG monitoring in clinical trials was less than adequate. Now, drugs with intense QT-prolonging potential will be discarded earlier in the development process, after the results of nonclinical studies or following early-phase clinical trials when ECGs are monitored systematically.

Nevertheless, we considered a scenario in which a drug with a positive TQT study failed to reach the market, thereby potentially justifying the regulation. For this purpose we used the example of a highly potent QT-prolonging drug that was withdrawn from the market; levacetylmethadol, approved in 1997 for opiate addiction, was withdrawn in 2001.[15] Approximately 33,000 patients were exposed to the drug worldwide during 1997–2001,[16]

and the drug was withdrawn after 10 reports of ventricular arrhythmia.[15] Although no sudden cardiac deaths were reported to regulatory agencies, it is likely that some occurred. For the purpose of this scenario, we therefore assumed that all 10 cases resulted in a sudden cardiac death. The inclusion of these cases (assuming a mean QALY loss of 13 per sudden cardiac death) into the no-regulation scenario only slightly affected the cost-effectiveness of regulation: the ICER became €181,057 per QALY gained.

We did not consider the health benefits forfeited when a positive TQT study prevents an otherwise effective drug from reaching the market. In such a case, the health benefits lost would be substantial only if no alternative treatment is available for the target patient population. However, as **Figure 2** illustrates, if the health losses resulting from an effective drug not reaching the market are significant, they will further lower the total health gains of regulation.

Our study shows that the economic evaluation of drug regulation is not without challenges. Measuring patient-specific characteristics such as life expectancy and health-related quality of life (HRQL) is crucial to estimating health gains; in practice, however, such estimates will be based only on the data in the literature. In addition, if drug regulation is intended to increase health across patient populations, estimating health gains will become increasingly complex. Therefore, we propose that in such a scenario one should start by estimating regulatory cost-effectiveness for patient groups in which maximum health gains could be expected.

Our study has several limitations. The analysis should be viewed as a best-case scenario for the regulation in terms of number of users (the assumption being that all new users of antipsychotic drugs in Europe and the United States start using the prototype QT-prolonging drug) and 100% compliance with and effectiveness of ECG monitoring. In clinical practice, the compliance with monitoring recommendations is generally low.[17] In addition, as the predictive value of single ECGs recorded sporadically is believed to be well below 100%, the net effect in clinical practice is a further decrease in health gains and an increase in the costs per QALY gained (**Table II**).

Uncertainty exists regarding the estimates we used to calculate health effects: the precise incidence of drug-induced sudden cardiac death in users of antipsychotic drugs is not known. Our estimates combined the best available evidence from the literature, but it is possible that the actual incidence of drug-induced sudden cardiac death is different. Given the rarity of drug-induced sudden cardiac death, the real incidence of such deaths might be lower than our estimate. The risk of a sudden cardiac death in users of other non-cardiac QT-prolonging drugs is even lower.[18–20] Our results therefore indicate that for non-cardiac QT-prolonging drugs as well, it would not be cost-effective to perform routine ECG monitoring of all new

users in clinical practice, unless mean QALY losses resulting from drug-induced sudden cardiac death in those users would be considerably higher than QALY losses in users of antipsychotic drugs.

Off-label use of antipsychotics might account for a significant proportion of total use. Our data - encompassing a representative patient population receiving antipsychotics, including off-label use - clearly identified a significant proportion of users >65 years of age. Among users <65 years of age, variations in the underlying diagnoses are likely to exist. Because we had no information on the specific diagnoses, we assumed two different indications: serious mental illness in users <65 years and dementia in users >65 years. In clinical practice, there may be more variation in diagnoses, and therefore in quality of life and life expectancy, than is reflected in the assumptions for our model. There are alternative regulatory scenarios that we did not consider because these are beyond the scope of our study. Such alternative scenarios include restricting the requirement for a TQT study to drugs for which nonclinical and/or early phase I clinical data suggest possible QT prolongation and substituting a TQT study with adequate pharmacokinetic/pharmacodynamics monitoring in early-phase clinical pharmacology studies.[21,22] Regulatory agencies could therefore consider alternatives to the current universal requirement of TQT studies for all drugs. These alternatives, as well as new regulatory measures, should also be subjected to analyses for cost-effectiveness.

The motivation for issuing regulations relating to drug safety might go beyond the goal of achieving measurable health gains; it might also involve reassurance and comfort considerations that lie beyond the health effects captured by QALYs. This may explain the high "costs per QALY gained" that we found vis-à-vis what is considered reasonable cost-effectiveness for medical interventions. In effect, however, regulatory measures intended to promote drug safety might also entail considerable additional costs in clinical practice.

Our study highlights the need to determine acceptable levels of risks related to the use of drugs and acceptable cost-effectiveness of safety-related regulatory actions. In a world of rising healthcare expenditures and increasing drug development costs, regulatory agencies and society at large should think carefully about what they are willing to pay for reassurance with respect to drug safety to the extent of determining the magnitude of very small risks. This is particularly relevant if determining these risks does not ultimately translate into substantial health gains, or when health gains can be achieved only by spending vast amounts of money.

Methods

Comparison of regulatory scenarios

Because a cost-effectiveness analysis compares at least two policy interventions, we compared two regulatory scenarios (**Figure 2**, **Table III**). In the first scenario (no regulation), ICH E14 is not applied, and therefore TQT studies are not performed during the clinical development of the drug; as a result, QT-prolonging drugs might enter the market and their users would be at risk of drug-induced TdP and sudden cardiac death. This scenario would increase health-care costs associated with sudden cardiac death.

In the second scenario (regulation), all new drugs undergo a TQT study and an antipsychotic drug will enter the market after a TQT study has quantified its QT-prolonging potency. All new users of the QT-prolonging antipsychotic drug are assumed to undergo one baseline and one follow-up ECG. ICH E14 explicitly refers to several implications of a positive TQT study, including a label warning about the proarrhythmic risk and recommendations for ECG monitoring of patients.[8] Therefore, performing ECGs in clinical practice is both a direct result of the regulation and essential for achieving any potential health gains as a result of the regulation. We set the number of ECGs at two in our base-case analysis because this is the minimum number of ECGs necessary to detect QT prolongation. In practice, more than two ECGs may be recorded for users of QT-prolonging drugs if the dose is altered or the patient is switched to an alternative drug.

We compared the regulation scenario with the no-regulation scenario for a prototype antipsychotic; in the regulation scenario, drug-induced sudden cardiac deaths are prevented, but costs of TQT studies and ECG monitoring are incurred. We analyzed both regulatory scenarios for the combined 800 million US and European Union (EU) population.[23,24]

The items in the bold-bordered boxes in **Figure 2** are taken into account in our analysis. In our main analysis, we do not include the situation in which a positive TQT study results in a drug not reaching the market. However, we address such a scenario in the Discussion section. **Figure 2** depicts the total impact of ICH E14 on clinical drug development. Health effects are drug-specific and are expressed as patient-specific characteristics (i.e., life expectancy and HRQoL).

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Table III: Regulatory Scenarios

Scenarios	Measures	Costs	Health Effects
1: No regulation	No TQT studies will be performed	Healthcare costs SCDs	Health losses (SCDs) due to QT-prolonging drugs entering the market
2: Regulation	TQT studies mandatory for all drugs under development	Costs of TQT studies	No health losses (SCDs) due to QT-prolonging drugs entering the market
	ECG monitoring of patients taking QT-prolonging drugs that enter the market	Costs of ECG monitoring of patients	

Abbreviations: TQT thorough QT/QTc; SCD sudden cardiac death; ECG electrocardiograph.

Model

We used a dynamic population model that calculated the health effects (life years gained, sudden cardiac deaths prevented, QALYs gained) and costs (in year 2009 Euros) resulting from the regulation. Our analysis looked at effects over 20 years with a 1-year cycle length (**Figure 3**). A 20-year period was chosen as the time horizon so as not to bias the results in favor of any one scenario.[25] The model was developed in Microsoft Excel. Three sources of data were used for the model parameters: published data concerning QTc prolongation and sudden cardiac deaths, the Dutch Drug Information Database (GIP) for the number of new and total users of antipsychotics in the Netherlands in 2009 (by 10-year age groups),[26] and ClinicalTrials.gov for information on TQT studies.

Of 69 TQT studies registered with ClinicalTrials.gov, 47 were reported as "completed" at the time of the search (5 positive studies, 18 negative studies, 24 studies with no reported results). Of the 5 positive TQT studies reported, 3 involved antipsychotic drugs. The other positive studies were for pazopanib, indicated for advanced renal cell carcinoma, and granisetron, indicated for nausea caused by chemotherapy/radiation therapy. In users with diminished life expectancy associated with these conditions, health losses due to proarrhythmic QTc prolongation will be negligible.

Not all TQT studies are registered with ClinicalTrials.gov. eResearch Technology Inc (a centralized ECG laboratory that analyses TQT studies) has performed more than 150 TQT studies.[27] Therefore, we assumed that a total of 150 TQT studies had been performed by 2009 as a direct consequence of the ICH E14 regulation, and that these included all QTc-prolonging drugs entering the market.

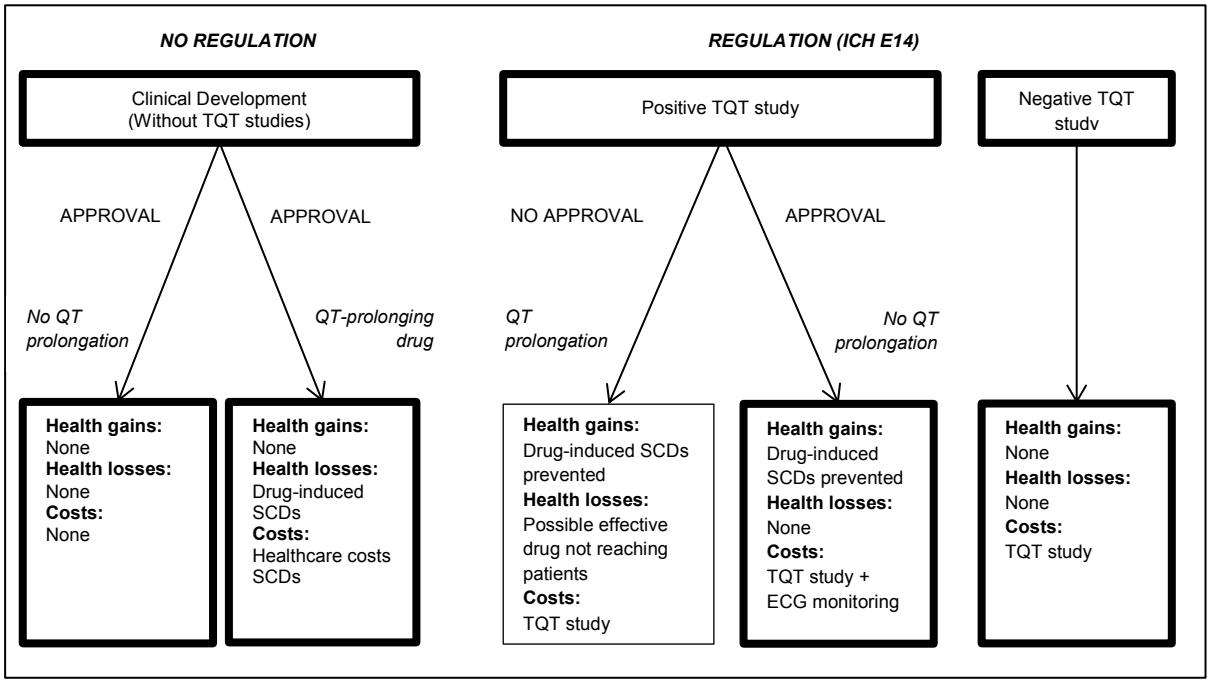


Figure 2: Impact of ICH E14 on clinical drug development. The 'No regulation' scenario illustrates that if no TQT studies are performed as part of clinical development, QT-prolonging drugs might enter the market and could cause drug-induced sudden cardiac deaths. The 'Regulation' scenario illustrates what the impact of ICH E14 is on both QT-prolonging as non-QT prolonging drugs. Abbreviations: TQT thorough QT/QTc, SCD sudden cardiac death, ECG electrocardiograph.

QTc prolongation

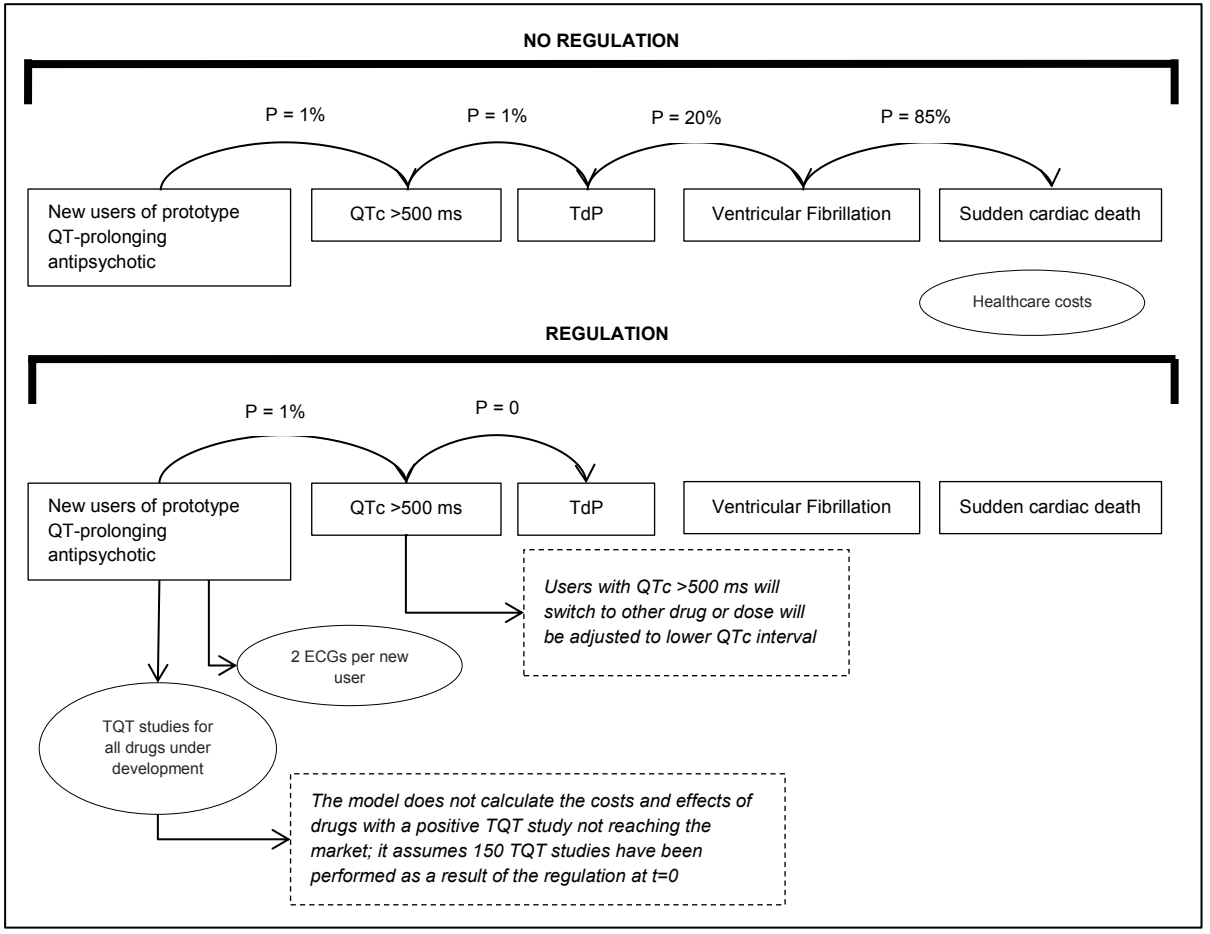
The reported proportion of patients that develop QTc prolongation while on treatment with antipsychotic drugs ranges from 0 to 38% depending on the cutoff points used in different studies.[10] QTc intervals ≤440 ms in male patients and ≤470 ms in female patients are normal, whereas a QTc interval of ≥500 ms is considered proarrhythmic.[28,29] Given that proarrhythmia is typically associated with QTc intervals ≥500 ms, this is a clinically relevant cutoff point. Using this cutoff, the incidence varied from 0% to 2%.[30] Therefore, we set the probability of proarrhythmic QTc prolongation in clinical practice at 1% in users of a QTc-prolonging antipsychotic.

TdP has a reported frequency of ~1 in 10,000 users of QTc-prolonging antipsychotics, irrespective of QTc interval.[31] We set the probability of TdP in users with proarrhythmic QTc prolongation at 1%. TdP is usually self-terminating: approximately 20% of cases develop into ventricular fibrillation, which has a mortality rate of 85% (**Figure 3**, **Table IV**).[31–33]

Characteristics of new users

The model calculated health effects for the population of new users of antipsychotic drugs—those who had received at least one prescription for any antipsychotic during the previous one year but who had not received a prescription for any antipsychotic drug in the nine months preceding that prescription—in Europe and the United States. Antipsychotic drugs are typically prescribed for schizophrenia, schizoaffective disorder, and other serious mental illnesses. The total number of users of antipsychotic drugs in the Netherlands in 2007 was 258,130 (population 16.4 million, 1.6% of the population),[26] and the number of users in the United States in 2007 was 3.9 million (population 285.5 million, 1.4% of the population),[34] showing similar prevalence of antipsychotic drug use.

Figure 3 : Outline of the dynamic population model. Abbreviations: ms milliseconds, TQT thorough QT/QTc study ECG electrocardiograph. A rectangular box denotes a health effect, an oval box denotes costs, a dashed box denotes explanation. In the no regulation scenario, a prototype QTc prolonging antipsychotic (without its proarrhythmic liabilities being characterized during clinical development) is introduced and all annual new users in Europe and the US (1 million) will start using the prototype antipsychotic. Of those new users, 1% will develop a QTc interval >500 ms. 1% of cases of proarrhythmic QTc prolongation will develop into TdP, which in 20% of cases will lead to ventricular fibrillation which is fatal in 85% of cases. Annual estimated incidence of a drug-induced sudden cardiac death in antipsychotic users = 17 per 1 million users. In the regulation scenario, TQT studies are performed for all drugs under development (150 during 2003-2009). Therefore a prototype QTc prolonging antipsychotic is introduced and all annual new users in Europe and the US (1 million) will start using the prototype antipsychotic. All new users will undergo 2 ECGs to detect proarrhythmic QTc prolongation. All users with QTc >500 ms will switch to other drug or dose will be adjusted to lower QTc interval <500 ms. The model assumes 100% effectiveness and compliance of ECG monitoring leading to the regulation being 100% effective in preventing drug-induced sudden cardiac deaths. Cycle length is 1 year. Model duration is 20 years.


NO REGULATION
P = 1%
P = 1%
P = 20%
P = 85%
New users of prototype QT-prolonging antipsychotic
QTc >500 ms
TdP
Ventricular Fibrillation
Sudden cardiac death
Healthcare costs
REGULATION
P = 1%
P = 0
New users of prototype QT-prolonging antipsychotic
QTc >500 ms
TdP
Ventricular Fibrillation
Sudden cardiac death
Users with QTc >500 ms will switch to other drug or dose will be adjusted to lower QTc interval
2 ECGs per new user
TQT studies for all drugs under development
The model does not calculate the costs and effects of drugs with a positive TQT study not reaching the market; it assumes 150 TQT studies have been performed as a result of the regulation at t=0

In 2009, 22,535 persons started using antipsychotics in the Netherlands (9% of the total users).[26] Extrapolating from this ratio, we assumed approximately 1 million new users in Europe and the United States in 2009. We made the assumption that the risk of proarrhythmic QTc prolongation exists only in the first year after drug use is started: patients who develop TdP on a QT-prolonging drug usually do so within the first year after commencing use.[28,35]

On average, patients with serious mental illness live 25 years less than the general population.[36–38] Therefore, we set 65 years as the total life expectancy of users of antipsychotic drugs, with an HRQoL of 0.74 (**Table IV**).[39] We used new-user data to estimate the weighted (by age distribution) QALY loss from sudden cardiac death. To avoid underestimation of the health effects, we set life expectancy at 70 years for users currently between 45 and 65 years of age. New users were unevenly distributed among age groups: one-third of them were >65 years of age. The likelihood of dementia developing into psychosis or agitation, often requiring treatment with antipsychotic drugs, is 60–80%.[40] We therefore assumed that new users >65 years of age were patients with dementia. We set the mean total life expectancy at 76.7 years for the 64–74 age group and 83 for those ≥75 years of age (**Table IV**).[41] The mean HRQoL of the older group was 0.50.[42] Combining these estimates, a sudden cardiac death in the unregulated scenario entails an average health loss of 17.9 life years and 12.9 QALYs (life years corrected for HRQoL).

Costs

The costs of a TQT study are hardly ever reported in the literature; they vary depending on design, timing, and location of the study and can cost up to €2–4 million. We set a conservative mean cost of one TQT study at €1 million.[43] The cost of an ECG is $35–50 in the United States[44] and €20 in the Netherlands.[45] We therefore set the cost of one ECG at €20. Health-care costs (pre-hospital, ambulance, emergency room, in-hospital) were set at €2,500 per sudden cardiac death.[46]

Table IV: Parameter estimates

Parameter	Value	Range	Distribution	Source
Proarrhythmic QTc prolongation	0.01	0.002 - 0.02	Beta	[10,30]
TdP	0.01	-	-	[31]
VF	0.2	-	-	[31,32,33]
SCD	0.85	-	-	[33]
Cost per TQT study	€1,000,000	€150,000 – €2.7 million	Gamma	[33,35]
Cost per ECG	€ 20	€3.5 - €66	Gamma	[36]
Number of TQT studies performed 2003-2009	150	-	-	[27]
Healthcare costs SCD	€ 2,500	€280 - €10,200	Gamma	[37]
Number of ECGs per patient	2	-	-	-
Life expectancy user <65 years	65	49 - 82	Normal	[38,39,40]
Life expectancy user 45-65 years	70	54 - 89	Normal	-
Total life expectancy user >65 years	76.7	57 - 93	Normal	[41]
Total life expectancy user >75 years	83	66 - 101	Normal	[41]
HRQOL user <65 years	0.74	0.58 - 0.86	Beta	[42]
HRQOL user antipsychotic >65 years	0.5	0.35 - 0.64	Beta	[43]
Weighted life years lost per SCD	17.9	-	-	Computed
Weighted QALY loss per SCD	12.9	-	-	Computed

Abbreviations: TdP Torsade de pointes, VF ventricular fibrillation, SCD sudden cardiac death, TQT thorough QT/QTc, ECG electrocardiograph, HRQOL health-related quality of life, QALY quality-adjusted life year. The weighted life years lost and QALY losses are weighted by the distribution of number of users per age group. All ranges and distributions refer to the parameters that were made probabilistic for the probabilistic sensitivity analysis. See online-only supplement for a more detailed explanation of the probabilistic sensitivity analysis and the distributions used.

Sensitivity analyses

We used univariate, bivariate, and probabilistic sensitivity analyses to demonstrate the impact of varying model parameters on our results. The costs of a TQT study were varied to demonstrate the impact of a lower (€500,000) or higher (€2 million) cost per TQT study. The total number of TQT studies performed was varied from one to 300. One TQT study reflects a model assumption in which only the TQT study performed for our prototype antipsychotic is a relevant cost. This could be the case if a strategy could be developed to effectively target only drugs that need a TQT study, rather than all drugs under development. A total of 300 TQT studies carried out during 2003–2009 was chosen as the upper limit, given that our base-case estimate (150 TQT studies) is a conservative one. ECG costs were varied from a low estimate of €10 to a higher estimate of €50 to reflect possible cost differences between the

United States and Europe. Healthcare costs of a sudden cardiac death were increased to €25,000 to reflect possible differences in costs between Europe and the United States. The percentage of users with QTc prolongation was varied between 0.5 and 2% to reflect the impact of proarrhythmic potential on the results. The annual number of new users was lowered to 100,000, which might reflect a more realistic number of annual new users of a specific antipsychotic drug, given that several antipsychotic drugs are licensed for use in Europe and the United States. The base-case of the maximum number of new users is 1 million, per user data from the Netherlands and the United States. We lowered compliance with ECG monitoring (base-case 100%) to 30% of users, which is a more realistic compliance rate in clinical practice. We also lowered compliance with ECG monitoring to 30% while simultaneously simulating the avoidance of 80% of sudden cardiac deaths. This last analysis reflects a scenario in which the effective identification of each individual patient's risk factors for QTc prolongation would result in preventing 80% of all drug-induced sudden cardiac deaths.

Cost-effectiveness ratios

The ICERs[47] are given by

$$ICER = \frac{\left(\left(\sum_{t=0}^{T} \frac{C_{reg}}{(1+r)^{t-1}}\right) + C_{tqt}\right) - \sum_{t=0}^{T} \frac{C_{noreg}}{(1+r)^{t-1}}}{\sum_{t=0}^{T} \frac{H_{reg}}{(1+r)^{t-1}} - \sum_{t=0}^{T} \frac{H_{noreg}}{(1+r)^{t-1}}} \quad (1)$$

where C_{reg} are annual costs of regulation; C_{tqt} are the costs of TQT studies at t = 0 (cycle length = 1 year); C_{noreg} are the costs in the no-regulation scenario; H_{reg} (for regulation) and H_{noreg} (for no regulation) are the annual health effects in life years gained, sudden cardiac deaths prevented or QALYs gained; r is the discount rate. The total costs for each of the scenarios are calculated by summing all costs over 20 years. The total health effects are also calculated by summing all health effects over 20 years. In our calculations, we used the discount rate in the Netherlands: 1.5% for health effects and 4% for costs.[48] We also report results calculated using the US discount rate of 5% for both health effects and costs.[49]

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Appendix 6.A: Additional information results

Model assumptions

Time horizon

A 20-year time horizon was chosen in the model. In cost-effectiveness analysis, the choice of time horizon should not bias the analysis in favor of one intervention over the other.[1] The costs of performing thorough QT/QTc (TQT) studies occur in year 0 while the costs of ECG monitoring occur during year 1-20 and the health benefits also occur during year 1-20. As it is reasonable to assume a new antipsychotic entering the market (given that it is not withdrawn) will remain on the market and will be used for several years, choosing a short-term perspective (e.g. 5 years) would weigh the regulation costs more heavily as health benefits occurring further in the future would be discarded.

Incremental cost-effectiveness ratios

The incremental cost-effectiveness ratio (ICER) is calculated as follows: the sum of all costs of regulation is subtracted by the sum of all costs of no regulation. Also, the sum of all health benefits of regulation is subtracted by the sum of all health benefits of no regulation. Consequently, the difference in costs is divided by the difference in health benefits. The ICER in costs per quality-adjusted life year (QALY) gained can be interpreted as follows: if the regulation is implemented, this is the amount society will have to pay in order to gain one QALY. The ICER in costs per sudden cardiac death avoided can thus be interpreted as follows: if the regulation is implemented, this is the amount society will have to pay to prevent one drug-induced sudden cardiac death.

The incremental cost-effectiveness ratios (ICER) are given by

$$ICER = \frac{\left(\left(\sum_{t=0}^{T} \frac{C_{reg}}{(1+r)^{t-1}}\right) + C_{tqt}\right) - \sum_{t=0}^{T} \frac{C_{noreg}}{(1+r)^{t-1}}}{\sum_{t=0}^{T} \frac{H_{reg}}{(1+r)^{t-1}} - \sum_{t=0}^{T} \frac{H_{noreg}}{(1+r)^{t-1}}}$$

where C_{reg} are annual costs of regulation; C_{tqt} are the cost of TQT studies at t=0 (cycle length=1 year); C_{noreg} are the costs in the no regulation scenario; H_{reg} for regulation and H_{noreg} for no regulation are the annual health effects in life years gained; sudden cardiac deaths prevented or QALYs gained; r is the discount rate. We used the Dutch discount rate of 1.5% for

health effects and 4% for costs and also report results with the US discount rate of 5% for both health effects and costs.
In the model, 1 million new users enter the unregulated scenario as antipsychotic users each year. Of those users, 17 per 1 million users will die from a drug-induced sudden cardiac death. Healthcare costs of a sudden cardiac death occur in this scenario.

In the regulation scenario, 1 million new users enter the model each year. All new users undergo two ECGs to rule out proarrhythmic QT prolongation. Users who develop proarrhythmic QTc prolongation are either switched to a non-QT-prolonging drug or the dose is lowered. It is assumed that the ECG monitoring is 100% effective: no drug-induced sudden cardiac deaths occur in this scenario. Costs of TQT studies do occur as costs of ECG monitoring.

The model calculates all costs and health benefits in each scenario, over the total time horizon of 20 years. In the no regulation scenario no health benefits occur, as no drug-induced sudden cardiac deaths are prevented.

Quality-adjusted life years

A QALY is a measure of health that is calculated by correcting the life expectancy of a person for the health-related quality of life that person will spend his or hers life in. For example, if an antipsychotic user of 60 years has a life expectancy of 70, that person is expected to live for 5 more years. However, if the user's health-related quality of life (where a value of one (maximum) is equal to full health, and any health state lower than one corresponds with a health state not equal to full health, with a value of 0 representing death) is 0.50, then the number of QALYs is 5*0.50=2.5 QALYs. One QALY can therefore be interpreted as one life year of full health.

Probabilistic sensitivity analysis (PSA)

In a PSA, several or all model parameters are given a distribution with a mean value and standard deviation. A PSA is performed to explore the uncertainty surrounding the model parameters. It shows the impact on the results when the model parameters are not fixed but are varied. Given the different parameter distributions, a total of 10,000 iterations are performed. During each iteration, a random value is drawn for the provided distribution for each parameter. Consequently, the incremental costs and effects are calculated. This results in 10,000 different ICERs, one corresponding with each iteration. The results of the PSA can be seen in the cost-effectiveness plane (**Figure 1**). Clearly, the variation in the model parameters results in different ICERs. Usually, patient-level data is used to fit distributions for parameters in a PSA. As our parameters were estimates from the literature, we felt it was not

appropriate to fit the distributions for the moments reported in some of the sources as this would address solely the uncertainty of the underlying sample in the source of our estimate and not the uncertainty of our model. Therefore we fitted the parameter distributions to wide ranges for all parameters.

Cost parameters

All cost parameters were assumed to follow a gamma distribution which can range from 0 to positive infinity. The gamma distribution can be expressed as functions of these parameters: $\vartheta \sim \text{gamma}(\alpha,\beta)$ with mean=$\alpha\beta$ and variance $s^2 = \alpha\beta^2$. For all cost parameters, the mean was the estimate reported in **Table IV** and for all parameters a standard deviation of ½ mean was taken as to allow for a wide distribution range.

Health effects parameters

For all life expectancy values we assumed a normal distribution with a standard deviation of 5 years. The ranges (the lowest and highest values reported for all iterations) can be found in **Table IV**. It is a pragmatic approach to fit a beta distribution (constrained from 0 to 1) for utilities not close to 0.[2] Therefore we assumed a beta distribution for the two utilities in the model: $\vartheta \sim \text{beta}(\alpha,\beta)$ with mean $\alpha/(\alpha+\beta)$ and variance $(\alpha\beta)/(\alpha+\beta)^2(\alpha+\beta+1)$. For the health state with a value of 0.74 we assumed α=74 and β=26. The lowest and highest values for all iterations were 0.58 and 0.86. For the health state with a value of 0.50 we assumed α=50 and β=50. The lowest and highest values for all iterations were 0.35 and 0.64. For the probability of proarrhythmic QT prolongation we used a beta distribution as is standard for probabilities.[2] We assumed α=10 and β=999. The parameter ranged from 0.002 to 0.02 for all iterations.

PSA results

The cost-effectiveness plane which depicts the ICERs resulting from the 10,000 iterations can be found in **Figure 1**. Of the 10,000 iterations, 6.3% of ICERs were below €80,000 and 13.1% were below €100,000 per QALY gained. In other words, based on the uncertainty surrounding our estimates, there is a 86.9% that the real incremental cost-effectiveness of ICH E14 is higher than €100,000 per QALY gained.

Furthermore, the PSA results also show that 28.9% of the ICERs are above €250,000 per QALY gained and 7.7% of ICERs are above €400,000 per QALY gained. This indicates that it is likely that ICH E14 is not cost-effective compared to not implementing ICH E14.

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Chapter 7

The cost-effectiveness of Periodic Safety Update Reports (PSURs) for biologicals

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Summary

We analyzed the cost-effectiveness of all periodic safety update reports (PSURs) submitted for biologicals in Europe from 1995 to 2009. We evaluated two regulatory scenarios: Full Regulation (PSUR reporting) and Limited Regulation (no PSUR reporting). PSUR reporting during the period revealed two urgent safety issues for biologicals: (i) distant spread of botulinum toxin and (ii) edema/fluid collection from off-label use of dibotermin-alfa. We used Markov-chain life tables to calculate effects of PSURs. The incremental cost-effectiveness ratio of full versus limited regulation for the base-case scenario was €342,110 per quality-adjusted life year gained. Results indicate that PSUR reporting costs are unlikely to outweigh their health gains.

Introduction

The benefit-risk profile of new medicinal products in real-life patient populations is usually not fully established upon market entry, giving cause for Europe's comprehensive pharmacovigilance system.[1] The main pillar of pharmacovigilance has historically been the voluntary reporting of adverse drug reactions (ADRs) in the scientific literature and national reporting schemes such as the United Kingdom's "yellow card." In recent decades, the pharmacovigilance toolkit has been complemented with post-authorization safety studies (PASS).[2] A key regulatory vehicle to communicate the outcomes of pharmacovigilance activities deployed by a product's marketing authorization holder (MAH) is the Periodic Safety Update Report (PSUR), which summarizes a product's worldwide safety data and facilitates periodic assessment of its benefit-risk profile.[3] MAHs are obligated to submit a PSUR every six months during the first two years after marketing authorization, annually through years 3 to 5, and every three years for the remaining life-cycle of the product, or if requested by regulatory authorities.[4] If a new safety issue is identified, several regulatory actions can be taken: new safety information can be added to the product's summary of product characteristics (SPC) through so-called 'Type II variations', a Direct Healthcare Professional Communication (DHPC) can be sent to physicians to alert them of the safety issue, or a product's marketing license may be suspended or revoked.

In most Western countries, rising healthcare expenditures have resulted in increasing pressure regarding cost containment. Health Technology Assessment is an established tool to assess the added value of new healthcare technologies, but has also been demonstrated a feasible approach to the evaluation of drug regulatory requirements.[5] A regulatory cost-effectiveness analysis can assess whether drug regulation provides value for money.[6] PSURs result in considerable expenditure; an average MAH submits more than 100 PSURs annually and a single PSUR costs up to €28,000.[7,8] The total number of submitted PSURs throughout the European Economic Area (EEA) in 2004 was over 17,000.[8] Whether the costs associated with preparing and assessing PSURs are justified by the health gains they generate requires assessing the effectiveness, or cost-effectiveness, of PSURs. Because of the large number of PSURs that are annually submitted throughout the European Union (EU), we included a selection of all marketed products in Europe. A previous study analyzed the outcome of PSUR evaluations of all biologicals centrally authorized in the EU.[9] Therefore, we assessed the cost-effectiveness of all PSURs submitted during 1995-2009 for biologicals, using a societal perspective.

Results

Base-case scenario

Ebbers et al. reported that of all the DHPCs issued in the EU for biologicals between 1995 and 2009, PSURs contributed to the identification of two urgent safety issues: distant spread of botulinum toxin and edema/fluid collection after off-label use of dibotermin-alfa.[10] The total estimated costs of full regulation were €44,748,955 and total quality-adjusted life years (QALYs) for the scenario were 434,605. The total estimated limited regulation costs were €31,298,691 with QALYs of 434,566 (**Table I**). The incremental cost-effectiveness ratios (ICERs) were calculated as follows:

$$ICER = \frac{\sum_{t=0}^{T} costs\ Full\ Regulation - \sum_{t=0}^{T} costs\ Limited\ Regulation}{\sum_{t=0}^{T} QALYs\ Full\ Regulation - \sum_{t=0}^{T} QALYs\ Limited\ Regulation} \quad (1)$$

The total incremental costs of regulation versus limited regulation were €13,450,264 and total incremental QALYs were 39. The ICER of full regulation versus limited regulation for the base-case scenario (with assumed risk reduction of 25%) was €343,110 per QALY gained (not discounted; see Methods). The total societal (direct and indirect) costs that were prevented by the full regulation scenario were €1,807,104, but the additional total regulatory costs of full regulation were €15,257,368.

Discounting costs and effects starting in 1995 resulted in an ICER of €335,802 versus €366,524 when discounting from 2012 onwards. A scenario in which the European Medicines Agency (EMA) fees were used as PSUR cost estimates (1995-2009, corrected for inflation) resulted in an ICER of €1,192,362. When only direct costs (regulatory and healthcare) were taken into account, the ICER was €359,566. A scenario in which the pharmacovigilance system under limited regulation was assumed to be more effective than the base-case scenario (safety issues were detected after 2.5 years instead of 5 years) resulted in an ICER of €775,408 because the incremental costs remained unchanged and the incremental effects decreased from 39 (base-case) to 19 QALYs.

Table I: Results cost-effectiveness analysis

FULL REGULATION		LIMITED REGULATION		Incremental costs & effects	ICER
Base case					
Total PSUR costs	€ 15,257,368	Total PSUR costs	€ 0		
Total botulinum toxin costs	€ 29,360,140	Total botulinum toxin costs	€ 31,158,644		
Total rhBMP-2 costs	€ 131,447	Total rhBMP-2 costs	€ 140,048		
Total costs	**€ 44,748,955**	**Total costs**	**€ 31,298,691**	€ 13,450,264	
Total QALYs botulinum toxin	352,057	Total QALYs botulinum toxin	352,019		
Total QALYs rhBMP-2	82,548	Total QALYs rhBMP-2	82,547		
Total QALYs	**434,605**	**Total QALYs**	**434,566**	39	**€ 343,110**
Healthcare perspective					
Total PSUR costs	€ 15,257,368	Total PSUR costs	€ 0		
Total botulinum toxin costs	€ 18,899,056	Total botulinum toxin costs	€ 20,056,808		
Total rhBMP-2 costs	€ 64,792	Total rhBMP-2 costs	€ 69,036		
Total costs	**€ 34,221,217**	**Total costs**	**€ 20,125,844**	€ 14,095,373	
Total QALYs botulinum toxin	352,057	Total QALYs botulinum toxin	352,019		
Total QALYs rhBMP-2	82,548	Total QALYs rhBMP-2	82,547		
Total QALYs	**434,605**	**Total QALYs**	**434,566**	39	**€ 359,566**
Detection safety issues more effective (2.5 years)					
Total PSUR costs	€ 15,257,368	Total PSUR costs	€ 0		
Total botulinum toxin costs	€ 29,360,140	Total botulinum toxin costs	€ 30,143,329		
Total rhBMP-2 costs	€ 131,447	Total rhBMP-2 costs	€ 134,752		
Total costs	**€ 44,748,955**	**Total costs**	**€ 30,278,081**	€ 14,470,874	
Total QALYs botulinum toxin	352,057	Total QALYs botulinum toxin	352,039		
Total QALYs rhBMP-2	82,548	Total QALYs rhBMP-2	82,547		
Total QALYs	**434,605**	**Total QALYs**	**434,586**	19	**€ 775,408**

Table I continued					
Discounting, 1995=t0					
Total costs	€ 25,147,927	Total costs	€ 15,440,860	€ 9,707,067	
Total QALYs	321,651	Total QALYs	321,623	29	**€ 335,802**
Discounting, 2012=t0					
Total costs	€ 40,165,968	Total costs	€ 26,716,128	€ 13,449,840	
Total QALYs	401,294	Total QALYs	401,257	37	**€ 366,524**
With EMA fees for regulation costs					
Total costs	€ 78,040,527	Total costs	€ 31,298,691	€ 46,741,835	
Total QALYs	434,605	Total QALYs	434,566	39	**€ 1,192,362**

Assumption base-case: risk reduction 25% for both safety issues. PSUR, periodic safety update report, rhBMP-2, recombinant human bone morphogenetic protein-2,
Abbreviations: QALY, quality-adjusted life year, ICER, incremental cost-effectiveness ratio

Table II: Sensitivity analyses

Parameter	Lower value:	Higher values:			
PSUR-related parameters					
Risk reduction *(25%)*	**10%**	**50%**	**70%**	**90%**	**100%**
ICERs:	€ 927,668	€ 148,250	€ 92,572	€ 61,636	€ 50,808
Costs Regulator hour *(€49)*	**€ 25**	**€ 75**	**€ 100**		
ICERs:	€ 329,620	€ 357,724	€ 371,775		
Costs of small PSUR *(€6,000)*	**€ 3,000**	**€ 12,000**			
ICERs:	€ 310,294	€ 408,741			
Costs of medium PSUR *(€14,000)*	**€ 7,000**	**€ 28,000**			
ICERs:	€ 313,845	€ 401,639			
Costs of large PSUR *(€28,000)*	**€ 14,000**	**€ 56,000**			
ICERs:	€ 224,357	€ 580,616			
Botulinum toxin parameters					
Probability mild botulism *(0.4%)*	**0.04%**	**0.60%**	0.80%	**1.00%**	
ICERs:	€ 379,134	€ 325,563	€ 309,496	€ 294,729	
Probability moderate botulism *(0.09%)*	**0.009%**	**0.15%**	**0.20%**	**0.40%**	
ICERs:	€ 424,511	€ 298,770	€ 268,793	€ 187,182	
Probability severe botulism *(0.01%)*	**0.001%**	**0.02%**	**0.05%**	**0.10%**	
ICERs:	€ 964,310	€ 186,994	€ 160,243	€ 13,304	
rhBMP-2 parameters					
Use of rhBMP-2 *(1%)*	**0.1%**	**10%**	**20%**	**30%**	
ICERs:	€ 353,070	€ 267,239	€ 214,011	€ 178,079	
Probability of edema *(1%)*	**0.1%**	**5%**	**10%**	**20%**	
ICERs:	€ 353,070	€ 267,239	€ 214,011	€ 178,079	
Probability of hospitalization *(30%)*	**1%**	**10%**	**60%**	**90%**	
ICERs:	€ 353,831	€ 350,434	€ 332,669	€ 322,834	
Costs operation *(€1,094)*	**€ 600**	**€ 2,200**	**€ 5,000**	**€ 10,000**	
ICERs:	€ 343,128	€ 343,068	€ 342,964	€ 342,777	

The base case values for all parameters are given in brackets. For each sensitivity analysis, the value of one parameter in changed and the corresponding new ICER is reported. Abbreviations: PSUR periodic safety update report; ICERs incremental cost-effectiveness ratios; rhBMP-2 recombinant bone morphogenetic protein.

Sensitivity analysis

We performed univariate sensitivity analyses for all key model parameters (**Table II**). Only two produced ICERs in a range that could be considered cost-effective: (i) a risk reduction (base-case: 25%) of 100% (ICER: €50,808 per QALY), or (ii) a probability of 0.1% per botulinum toxin injection of severe botulism (base-case: 0.01%) (ICER: €13,304 per QALY). All other

sensitivity analyses did not result in favorable cost-effectiveness at a €100,000 per QALY threshold except for percentage risk reductions, which produced an ICER of €92,572 per QALY at 70% and an ICER of €61,636 per QALY at 90%. The risk parameters for mild (base-case: 0.4%) and moderate (base-case: 0.09%) botulism had little effect: at a probability of 1% for mild botulism the ICER became €294,729 per QALY gained and at a probability of 0.4% for moderate botulism the ICER became €187,182 per QALY gained.

We also performed a probabilistic sensitivity analysis (PSA), in which all parameters are varied together by fitting a distribution to the parameters and performing a Monte-Carlo simulation with 10,000 iterations (**Figure 1**, **Appendix 7.A**). Nearly 96% (95.7%) of the iterations resulted in ICERs with positive incremental effects and positive incremental costs. A small number (0.01%) of the iterations resulted in positive incremental effects and negative incremental costs; 4.2% of the iterations resulted in positive incremental costs and negative incremental effects, even though the risk reduction parameter was positive in all iterations. The utilities fitted to the disease states in the life-tables were, however, also made probabilistic, which in some iterations resulted in a lower assigned utility for disease states which are assumed to have a higher utility in the base-case scenario. This issue cannot be resolved by fitting less wide distributions, because doing so would falsely reflect less uncertainty. Of the 95.7% iterations with positive incremental costs and effects, only 1.2% resulted in an ICER of <€50,000 per QALY gained and 3.3% resulted in an ICER of <€80,000 per QALY gained.

Discussion

Our results indicate that PSUR reporting for biologicals during 1995-2009, when compared to a regulatory scenario in which PSUR reporting would not have been mandatory, resulted in an incremental cost-effectiveness of about €343,110 per QALY gained. Although no explicit maximum willingness to pay threshold exists for healthcare interventions, different thresholds have been applied for reimbursement decisions varying from £30,000 per QALY in the United Kingdom, €80,000 per QALY in the Netherlands (with high disease severity), and $50,000-$100,000 in the US. All these thresholds are considerably lower than our base-case estimate. Sensitivity analyses indicate that the incremental cost-effectiveness of PSUR reporting for biologicals had been more favorable if the risk reduction of the two urgent safety issues had been 100% effective, or if the risk of severe botulism following botulinum toxin injections had been 10-fold higher than our estimate (1 per 1,000 patients per injection as opposed to 1 in 10,000 patients per injection in the base-case analysis). PSUR reporting did result in lower healthcare costs and more health, yet the total costs of compliance with PSUR reporting far outweigh the beneficial outcomes. The PSA furthermore indicates, albeit

considerable uncertainty surrounding our model estimates and assumptions, a slim likelihood that PSUR reporting for biologicals would be cost-effective.

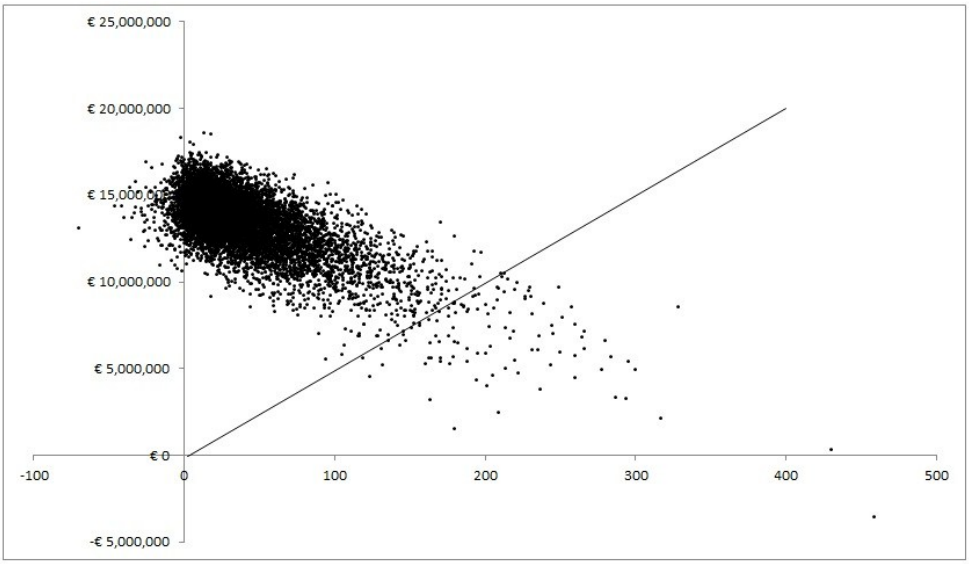

Figure 1. Cost-effectiveness plane. The results of the Monte-Carlo simulation (10,000) iterations are plotted in this graph. Each iteration resulted in an incremental cost-effectiveness ratio (ICER). The line indicated the threshold of 50,000 per QALY gained.

In our analysis, we conservatively assumed that, had PSUR reporting not been deployed for biologicals during 1995-2009, both urgent safety issues would have gone unnoticed for another five years. It might be, however, that these safety issues would have been identified through other pharmacovigilance instruments, most notably, the scientific literature or national pharmacovigilance centers. The new pharmacovigilance legislation mandates that EMA and national authorities will become responsible for periodic signal detection through screening spontaneous reports and literature case reports.[11] For both safety issues, case reports had emerged in the literature years before the respective DHPCs were issued. A sensitivity analysis, in which the period of detecting the safety issues between the two regulatory scenarios was set to 2.5 years instead of 5 years, resulted in an ICER of €775,408 per QALY gained, since the incremental effects do not change compared to the base-case scenario yet the health effects decrease. Furthermore, the effectiveness of PSURs is determined by the risk reduction achieved in clinical practice. This stipulates the need for effective strategies to not only communicate an identified risk to the medical community, but to also change prescribing and treatment behavior.

Our study has several limitations. A major challenge has been to find empirical estimates for all required model parameters to perform a cost-effectiveness analysis. We systematically searched the scientific literature but in some cases we had to resort to expert opinion. This resulted in considerable uncertainty regarding some model parameters. We performed extensive sensitivity analyses varying model parameters and assumptions to determine how these variations changed our results. Only two model parameters (risk reduction after the safety issues are detected and the risk of severe botulism) resulted in an ICER below a €50,000 per QALY threshold. We estimated the number of botulinum toxin users in the European Union (EU) to be 18,081 in 2001, based on the number of cervical dystonia patients and the percentage of patients treated. We did not take other therapeutic indications into account, for three reasons: (i) the indication for the botulinum toxin product approved in 2001 was for cervical dystonia patients only, (ii) the DHPC explicitly stated that the risk of iatrogenic botulism existed at therapeutic doses only (as opposed to cosmetic use), and (iii) health utilities are indication-specific. There are, however, other therapeutic indications for botulinum toxin products (**Appendix 7.B**). The ICER was €96,683 per QALY gained when we increased the total number of patients to 50,000, and €25,085 per QALY gained when increased to 100,000.

For regulatory costs, we included only the hours spent on PSUR assessment in our base-case analysis. Recently, the EMA proposed new PSUR-assessment fees, covering all costs related to PSUR assessment. If these proposed fees are truly representative of the regulator cost for a single PSUR assessment, the ICER would become more than €1 million per QALY gained, and therefore much more unfavorable than the base-case results.

We used several estimates for the Netherlands (hospital costs, productivity costs, spinal fusions performed annually) that we extrapolated to the EU-27 population. Regional cost and clinical practices differ between countries. Although regional costs and clinical practices differ, we did not find empirical evidence of large differences between countries. We cannot, however, exclude the possibility that rhBMP-2 (recombinant human bone morphogenetic protein-2; following the scientific literature we use this name for Dibotermin-alfa) is used more often in some countries or that the risk of iatrogenic botulism varies across regions.

A PSUR summarizes worldwide safety data. For rhBMP-2, usage levels in spinal fusions (both on- and off-label) were much higher in the US than in Europe. Although sensitivity analysis demonstrated that even at US usage rates (in 30% of spinal fusions), the ICER remained €178,079 per QALY gained, it illustrates that the cost-effectiveness of PSURs in preventing urgent safety issues depends on the total population at risk.

It is possible that PSUR reporting has contributed to identifying more than the two urgent safety issues for biologicals identified by Ebbers et al.[10] The cost-effectiveness of PSUR

reporting would increase with the number of urgent safety issues detected, provided that a substantial risk reduction would have followed a DHPC and that measures to reduce the ADR risk would not invoke substantial healthcare costs. Additionally, we disregarded all instances in which PSURs identified non-urgent safety issues (Type II variations); in such cases PSURs were more often the source of regulatory action.[10]

More stringent regulatory requirements are regarded as a barrier to drug innovation and driver of research and development costs.[12,13] Healthcare systems are under growing cost pressure and therefore regulatory requirements should be assessed for their capacity to increase drug safety in a cost-effective manner. Our results indicate that it is unlikely that PSUR reporting for biological during 1995-2009 has been cost-effective, however, PSUR reporting produces considerable costs, for both regulatory authorities as pharmaceutical companies. It could be questioned what the contribution of PSUR reporting to promoting drug safety is in addition to other pharmacovigilance instruments. Regulatory authorities should start defining and measuring the intended health effects of regulatory requirements, especially if these requirements yield high costs of compliance. Rational regulation at acceptable costs could make a substantial contribution towards more sustainable drug development.

Methods

Regulatory Scenarios

As a cost-effectiveness analysis is always comparative, we evaluated two regulatory scenarios: a scenario with PSUR reporting ('Full Regulation') and a scenario without PSUR reporting ('Limited Regulation') (**Figure 2**, **Table III**). Full regulation is the pharmacovigilance system (pre-2012), encompassing of spontaneous ADR reports and PASS as the two main sources of post-marketing drug safety information, and Risk Management Plans (RMPs) and PSURs as regulatory instruments. The combination of these instruments and activities comprise the pharmacovigilance framework (for biologicals) in Europe.

Under the limited regulation scenario, we assumed that all parts of the pharmacovigilance system were in place from 1995 to 2009 except for PSUR reporting (**Figure 2**); in other words, detection of safety signals and subsequent communications might not have been optimal. We thus assessed all urgent safety issues (i.e., type II variations accompanied by a DHPC) that occurred for biologicals in that period.[10]

From 1995 to 2009, 24 urgent safety issues were identified for all biologicals.[10] We assessed how often a PSUR identified the safety issue, which was positive if any European Public

Assessment Report (EPAR), SPC, or DHPC text referred to a PSUR evaluation.[10] Two of 24 urgent safety issues were identified through PSURs: distant spread of botulinum toxin and edema/fluid collection after off-label use of dibotermin-alfa. The effectiveness of PSUR reporting (full regulation) is thus determined by the increased health in users of these two products. The relevant costs and health effects for both regulatory scenarios are summarized in **Table III**.

Table III: Regulatory scenarios.

FULL REGULATION (Pharmacovigilance)		LIMITED REGULATION (Pharmacovigilance without PSURs)	
Costs	**Health effects**	**Costs**	**Health effects**
PSUR reporting MAHs 1995-2009	All urgent safety issues detected	Costs related to urgent safety issue rhBMP-2	Health losses due to urgent safety issue rhBMP-2
PSUR evaluation EMA 1995-2009		Costs related to urgent safety issue botulinum toxin	Health losses due to urgent safety issue botulinum toxin

Only costs and health effects that differ between the regulatory scenarios are included. Under the full regulation, all parts of the pharmacovigilance system are implemented. Relevant costs are all PSUR-related costs and costs of DHPCs for both products. Relevant health effects are that all urgent safety issues will be identified. Under the limited regulation, the pharmacovigilance system is implemented but without any PSUR reporting. It is assumed 2 urgent safety issues relating to two biologicals will go undetected. Therefore relevant costs include those related to the two urgent safety issues, in the period after a DHPC is issued for these safety issues. PSUR, periodic safety update report. DHPC, direct healthcare professional communication.

PSUR- identified urgent safety issues

Botulinum toxin type B was approved in January 2001 and is indicated for the treatment of cervical dystonia. In March 2007 a DHPC was issued, warning healthcare professionals about rare but serious side effects related to the peripheral spread of botulinum toxin. rhBMP-2 was approved for use in tibia fractures in 2002 and for anterior lumbar spine fusion in February 2005. In September 2007 a DHPC was issued alerting physicians to the risk of complications (e.g. pseudocysts, localized edema, implant site effusion) after unapproved use in posterior lumbar spine surgery, or after inappropriate use (e.g. overfilling the implant/cage). These complications can lead to nerve compression, neurological deficit, or pain, and clinical intervention has been needed when symptoms persisted.

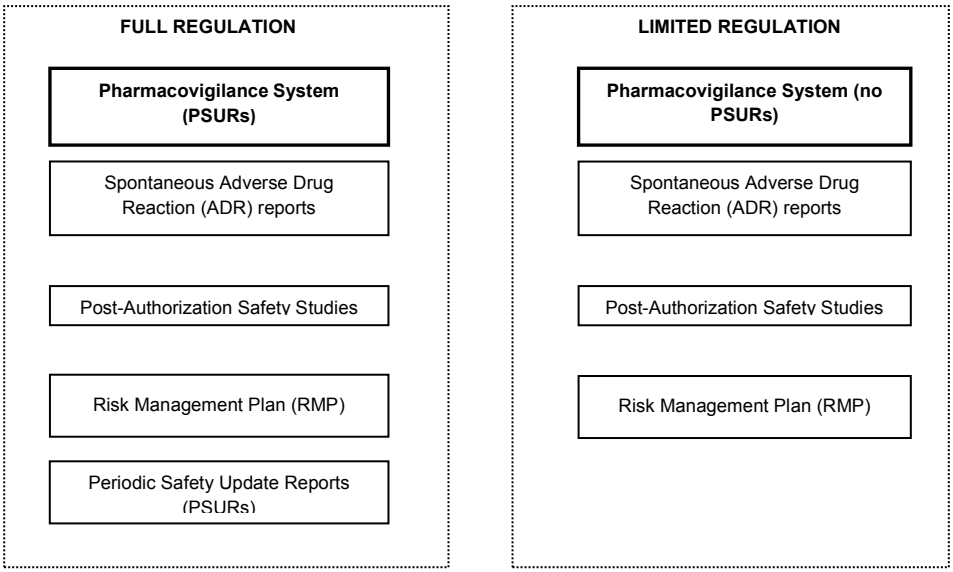

Figure 2: Two regulatory scenarios

We assumed that under both regulatory scenarios these safety issues would have developed. Under the full regulation scenario, PSUR reporting resulted in the detection of the safety issues and DHPCs were consequently issued. Under limited regulation however, no PSURs are required and therefore the safety issues would have gone unnoticed or would have been detected later. For botulinum toxin, we assumed that in the limited regulation scenario the safety issue would have been detected ten years after marketing authorization (January 2012). For rhBMP-2, we assumed the safety issue would have been detected in 2012 also (five years after the indication was approved) given the highly publicized controversy in the US regarding the off-label use of rhBMP-2 in spinal fusions.[14]

There is little empirical evidence concerning the effect of a DHPC in reducing ADR incidence. A systematic review of the impact of drug safety warnings identified 52 studies, 45% of which used volume (i.e. drug use) as the outcome measure of the assessed impact and four of which used spontaneous ADR reporting, mortality, or ADR incidence.[15] In two of those four studies the rate of ADR reports increased after the safety warning, most likely due to underreporting before the safety warning was issued.[16,17] A study investigating the impact of a safety warning regarding oral contraceptives and venous thromboembolism found no difference in ADR cases before and after the warning.[18] An ecological study regarding the use of COX-2 inhibitors and rates of gastrointestinal hemorrhage and myocardial infarction found no strong evidence of a long-term impact of regulatory action on hospital admission

rates related to the ADRs.[19] A recent study concerning the impact of DHPCs on drug use volume in the Netherlands found that 32.8% of DHPCs resulted in a long-term significant decrease of use, with a mean volume decrease of 26.7%.[20] Drug volume was assessed for ambulatory care, however, whereas both products in our study are primarily dispensed for hospitalized patients. Notwithstanding, we assumed the incidence of both safety issues decreased by 25% after the DHPCs were issued with PSUR reporting.

Model structure

An extensive description of the assumptions regarding all model parameters can be found in **Appendix 7.B**, **Appendix 7.C** and **Appendix 7.D** and the model parameters are provided in **Table IV**. The model started in 1995, the year the central authorization procedure was initiated (when PSUR reporting starts under full regulation), with a time horizon of 34 years. The model comprised five life tables: : one Markov-chain life table calculating costs and effects for botulinum toxin for each of the regulation scenarios (full and limited), one dynamic population life table calculating costs and effects for rhBMP-2 for each scenario, and one life table calculating the costs of PSUR reporting under full regulation (**Figure 3**). The structures of the life tables for each safety issue were identical except for the transition probabilities, as they varied under the full and limited regulation scenarios with the assumptions regarding ADR risks. Under the full regulation scenario, we assumed the risk of both safety issues was reduced by 25% after the DHPC was issued. Under the limited regulation scenario, no DHPC was issued in 2007 but we assumed the risk reduction occur in 2012. The differences in costs and effects for both safety issues therefore occurred between 2007 and 2012, and the transition probabilities of the life tables become identical after 2012. The model calculated the health effects in QALYs. A QALY corrects life years lived with the health-related quality of life. One QALY therefore can be interpreted as one year lived in full health.

The botulinum toxin life table consisted of five possible health states following treatment: no ADR, dysphagia, mild botulism, moderate botulism, severe botulism, and death. Cycle length was 13 weeks based on average treatment intervals of 12 weeks (13 weeks was chosen for calculating convenience).[21] We estimated a total of 18,000 patients with an average age of 50 would enter the model January 2001 (averaged estimated number of cervical dystonia patients in EU-27 undergoing botulinum toxin injections).[21] Death (22.5% after severe botulism) was the only absorbing state. As we assumed all-cause mortality in cervical dystonia patients would be equal under both regulatory scenarios, we did not include the state in the model. Transition probabilities, direct and indirect costs, and utilities for all health states can be found in **Table IV**.

The life tables for rhBMP-2 had a one-year cycle length with 33,848 patients (all estimated off-label lumbar fusions in EU-27) entering the model annually (mean age 50 years). The life tables consisted of two health states: lumbar operation-no complications and edema-hospitalization. All transition probabilities, utilities, and direct and indirect cost estimates are listed in **Table IV**.

MAH and regulatory costs

Under the full regulation scenario, relevant costs included all PSUR-related costs for the pharmaceutical industry and regulatory agencies during the 1995-2009 period. For a pharmaceutical company, a small PSUR (< 100 ADR cases, 76 preparation hours) costs €6,000, a medium PSUR (101-500 cases, 173 hours) costs €14,000 and a large PSUR (>500 cases, 362 hours) costs €28,000 (all in 2006 euros).[7,8] We also took marketing periods into account: in our PSUR sample, the distribution of small, medium, and large PSURs was 65%, 16%, and 19% for 6-month PSURs, 29%, 17%, and 54% for 1-year PSURs, and 30%, 20%, and 50% for more than 1-year PSURs (**Table II**).[9] For all marketed biologicals during 1995-2009 we estimated the number of PSURs that would have been submitted after market approval. More than 50% of all biologicals older than 5 years still follow the annual reporting scheme.[9] Therefore we assumed 50% of products >5 years marketed followed the 1-year reporting scheme and 50% followed the 3-year scheme. This resulted in an estimated total of 964 reported PSURs for all biologicals during 1995-2009. Using the small, medium and large distribution among 6-month, 1-year, and 3-year PSURs from our sample, the total estimated costs of all PSURs were €14.2 million during 1995-2009 for pharmaceutical companies.[9]

Every submitted PSUR for a biological is assessed by the EMA. PSUR costs are estimated by the time spent preparing it (the MAH) and assessing it (the regulatory authority). Regulatory estimates of PSURs obtained from two European Competent authorities were 7 rapporteur hours per small PSUR, 15 hours (medium), and 40 hours (large). We used 25% of the rapporteur time to estimate the co-rapporteur hours per PSUR. We assigned a cost of €49 per hour for a public official in the EU-27.[8] The total estimated regulatory PSUR cost was €1,079,645 for our 15-year period. The EMA has proposed new fees for PSUR assessment (€40,150 for a PSUR on a biological marketed for less than two years and €80,300 for a biological marketed more than 2 years.[22] We used these fees as cost estimates in a sensitivity analysis.

Table IV: All model parameters

Parameter	Value	Source	Distribution	Parameter	Value	Source	Distribution
General				**Botulinum toxin - followed**			
PSUR small costs	€ 6,000	[8]	Normal	House days mild	5	[24]	Normal
PSUR medium costs	€ 14,000	[8]	Normal	House days moderate	7	[24]	Normal
PSUR large costs	€ 28,000	[8]	Normal	Hospital days moderate	7	[24]	Normal
Proportion S-M-L PSURs 6-month	65%-16%-19%	[9]		Bed days moderate	7	[24]	Normal
Proportion S-M-L PSURs 1-year	29%-17%-54%	[9]		House days severe	53	[24]	Normal
Proportion S-M-L PSURs 3-year	30%-20%-50%	[9]		Hospital days severe	53	[24]	Normal
Inpatient day university hospital	€ 575	[25]	Normal	Intensive care days severe	30	Assumption	Normal
Intensive care unit	€ 2,183	[25]	Normal	Bed days severe	23	[24]	Normal
Productivity costs per hour	€ 30.02	[25]	Normal	Productivity days lost moderate	21	[24]	Normal
Informal care per hour	€ 12.50	[25]	Normal	Productivity days lost severe	159	[24]	Normal
Productivity hours lost per sick day	8	Assumption	Normal	**rhBMP-2**			
Hours of informal care per bed day	8	Assumption	Normal	Spondylodese procedures NL	2,203	[26]	
Botulinum toxin				Percentage lumbar off-label	60%	[27,28]	Beta
Proportion of CD patients treated	80%	[29]	Beta	Probability edema	1%	[27,30]	Beta
Mean number CD patients 2001	22,601	Calculated		Probability hosptitalization	30%	EudraVigilance, expert opinion	Beta
Mean age CD patients	50	[21]		Use of rhBMP-2	1%	expert opinion	Beta
Life expectancy CD patient	80	EU-27 LE weighted by male/female ratio		Hospital days required	3	expert opinion	Normal
Utility treatment	0.71	[31]	Beta	Productivity days lost swelling	10	expert opinion	Normal
Utility dysphagia	0.66	[31]	Beta	Costs operation	€ 1,094	[32]	Normal

Table IV continued							
Utility mild	0.66	[31]	Beta	utility index 1 year - fluid collection	0.500	[33]	Beta
Utility moderate	0.31	calculated	Beta	utility index 1 year - no complication	0.621	[33]	Beta
Utility severe	0.00	Expert opinion		utility index 2 years	0.638	[33]	Beta
Utility death	0.00	Expert opinion		utility index 3 years	0.630	[33]	Beta
P dysphagia	17%	[21]	Beta	utility index 4 years	0.646	[33]	Beta
P mild botulism	0.40%	[21]	Beta	utility index 5 years	0.653	[33]	Beta
P moderate botulism	0.09%	[21]	Beta				
P severe botulism	0.01%	[21]	Beta				
P death	22.5%	[24]	Beta				

Values are base-case assumptions. Distribution indicates the distribution used for probabilistic sensitivity analysis. See **Appendix 7.A** for detailed description of all parameter assumptions that were made and Appendix IV for probabilistic sensitivity analysis details. Abbreviations: CD Cervical dystonia

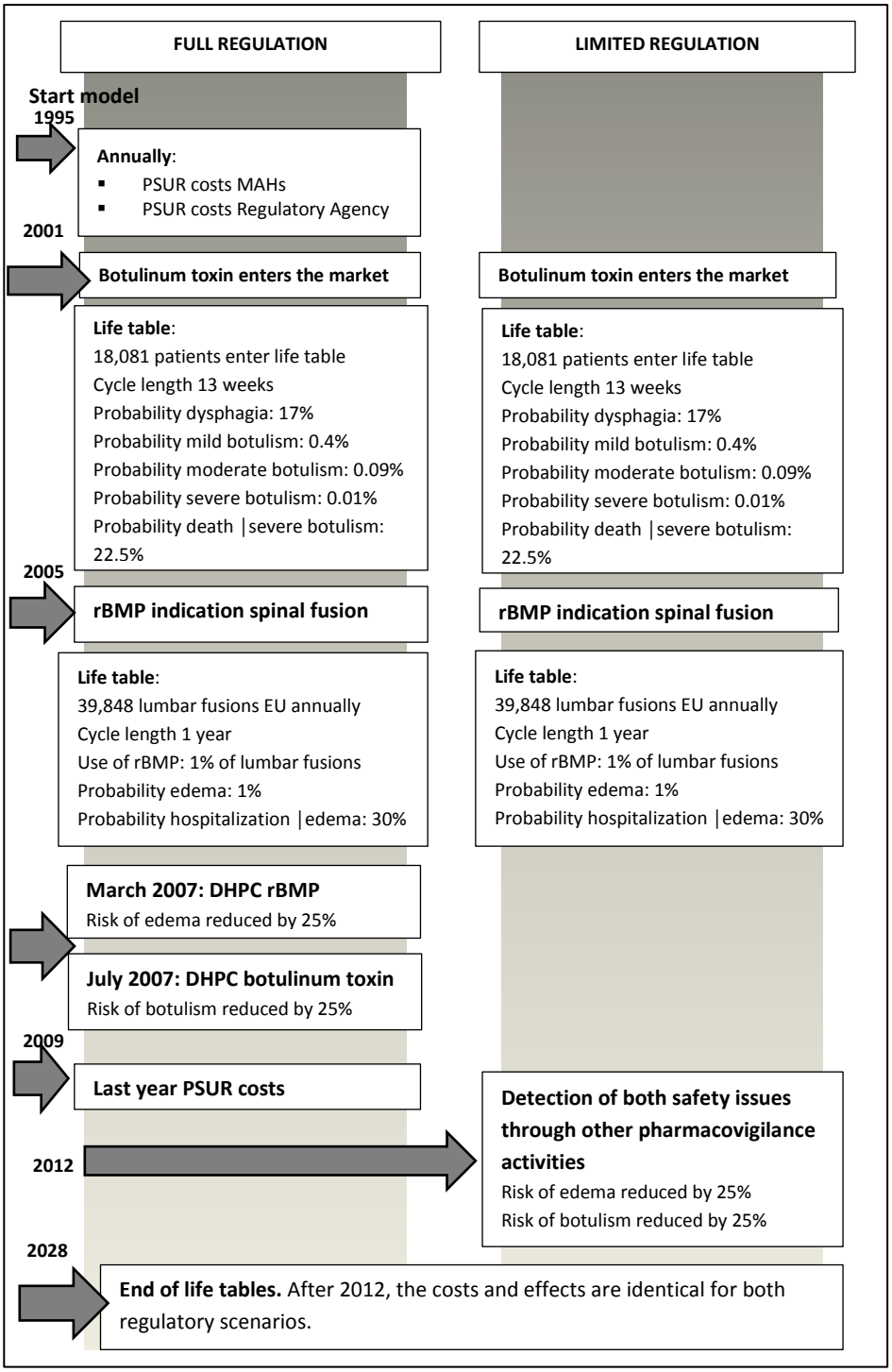
FULL REGULATION
LIMITED REGULATION
Start model
1995
Annually:
PSUR costs MAHs
PSUR costs Regulatory Agency
2001
Botulinum toxin enters the market
Botulinum toxin enters the market
Life table:
18,081 patients enter life table
Cycle length 13 weeks
Probability dysphagia: 17%
Probability mild botulism: 0.4%
Probability moderate botulism: 0.09%
Probability severe botulism: 0.01%
Probability death | severe botulism: 22.5%
Life table:
18,081 patients enter life table
Cycle length 13 weeks
Probability dysphagia: 17%
Probability mild botulism: 0.4%
Probability moderate botulism: 0.09%
Probability severe botulism: 0.01%
Probability death | severe botulism: 22.5%
2005
rBMP indication spinal fusion
rBMP indication spinal fusion
Life table:
39,848 lumbar fusions EU annually
Cycle length 1 year
Use of rBMP: 1% of lumbar fusions
Probability edema: 1%
Probability hospitalization | edema: 30%
Life table:
39,848 lumbar fusions EU annually
Cycle length 1 year
Use of rBMP: 1% of lumbar fusions
Probability edema: 1%
Probability hospitalization | edema: 30%
March 2007: DHPC rBMP
Risk of edema reduced by 25%
July 2007: DHPC botulinum toxin
Risk of botulism reduced by 25%
2009
Last year PSUR costs
2012
Detection of both safety issues through other pharmacovigilance activities
Risk of edema reduced by 25%
Risk of botulism reduced by 25%
2028
End of life tables. After 2012, the costs and effects are identical for both regulatory scenarios.

Figure 3. Model outline. The model consists of five separate life tables: botulinum toxin limited and full regulation (2001-2028), rBMP limited and full regulation (2005-2028), and PSUR costs (1995-2009). Abbreviations: MAH Market authorizaton holder; rBMP Bone morphogenetic protein; DHPC Direct healthcare professional communication; PSUR Periodic Safety Update Report.

Discounting

Discounting is usually applied in economic evaluations to allow for time preferences (benefits today are more valuable than future benefits) and uncertainty. We performed a retrospective analysis, however, in which part of the costs and effects occur in the past (and are corrected for inflation using the EU-27 Harmonized Indices of Consumer Prices (HICPs).[23] The model takes a lifetime perspective to estimate the total costs and effects of the two regulatory scenarios. The difference between the costs and effects of the two regulatory scenarios originates in the years 2007-2012, during which the reporting of the urgent safety issues between the full and limited regulation scenarios varies. Some of the relevant health effects occur after 2012, as some cases of botulism that would have occurred under limited regulation were prevented by full regulation. To allow the estimation of all health effects a lifetime perspective needs to be used. As these events have occurred in the past, we are certain about their occurrence and therefore the base case results are not discounted. We did include two alternative scenarios to demonstrate the impact of discounting: we discounted all costs and effects (4% and 1.5% respectively and according to Dutch guidelines) using 1995 as t=0 and another scenario discounting all future costs and effects using 2012 as t=0.

Sensitivity analysis

Because of our several assumptions regarding model parameters and combinations of sources of evidence to estimate the parameters, we undertook extensive sensitivity analyses to investigate the impact of varying model assumptions on the results. We varied all key model assumptions through univariate sensitivity analyses. We also performed a PSA in which a distribution is fitted to a set of model parameters to express their uncertainty and used a sampling process (Monte-Carlo simulation) used to indicate how the results are impacted by this uncertainty (**Table IV, Appendix 7.A**).

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Appendix 7.A: Probabilistic sensitivity analysis

In order to demonstrate the combined uncertainty of the model parameters, we performed a probabilistic sensitivity analysis (PSA). A PSA is performed by fitting a distribution to all or a selection of model parameters. Subsequently, a sampling procedure (Monte-Carlo simulation) is performed. During the simulation, a value is drawn from its fitted distribution for each probabilistic parameter and the costs, effects, and incremental cost-effectiveness are subsequently calculated. This process is repeated 10,000 times (iterations). Each iteration, corresponding to one ICER, is plotted in a cost-effectiveness (CE) plane (Figure 1). The CE plane demonstrates the variability or uncertainty surrounding our model estimates. We calculated how many of the iterations resulted in (a) lower incremental effectiveness and lower incremental costs, (b) higher incremental effectiveness and lower costs, (c) lower incremental effectiveness and higher costs, and (d) higher incremental effectiveness and higher costs. For the iterations under (d), we used a threshold of €50,000 per quality-adjusted life year gained (QALY) for the maximum willingness to pay per QALY for those iterations resulting in higher effectiveness and higher costs.

Distributions and ranges

It is common practice to use a beta distribution (that is bounded between 0 and 1) for probabilities, and for utilities that are not close to zero. Therefore, we fitted a beta distribution for all probability and utility estimates. The moments of the distributions are given in table A5. We had no sample information available for any of our parameters, which can be used to estimate the range of uncertainty and subsequent moments of the distribution. Therefore, we estimated the distribution moments α and β by taking the point estimate and a relatively large standard deviation (Briggs et al. 2006).

It is common to use a gamma distribution for patient-level cost estimates (Briggs et al. 2006). However, it would not be appropriate to fit such a distribution to the PSUR cost estimates, as well as our other cost estimates, as there is no reason to assume these would follow a gamma distribution. Therefore we used a normal distribution with a wide range. For these cost estimates, we had no sample information to estimate the distribution moments either. Therefore we set the standard deviation to $1/10^{th}$ of the mean to estimate a normal distribution for all cost parameters. All parameters, their distributions and distribution moments are provided in table A1.

PSUR-related parameters	base case value	Distribution	St. Dev.	Alpha	Beta
PSUR small costs	€ 6,000	Normal	600		
PSUR medium costs	€ 14,000	Normal	1400		
PSUR large costs	€ 28,000	Normal	2800		
Costs per regulator hour					
Hours rapporteur MHRA small PSUR	7	Normal	0.7		
Hours co-rapporteur MHRA small	1	Normal	0.1		
Hours rapporteur MHRA medium PSUR	15	Normal	1.5		
Hours co-rapporteur MHRA medium	3	Normal	0.3		
Hours rapporteur MHRA large PSUR	40	Normal	4		
Hours co-rapporteur MHRA large	8	Normal	0.8		
General parameters					
Risk reduction	0.25	Beta	0.1	4.4	13.3
Inpatient day university hospital	€ 575	Normal	5.8		
Intensive care unit	€ 2,183	Normal	218.3		
Productivity costs per hour	€ 30.02	Normal	3.6		
Informal care per hour	€ 12.50	Normal	1.3		
Productivity hours lost per sick day	8	Normal	0.8		
Hours of informal care per bed day	8	Normal	0.8		
Botulinum toxin parameters					
Proportion of CD patients treated	80%	Beta	0.1	12.0	3.0
% of people with paid work age 50-65 NL 2011*	0.6	Beta	0.1	13.8	9.2
Utility treatment	0.71	Beta	0.1	13.9	5.7
Utility dysphagia	0.66	Beta	0.1	14.2	7.3
Utility mild	0.66	Beta	0.1	14.2	7.3
Utility moderate	0.31	Beta	0.1	6.3	14.1
P dysphagia	17%	Beta	0.02	59.8	292
P mild botulism	0.40%	Beta	0.001	15.9	3,967
P moderate botulism	0.09%	Beta	0.0001	80.9	89,837
P severe botulism	0.01%	Beta	0.0001	1.0	9,997
P death	22.5%	Beta	0.05	15.5	53.3
House days mild	5.00	Normal	0.5		
House days moderate	7.00	Normal	0.7		
Hospital days moderate	7.00	Normal	0.7		
Bed days moderate	7.00	Normal	0.7		
House days severe	53.00	Normal	5.3		
Hospital days severe	53.00	Normal	5.3		
Intensive care days severe	30.00	Normal	3		
Bed days severe	23.00	Normal	2.3		

Productivity days lost moderate	21.00	Normal	2.1		
Productivity days lost severe	159.00	Normal	15.9		
rhBMP-2 parameters					
Percentage lumbar off-label	60%	Beta	0.1	13.8	9.2
Probability edema	1%	Beta	0.008	1.5	152.2
Probability hosptitalization	30%	Beta	0.1	6.0	14.0
Use of dibotermin	1%	Beta	0.008	1.5	152.2
Hospital days required	3	Normal	0.3		
Productivity days lost swelling	10	Normal	0.1		
Costs operation	€ 1,094	Normal	109.4		
utility index 1 year - fluid collection	0.500	Beta	0.1	12.0	12.0
utility index 1 year - no complication	0.621	Beta	0.1	14.0	8.5
utility index 2 years	0.638	Beta	0.1	14.1	8.0
utility index 3 years	0.630	Beta	0.1	14.1	8.3
utility index 4 years	0.646	Beta	0.1	14.1	7.7
utility index 5 years	0.653	Beta	0.1	14.1	7.5

Table 7.A: All probabilistic parameters and distributions used for probabilistic sensitivity analysis.

Appendix 7.B: All indications for botulinum toxin

Three types of botulinum toxin products with therapeutic indications are marketed in the European Union: BOTOX (botulinum toxin type A), Dysport (botulinum toxin type A), and NeuroBloc (botulinum toxin type B). NeuroBloc is the only product that was approved between 1995-2009 and therefore was included in our analysis, yet, the urgent safety issue (botulism after therapeutic use) and consequent DHPC was issued for all botulinum toxin products. NeuroBloc only has an indication for cervical dystonia. As this was the product of interest in our analysis, we did not take other therapeutic indications into account. However, the other two botulinum toxin products have more therapeutic indications that we have summarized here (all indications during 1995-2009), including the maximum recommended dose (taken from the Summary of Product Characteristics (SPC)) of all the products.

Dysport has additional therapeutic indications for blefarospasm, hemifacilispasm, axillary hyperhidrosis, and spasticity of the arm after stroke. BOTOX has one additional indication for equinus foot due to cerebral palsy in peadiatric patients. All indications and their respective maximum recommended dose (unique for each product) are summarized in table 7.B1.

Product	Name	Indication	Maximum dose
NeuroBloc	botulinum toxin type B	Cervical dystonia	10,000 U
Dysport	botulinum toxin type A	Cervical dystonia	1,000 U
Dysport	botulinum toxin type A	Blefarospasm	40 U per eye
Dysport	botulinum toxin type A	Hemifacilispasm	40 U per eye
Dysport	botulinum toxin type A	axillary hyperhidrosis	200 U per arm
Dysport	botulinum toxin type A	Spasticity arm after stroke	1000 U
BOTOX	botulinum toxin type A	Cervical dystonia	200 U
BOTOX	botulinum toxin type A	Blefarospasm	25 U per eye
BOTOX	botulinum toxin type A	Hemifacilispasm	25 U per eye
BOTOX	botulinum toxin type A	axillary hyperhidrosis	50 U
BOTOX	botulinum toxin type A	Spasticity arm after stroke	360 U
BOTOX	botulinum toxin type A	Equinus foot due to pediatric cerebral palsy	4 U/kg

Table 7.B1: indications and maximum recommended dose per indications. The units (U) are not interchangeable between the different products

Table 7.B1 shows that for most therapeutic indications, the maximum dose is much lower than the dose used in cervical dystonia patients. We have provided a (rough) estimate of the total number of annual patients for each indication in the EU, using published prevalence or incidence estimates (Table 7.B2).

Indication	Estimated incidence / prevalence EU	Estimated annual patients EU	Source
Cervical dystonia	57 per 1 million people	28,482	Warner (2000)
Blefarospasm	36 per 1 million people	17,989	Warner (2000)
Hemifacilispasm	98 per 1 million people	48,969	Nilsen & Dietrich (2004)
axillary hyperhidrosis	1.4% of population	6,995,612	Strutton et al. (2004)
Spasticity arm after stroke	Stroke: 112 per 100,000, incidence all spasticity after stroke: 38% of surviving patients, of which 83% arm is affected	176,513	Watkins et al. (2002) Bejot et al. (2007)
Equinus foot due to pediatric cerebral palsy	Spastic CP 2.1 per 1,000 births, severe walking restrictions in 32% of spastic CP patients	3,609	Andersen et al. (2008)

Table 7.B2. Prevalence or incidence and estimated annual number of patients in the European Union.

The potential number of patients who would be eligible for botulinum toxin treatment for spasticity after stroke is quite large (Table A3). Yet, botulinum toxin treatment is not a first-in-line treatment for post stroke spasticity (Sheean 2009). Therefore we find it unlikely that a large group of these patients will be treated with botulinum toxin, although we were not able to find estimates of botulinum toxin treatment among these patients.

The largest estimated number of patients is the number of patients with axillary hyperhidrosis (almost 7 million people estimated in the EU (Strutton et al 2004)). The proportion of these people receiving botulinum toxin treatment is not known, however, it was indicated that of the identified patients with axillary hyperhidrosis, only about 30% of these patients consults a healthcare professional about their condition. Furthermore, only about 33% of the patients indicated that their symptoms were barely tolerable or intolerable, as opposed to tolerable symptoms that never or barely interfered with their daily life. Therefore we assume only a small number of these patients will be treated with botulinum toxin injections. Furthermore, the maximum recommended dose for these patients is about 25% of the maximum recommended dose for cervical dystonia patients, putting them at much lower risk than those patients as well.

Appendix 7.C Sources used and assumptions made regarding the urgent safety issue of distant spread of botulinum toxin after therapeutic use

Mechanism of systemic spread

Several case reports describing patients experiencing symptoms of systemic spread after therapeutic use of botulinum toxin (both type A as type B) have been published (Bakheit et al. 1997, Bhatia et al. 1999, Tugnoli et al. 2002, Goldstein et al.2006, Souayah et al. 2006, Duffey et al. 2006, Crowner et al. 2007, Partikian et al. 2007, Roche et al. 2008, Coban et al.2010). The case reports varied in severity of symptoms that ranged from mild dysphagia to respiratory distress and paralysis. All cases reported symptoms (generalized weakness, fatigue) that are consistent with iatrogenic botulism and mean time until full recovery was 3.5 months.

Iatrogenic botulism is caused by botulinum toxin spreading by blood flow (Garner et al. 1993). Different mechanisms causing systemic spread of botulinum toxin have been proposed: accidental overdose (Brin 1997), accidental injection of botulinum toxin into the capillary field or venous system (Crowner et al 2010, Coban et al. 2010), very efficient local uptake and retrograde axonal transport via spinal motor neurons, or systemic distribution via blood circulation (Garner et al. 1993). The potency and consequent dose (in mouse units U) of botulinum toxin type A and type B are significantly different and have a dosage ratio of roughly 3:1 to 4:1 (Brin 1997). This could result in accidental overdose due to conversion errors (Brin 1997). However, severe systemic effects are unlikely as overdose would require intramuscular injection of many more vials of toxin than are required for treatment (Brin 1997).

The threshold systemic toxicity or lethal dose in humans is not known, but studies in primates suggest a clear dose-response relationship between dosage and severity of symptoms after both intravenous as intramuscular injections, and a dose of 40 U/kg causes systemic toxicity resembling botulism (Herrero et al. 1967, Scott and Suzuki 1988), which is consistent with a case report of a patient that developed iatrogenic botulisum after receiving a 40 U/kg dose (Crowner et al. 2007). Extrapolating the results from Herrero et al. (1967) and Scott and Suzuki (1988), results in an estimated lethal parental dose of nearly 3000 U of botulinum toxin type A (Brin 1997). The maximum recommended dose of botulinum toxin type A per treatment session is 300-400 U, making overdose an unlikely main cause of systemic spread. A large proportion of the case reports of systemic spread of botulinum toxin after

therapeutic use in a wide range of conditions were patients who had tolerated similar dosage well before developing botulism-like symptoms and several patients continued with injections after developing botulism without developing symptoms of systemic spread again (Crowner et al. 2010). Therefore we assumed that cases of systemic spread after botulinum toxin injection in cervical dystonia patients are mainly caused by accidental injection into the capillary field or venous system, causing iatrogenic botulism of varying severity.

Probability of iatrogenic botulism

The DHPC reported 'very rare reports' (post-marketing) of serious ADRs after therapeutic use of botulinum toxin, with symptoms related to the peripheral spread of botulinum toxin, which in 'extremely rare cases' had resulted in death. Two types of ADRs can be distinguished: peripheral or local spread beyond the injection site, that can cause dysphagia, speech difficulties and neck weakness, and systemic spread, which can cause general weakness, paralysis, and botulism-like symptoms. Peripheral spread however occurs frequently, is caused by local spread beyond the injection site, and is a non-preventable ADR.

Iatrogenic botulism will differ in severity. Mild botulism symptoms include malaise, fatigue, and weakness, have duration of 5 days, a fatality rate of 0%, and will result in 5 house days (Mauskopf and French 1991). Moderate botulism symptoms also include nausea/vomiting, diarrhea, abdominal pain, fever, headache, and dizziness, duration of 21 days, result in 7 hospital days, 7 bed days and 7 house days, and have a fatality rate of 0% (Mauskopf and French 1991). Severe botulism symptoms also include respiratory paralysis, muscular paralysis, and pulmonary infection, duration of 180 days, respiratory support is required, result in 90 hospital days (including 30 intensive care days), 30 bed days, and 60 house days, and have a fatality rate of 22.5% (Mauskopf and French 1991).

Cote et al (2005) reported a series of ADR reported to the Food and Drug Administration (FDA) after botulinum toxin injections for both therapeutic and cosmetic use. During 2002, a total of 217 serious ADRs were reported after therapeutic use (with therapeutic uses encompassing a number of therapeutic indications apart from cervical dystonia). Of these reports, several are consistent with symptoms of botulism (respiratory system (33), pneumonia (9), respiratory compromise (18), flu-like syndrome (10), muscle weakness (13), dysphagia (26), fatigue/malaise (3), among other reported symptoms), which is an indication that botulism-like symptoms do occur with therapeutic use (Cote et al. 2005). Furthermore, a total of 28 deaths were reported after therapeutic use, of which 6 were attributed to respiratory arrest, and 2 to pneumonia (1 confirmed aspiration pneumonia), which indicate the possibility of death caused by botulism (yet not confirmed). It is important to note that

26 of 28 deaths occurred in patients with underlying systemic diseases with elevated risk of death (Cote et al. 2005).

Kessler et al. (1999) reported all ADRs after long-term botulinum toxin injections (>2 years) in a group of 303 cervical dystonia patients that received a total of 3088 injections (Kessler et al. 1999). Dysphagia (symptom of peripheral spread) was reported in 17% of injections, which is consistent with the EPAR for botulinum toxin type B which lists dry mouth and dysphagia as very commonly reported symptoms (>1 in 10 patients). General weakness, a symptom of botulism, was reported in 0.5% of all injections. Therefore we assume a probability of 0.5% systemic spread per injection. Kessler et al. (1999) report vertigo/nausea in 0.1% of all injections which are symptoms of moderate botulism as defined by Mauskopf and French (1991). However, none of the other moderate botulism symptoms (diarrhea, abdominal pain, fever, malaise, weakness, and headache) are reported, and Kessler et al. (1999) conclude that there is no indication from their study that systemic effects become clinically relevant during long-term exposure to botulinum toxin type A (Kessler et al. 1999). We assumed an overall probability of botulism of 0.5% per injection (Kessler et al. 1999), and based on a reported dose-response relationship for systemic effects and the 0.1% probability of vertigo/nausea reported by Kessler et al. (1999) consistent with moderate botulism, we assumed out of all cases of botulism, 80% were mild and 20% were either moderate or severe (consistent with the 0.5% general weakness and 0.1% vertigo/nausea). Furthermore we assumed 90% of moderate/severe botulism cases were moderate and 10% were severe. Combined, these estimates resulted in risk per injection of 40 per 10,000 patients for mild botulism, 9 per 10,000 of moderate botulism, and 1 per 10,000 patients severe botulism with a mortality risk of 22.5%. We believe the real probability of moderate or severe botulism after injection in cervical dystonia patients under normal use is likely to be lower in clinical practice, as not all symptoms consistent with these disease states are reported by Kessler et al. (1999) and their study did not include a single case of severe botulism.

Utilities of different health states in botulinum toxin life tables

Treatment with no ADR was assigned a health utility of 0.71 (Hilker et al. 2001). The dysphagia health state was assigned a health utility of 0.66 (Hilker et al. 2001), the health state mild botulism was assigned a utility of 0.66, the moderate botulism health state was assigned a health utility of 0.31 (assigning a Dutch tariff (Lamers et al. 2005) valuation of EQ-5D health status of 32321 which was derived using the Mauskopf and French (1991) description of moderate botulism symptoms), health state severe botulism was assigned a utility of 0, and death 0.

Direct and indirect costs of iatrogenic botulism

We assigned no costs to the health state 'dysphagia' as these symptoms are minor and usually require no additional care. The direct and indirect costs of mild, moderate, and severe botulism are estimated based on Mauskopf and French (1991). For each disability state, we assumed 8 hours of productivity were lost per house/bed/hospital day, 60% of patients had paid work (CBS 2012), and 8 hours of informal care are required for each bed day. For mild botulism, 5 house days (but no additional care) are assumed. For moderate botulism, 7 hospital days, 7 bed days, and 7 house days are assumed (total duration 21 days). For severe botulism, 90 hospital days (of which 30 intensive care unit days), 30 bed days, and 60 house days were assumed (total duration 180 days). The probability of death after this state was 22.5%. See table 2 for cost parameters used. Total estimated direct and indirect costs per patient for mild botulism were €1,201, moderate botulism €5,355, and severe botulism €146,219. All patients surviving after severe botulism transitioned to moderate botulism after one cycle to allow for the duration (two model cycles, total duration 26 weeks) of severe botulism. We corrected the total length of house, bed, hospital and productivity losses days of severe botulism for those in the consequent moderate botulism state as to no overestimate the costs of severe botulism.

	Direct costs	Direct and indirect costs
Costs mild botulism case	€ 0	€ 924
Costs moderate botulism case	€ 4,351	€ 5,593
Costs severe botulism case	€ 103,745	€ 135,613

Table 7.C: Direct and indirect costs per case (in 2012 Euros)

Appendix 7.D Sources used and assumptions made regarding the urgent safety issue of fluid collection and edema after spinal fusion using rhBMP-2

Mechanism of edema after rhBMP-2 use in spinal fusion

rhBMP-2-induced inflammation may induce ADRs such as swelling, seroma formation, and implant size effusions (Choudry et al. 2012). The risk of such complications after the use of rhBMP-2 in lumbar fusions with posterior approaches (not indicated) was communicated by means of a DHPC in 2007. Several case reports of patients experiencing swelling complications after fusion surgery of different segments, including the lumbar and cervical spine, have been published (Perry et al. 2007, Shah et al. 2008, Shahlaie et al. 2008, McDonald et al. 2010, Muchow et al. 2010, Robin et al. 2010, Anderson et al. 2011, Lindley et al. 2011). The reports of fluid collection mentioned in the DHPC resulted in nerve compression, neurological deficit, or pain in more than 50% of the cases. Surgical removal has been required in cases where symptoms persisted.

Spine fusion procedures with rhBMP-2: probability of complications

In the Netherlands, 2,203 spinal fusion operations (spondylodese) were performed in 2010 (LMR 2012). Williams et al. (2011) and Cahill et al. (2009) reported large samples of fusion operations in the US and report a breakdown by different procedures. Assuming the off-label posterior lumbar approaches as referenced in the DHPC include interlaminar/facet fusion, posterolateral fusion, posterior lumbar interbody fusion, and transforanimal lumbar fusion, we estimated that 60% of all fusion procedures were posterior lumbar approaches (Williams et al. 2011, Cahill et al. 2009). Extrapolating the number of procedures in the Netherlands to the EU-27 population, we estimated a total of 66,414 fusion procedures per year in total of which 39,848 were posterior lumbar approaches.

In the US rhBMP-2 is used in about 35% of all lumbar fusions (Williams et al. 2011, Cahill et al. 2009). However, in the Netherlands and EU usage levels are much lower (Prof. Öner, personal communication). Many European countries finance hospitals through diagnosis-related groups (DRGs) where one tariff is used for a procedure. The costs of rhBMP-2 in the Netherlands are about €3,000 per kit, yet, the DRG for lumbar fusions does not cover the costs of rhBMP-2, creating a disincentive to use rhBMP-2 in lumbar fusions. The same disincentive has been reported for Germany (Alt and Heissel 2006). Although we have not been able to find data regarding the use of rhBMP-2 in lumbar fusions in other European

countries, widespread use of DRG-based financing systems throughout the EU leads us to believe that the Dutch situation is exemplary for the EU. Therefore we assumed that rhBMP-2 was used in 1% of all lumbar fusions (no/low quality autograft, very high probability of non-fusion with autograft).

Williams et al. (2011) report the number of cases that developed epidural hematoma/seroma after spinal fusion with dibotermin: 0.5% interlaminar/facet, 0.2% posterolateral, 0.3% posterior lumbar interbody fusion, and 0.3% transforaminal lumbar interbody fusion, out of a sample of 55,862 cases in total. Glassman et al. (2011) report a consecutive series of 1037 patients who underwent posterolateral fusion with dibotermin between 2003-2006. They report hematoma in 0.96% of patients, epidural hematoma in 0.29% of patients, and psoas hematoma in 0.77% of cases. Combining these studies, we estimated the probability of a swelling complication after posterior lumbar approaches using rhBMP-2 to be 1%.

The proportion of patients experiencing swelling complications that required clinical intervention has not been reported. We requested all ADR reports from the EudraVigilance database for rhBMP-2 up to January 4, 2012. A total of 33 ADR reports were submitted between 2007 and 2012, 31 of which were reported from Europe. The reports do not indicate however whether the use was in tibia fractures, on-label or off-label in spinal fusion. Of these reports, 11 reported symptoms related to fluid collections after the use of rhBMP-2: six reports of a (pseudo)cyst, two reports of implant site effusion, one report of implant site inflammation, one report of radicular syndrome, and one report of edema. Only two reports (radicular syndrome and implant site effusion) were not serious (i.e. not life-threatening or resulting in death; none actually resulted in death). Whether the ADR resulted in hospitalization was not reported for five of the serious cases, the pseudocyst and implant site inflammation did result in hospitalization, and all other reports did not result in hospitalization. For five of the cyst cases, it is not reported what the outcome was; all other ADRs were reported as resolved/recovered. Based on these ADR reports, we assumed that 30% of all cases of a swelling complication were serious and required surgical intervention. We assumed that surgical intervention entailed a reoperation to remove the swelling, resulted in three hospital days and 10 productivity days lost (i.e. two weeks).

Utilities used for the health states in the rhBMP-2 life tables

Health utility for operation-no complication was 0.621 in year one post-operation, 0.638 in year two, 0.630 in year three, 0.646 in year four, and 0.653 in year five and subsequent years (Glassman et al. 2012). We assumed patients in health state edema-hospitalization had a health utility of 0.500 (baseline in Glassman et al. 2012) during year one, 0.621 in year two, and all subsequent health utilities as reported by Glassman et al. (2012): patients experiencing the

safety issue therefore benefited from the operation with a one year delay due to the complications in year one.

Direct and indirect costs of edema after use of rhBMP-2

We assumed that 30% of all patients experiencing edema/fluid collection required a reoperation and were hospitalized for 3 days. Furthermore, we assumed they lost ten productivity days (two weeks). The estimated costs of the reoperation were €1,094 (based on the Dutch diagnosis-related group for a reoperation in lumbar fusion patients (NZA 2012)). All other costs (productivity costs, hospital day) were equal to the estimates used for the botulinum toxin model.

	Direct costs	Direct and indirect costs
Costs edema after rhBMP-2 use per patient	€ 2,988	€ 6,068

Table 7.D: Costs per patient with edema complications (in 2012 Euros)

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Chapter 8

General Discussion

"You can't have everything you want, you can't get something for nothing, and you should think about what you have to give up to get something you do want."

Scott Grosse and colleagues (In: Lessons from cost-effectiveness research for United States Public Health Policy. Annual Review of Public Health, 2007)

Introduction

The work in this thesis was dedicated to the valuation and evaluation of the drug regulatory framework by means of different methodological approaches. This final chapter contains a general discussion of the work reported in this thesis and consists of three parts. First, the main findings of this thesis are reported and discussed. **Chapter 6** and **chapter 7** present the application of health technology assessment (HTA) as a feasible tool to evaluate pharmaceutical regulation. As this concerns a novel methodological approach to pharmaceutical policy evaluation, the second part of this chapter is dedicated to a separate discussion of a number of identified methodological challenges and suggestions for future regulatory cost-effectiveness studies. The last part of this chapter is dedicated to a discussion of the scientific, societal, and monetary implications of our findings.

Main findings

The societal valuation of safety-related regulatory actions is high. **Chapter 2** reports a study into the willingness to pay (WTP) for the reduction of the risk for pure red cell aplasia (PRCA) in users of epoetin. The general public was willing to accept an average annual increase of €24.40 (median: €10) in their health insurance premium whereas chronic kidney disease patients were willing to accept an annual increase of €46.52 (median: €35). Acknowledging several possible biases that could have inflated these results, they nonetheless reflect a high societal (monetary) valuation of regulatory measures aimed at increasing drug safety. Furthermore, the WTP estimates might reflect altruistic or existence values regarding safety regulation: people derive utility from knowing that others are protected from drug safety risks, even if they will presumably never face the risk. Interestingly, risk *magnitude* was not significantly associated with WTP whereas risk *perception* was (two different PRCA risks were used: 4.5 per 10,000 patients and 45 per 10,000 patients). Respondents who felt the PRCA risk was substantial were willing to pay significantly more to avoid the PRCA risk than those respondents who felt the PRCA risk was small. In addition, this finding illustrates that the validity of WTP studies might be limited by the difficulty respondents have in interpreting small safety risks.

Benefit-risk assessment of pharmaceuticals was studied in **chapter 3** by means of a discrete choice experiment. We elicited benefit-risk preferences of (i) employees of a regulatory agency and (ii) a sample of academics. We found that both groups preferred pharmaceuticals with a low frequency and severity of adverse drug reactions, pharmaceuticals aimed at treating a high disease severity and with large health gains, and pharmaceuticals with no

therapeutic alternatives. The results indicate that health gains resulting from treatment were not valued equally to health losses resulting from adverse drug reactions. For both groups, a substantial proportion of respondents were not willing to trade-off a high risk of a life-threatening adverse drug reaction for a substantial health gain of recovering to full health from a disease that would have been fatal if not treated. Furthermore, regulators were less willing to trade off high risks for large health gains than the academics. These results indicate the existence of loss aversion regarding adverse drug reactions. Also, as we found that the general public was willing to pay considerably to avoid a small albeit severe drug safety risk (**Chapter 2**), and both regulators as well as academics strongly disliked pharmaceuticals with substantial safety risks, *even if* these safety risks were accompanied by large health gains (**Chapter 3**), we conclude that the regulation of drug safety risks is highly valued.

The methods employed in **chapter 2** (contingent valuation) and **chapter 3** (discrete choice experiment) are intended to measure preferences or values for non-market goods. In both studies respondents had to construct their preferences on the spot. Although little can be done to prevent different types of limitations when valuing non-market goods or policies, more effort should be made to gain insight into the cognitive process of constructing preferences. Face-to-face interviews or a group discussion following data collection could facilitate the elicitation of such feedback from respondents. Such activities would have helped in interpreting the results of both studies. Furthermore, future studies that deploy similar techniques to study benefit-risk assessment or the societal valuation of drug regulation should engage in such activities.

In order to determine whether the aims of the drug regulatory framework (i.e., to protect and promote public health) are sufficiently achieved at acceptable costs, the cost-effectiveness of drug regulatory requirements should be assessed (**chapter 4**). The feasibility of regulatory cost-effectiveness analysis was demonstrated in **chapters 6** and **7**. The guideline evaluated in **chapter 6** intends to increase drug safety through the prevention of drug-induced sudden cardiac deaths by mean of performing thorough QT/QTc studies. We identified an incremental cost-effectiveness ratio (ICER) of €187,175 per quality-adjusted life year (QALY) gained by this guideline, as compared to no regulation. Periodic Safety Update Reports (PSURs) aim to increase drug safety by detecting safety issues post-marketing. The ICER of PSUR reporting for biologicals was €342,110 per QALY gained (**chapter 7**). Both regulatory cost-effectiveness analyses found ICERs that are considerably higher than what would be considered 'favorable' for medical interventions.

There is no consensus regarding the willingness-to-pay per QALY threshold in the Netherlands or in most other Western countries. The United Kingdom uses a threshold of £30,000 per QALY gained to determine whether treatments should be reimbursed[1] and a

£50,000 per QALY gained threshold for life-extending treatments. A Dutch threshold of €20,000 to €80,000 per QALY, with the threshold depending on disease severity, was proposed in 2006[2] but thus far is not consistently applied in decision making. In the US, a $50,000-$100,000 per QALY threshold is commonly cited,[3] but decision making regarding reimbursement of treatments is fragmented within the US healthcare system. All of the willingness-to-pay per QALY thresholds mentioned here are considerably lower than the ICERs reported in **chapters 6** and **7**. However, the societal valuation of regulatory measures aimed at increasing drug safety is high (**chapter 2**) and health losses are not weighed equally to health gains (**chapter 3**). Therefore, the results of economic evaluations of healthcare programs (where effectiveness is achieved through health gains) and the economic evaluation of drug safety regulatory measures (where effectiveness is achieved through the prevention of health losses) cannot simply be valued within one decision-making framework without an assessment of the societal willingness to pay per QALY gained by drug safety regulation.

In both regulatory cost-effectiveness analyses (**chapter 6** and **chapter 7**), the effectiveness of the regulation is determined by reducing adverse drug reactions in patients. Compliance with safety regulation in clinical practice therefore is the essential mechanism through which increased public health is to be achieved. ECG monitoring of starting antipsychotic users in order to identify proarrhythmic QT prolongation resulted in health gains in **chapter 6**. In **chapter 7**, a Direct Healthcare Professional Communication (DHPC) lead to health gains as a result of PSUR reporting. Yet in both of these cases, compliance was found to be limited. It can be questioned, therefore, whether it would not be more efficient to increase the effectiveness of *existing* regulatory requirements rather than developing new safety-related regulations. Furthermore, new regulatory requirements hardly ever explicitly state how (i.e., through which mechanism) the requirement is expected to increase public health. This mechanism is either implicit or non-existent but essential to determine the cost-effectiveness of regulation. Therefore, regulators should be required to explicitly state how a new regulatory guideline is expected to increase public health (**chapter 4**).

Methodological considerations in regulatory cost-effectiveness analysis

One of the aims of this thesis was to establish whether health technology assessment could be used as a tool to evaluate the cost-effectiveness of drug regulation. Performing a regulatory cost-effectiveness according to the principles of economic evaluation as they are

outlined by Drummond et al. (2005)[4] is not problematic in most areas. We found that including direct and indirect costs, applying a discount rate to account for differential timing, and allowing for uncertainty regarding cost- and effectiveness estimates through the use of sensitivity analyses posed few challenges as compared to a cost-effectiveness analysis of a medical intervention. However, several methodological issues were identified that are inherent to the regulatory cost-effectiveness analysis. Here, we discuss the most important issues we identified and make recommendations for the future conduct of regulatory cost-effectiveness analysis.

Choosing the right comparator

A first encountered difference between the economic evaluation of a regulatory requirement and a medical intervention concerns the comparison of alternatives. Cost-effectiveness analysis is always comparative, with at least two alternatives included in the analysis.[4] When evaluating medical interventions, the standard treatment for patients is usually the logical comparator. In chapter 5, the cost-effectiveness of endovascular treatment for acute ischemic stroke patients was assessed. Intra-arterial thrombolysis is an experimental treatment for which a subset of acute stroke patients is eligible. As intravenous thrombolysis is the current standard treatment for acute ischemic stroke, the cost-effectiveness of endovascular treatment was assessed as compared to intravenous thrombolysis. Identifying a comparator in regulatory cost-effectiveness is less straightforward. When a regulatory requirement would be evaluated ex-ante, a sensible comparator would be the current standard, which often might be 'no regulation'. When a regulatory requirement already exists at the time of evaluation, which was the case in both **chapters 6** as **7**, several different strategies could be pursued.

We chose to compare 'regulation' to a (hypothetical) situation of 'no regulation'. Even if a situation of 'no regulation' whatsoever is not very realistic, comparing costs and health effects of a regulatory requirement to a 'no regulation' scenario enables the assessment of maximum achievable health effects, assuming that health losses due to safety issues are highest when there is no regulation in place aimed at preventing the adverse drug reaction. Given that many safety-related regulatory requirements are intended to increase public health through preventing adverse drug reactions, we believe that the potential health gains of a regulatory requirement should be established before identifying a range of different regulatory scenarios through which these health gains could be achieved - even though this would be an important second step of regulatory cost-effectiveness analysis. Therefore, for the selection of relevant alternatives in regulatory cost-effectiveness analysis, we recommend the use of a no-regulation comparator. If there are clear competing alternative regulatory scenarios identifiable, these scenarios should be included in the analysis as well.

Including the 'no regulation' scenario furthermore enables the assessment of opportunity costs. When a 'no regulation' baseline would not be included, this could result in the better of two generally undesirable regulatory scenarios being chosen.[5]

Identifying the patient population affected by the regulation

Regulatory requirements are sometimes implemented for a specific indication, drug, or patient population, but often requirements are implemented for all or a large group of drugs. This is a distinctive feature of a regulatory cost-effectiveness analysis. In **chapter 5**, the patient population consists of acute ischemic stroke patients admitted to the hospital within 4.5 hours of symptoms onset. In **chapter 7** however, the regulation is found to have impacted health in two very different patient populations: patients with cervical dystonia and lumbar spine fusion patients. Quantifying all patient characteristics, which is essential for estimating health effects, will become increasingly complicated when these characteristics need to be assessed for multiple patient populations. When a regulatory requirement is aimed at *all drugs*, quantifying its health effects and costs will be practically impossible. Yet in **chapter 6** we did evaluate a regulatory requirement aimed at all new drugs under development. In such a case, we recommend identifying those patient populations in which the *most* health gains are to be expected, which was the approach we took in **chapter 6** by assessing the health effects in a population of antipsychotic users. As a result, if the regulation is found to be not cost-effective in a population in which maximum health gains can be expected, one can infer a low likelihood that the regulation will be cost-effective in populations with lower expected health gains, given that costs associated with the adverse drug reaction are proportionate to its incidence (**Box 1**). An exception could be a situation in which the *combined* health gains *across* patient populations would result in significantly more health gains *without* an equal increase in costs associated with the regulation. For example, in **chapter 7**, all regulatory costs are invoked by PSUR reporting and there are no costs related to the prevention of the two safety issues that were identified. If PSUR reporting would have detected more urgent safety issues, the health gains of the regulation would have been higher but regulatory costs would have remained identical. This hypothetical example would have resulted in a more favorable ICER.

Evidence used for effectiveness and cost estimates

We found that the main issue in regulatory cost-effectiveness analysis concerns the ability to reliably establish the health effects and costs of the regulation. In cost-effectiveness analysis, establishing the health effects of an intervention (and its comparator) is preferably done through a clinical trial, systematic overview of clinical studies, or observational studies.[4] In **chapter 5**, the effectiveness of endovascular treatment and its comparator treatments are

estimated based on different published clinical studies. Cost estimates were used from a clinical trial (EDISSE) and health utility estimates originated from another trial (PRACTISE) and therefore were based on patient-level observations. In a randomized controlled trial, several measures are taken (e.g., randomization and strict in- and exclusion criteria to create homogenous patient groups) to minimize the possibility that any observed difference in health outcomes between treatment arms can be attributed to anything but the effect of the intervention. Modeling employed in economic evaluation therefore is based on observed differences in health outcomes in actual patients. In estimating the effectiveness of safety-related regulatory requirements, clinical trials are not a valid source for estimating health effects. Extensive post-marketing surveillance is required for marketed products *exactly because* clinical trials are insufficient for a complete safety profile of a pharmaceutical product.[6,7] Therefore, as clinical trials cannot be used to estimate the health effects of any regulatory requirement aimed at increasing public health through the prevention of adverse drug reactions, other types of evidence will have to be used.

As additional costs are usually invoked by implementing a regulatory requirement, the findings in chapters 6 and 7 described below stipulate the prerequisite that a new regulation should always result in substantial health gains accompanied by cost savings in order to become cost-effective:

In chapter 7, the costs of PSUR reporting amounting to €15.3 million during a 13-year period are not outweighed by the cost savings resulting from PSUR reporting, as the incremental costs remain €13.5 million, and health gains are modest at 39 incremental QALYs. A sensitivity analysis demonstrated, however, that a larger risk reduction (100%) resulting from the regulation could result in an incremental cost-effectiveness ratio of €50,808 per QALY gained.

In chapter 6, preventive measures to avoid drug-induced sudden cardiac deaths invoke additional costs as each starting user will have to undergo at least two electrocardiographs at €20 each. These additional costs are simply not outweighed by the health gains produced by the regulation and not even when assuming maximum achievable health gains.

Box 1: Safety-related regulatory requirements will not be cost-effective if they do not result in substantial health gains accompanied by cost savings.

In both regulatory cost-effectiveness analyses reported in this thesis, various sources, mostly from the scientific literature, were used to estimate all required parameters (i.e., direct- and indirect costs, health utilities, life expectancy, and drug utilization data). Combining different sources of evidence resulted in considerable uncertainty concerning the model parameters. Therefore sensitivity analysis was used to study the impact of uncertainty, apart from variation, on the outcomes. Especially when performing cost-effectiveness analysis using literature estimates as opposed to patient-level data, which will usually be the case in

regulatory cost-effectiveness analysis, the application of sensitivity analysis is essential. Therefore we recommend that, when performing univariate, multivariate, or probabilistic sensitivity analysis, a wide range (distribution) of possible input parameters are chosen in order to appropriately quantify uncertainty regarding model assumptions

In both **chapter 6** and **chapter 7**, we believe it is more likely we have overestimated, as opposed to underestimated, the adverse drug reaction risks. Suppose we perform a regulatory cost-effectiveness and conclude that the regulation aimed at preventing an adverse drug reaction is cost-effective, while in fact it is not (Type I error). The consequences of such a mistake would be efficiency losses, but it is unlikely that a regulatory requirement determined to be cost-effective would be removed from the drug regulatory framework. Yet, if we would conclude the regulation was not cost-effective for example due to underestimating a safety risk while in fact it is (Type II error), and the regulation would be changed or removed from the regulatory framework, the consequence of this type of error would be decreased public health. Considering the high social valuation of safety-related regulatory actions (**chapter 2**) and the finding that health losses are not evaluated equal to health gains (**chapter 3**), we believe that the first type of error (wrongfully concluding a regulation is cost-effective) will be more acceptable to society than the second type of error (wrongfully concluding a regulation is not cost-effective), even though opportunity costs would be invoked in such a situation.

"Safety first" and the price of precaution

The willingness-to-pay threshold per QALY gained by safety regulation cannot be assumed to be equal to any willingness-to-pay threshold per QALY for medical interventions. The societal monetary valuation of safety-related regulatory measures is high (**chapter 2**), and we found evidence for loss aversion with regard to drug safety risks (**chapter 3**), as respondents unequally traded off health gains and health losses. Furthermore, two regulatory cost-effectiveness analyses (**chapter 6** and **chapter 7**) identified high ICERs for regulatory measures aimed at increasing drug safety. In the final part of this chapter, the implications of our findings for the drug safety regulatory framework are discussed.

Safety first

The 'Vioxx debacle' is often named as one of the instigators of a shifted societal and regulatory focus on drug safety.[8,9] Vioxx (rofecoxib) was a widely prescribed anti-arthritis drug and was withdrawn from the market in 2004, after an increased risk of myocardial infarctions and stroke was found.[10] Nowadays, substantially more powerful safety-

evaluation methods are available[9] which were developed in response to '*a fundamental shift in the way society views medicine*'.[10] Before these new methods can be translated into actual public health benefits,[9] however, several unintended consequences of this shifted focus on drug safety should be addressed. First, more powerful tools to detect safety signals are likely to increase the number of false-positive safety signals.[9] This could distort the balance between promoting and protecting public health, where effective drugs with manageable or acceptable safety risks might have their marketing license revoked. Also, it could be argued that these regulatory developments are a response to an increasingly risk-averse society, yet convincing evidence that these developments reflect a societal preference is currently lacking.[9] Furthermore, a shifting focus on drug safety might increase public awareness of safety risks, which in turn could result in even more demand for high drug safety. This could be prevented, as argued by Eichler et al. (2009), by moving from *implicit* to *explicit* decision making with regard to benefit-risk assessment, which could add to greater consistency and transparency of regulatory decision making.[9] However, the European Medicines Agency stated in 2008 that 'intuitive expert judgment' was expected to remain the cornerstone of benefit-risk assessment,[11] which makes a transition to more explicit regulatory decision-making unlikely in the short-term.

This increased focus on drug safety only serves one of the two goals of drug regulation: safety-related regulatory requirements aiming to protect public health by ensuring unsafe drugs do not reach patients. High safety requirements do not only raise the bar for market introduction but also increase the costs of drug development.[12] If these high safety standards do not reflect a societal preference regarding drug safety levels, however, there merely is a *negative* impact on public health, as it would result in effective treatments with manageable or acceptable safety risks not reaching patients. This particular impact of the current drug regulatory framework is highly probable. The consequences of approving a harmful drug, as opposed to *not* approving a safe and effective drug, are much more serious to regulators,[13] and these consequences are much more visible to the public as well. According to Lundkvist & Jonsson (2004), cost-benefit studies of regulatory policy are therefore needed to aid regulators in rational decision-making, and to justify regulatory decision-making to the public.[13] However, cost-benefit analysis (in which both costs and effects are weighed in monetary terms), is not commonly applied, and monetary valuation of health benefits (i.e. by means of contingent valuation as used in **chapter 2**) has several methodological issues. Therefore, the application of health technology assessment in regulatory cost-effectiveness analysis, as demonstrated in this thesis, is a more feasible approach. Regulatory cost-effectiveness studies could facilitate a shift away from the current implicit regulatory decision making by identifying an explicit optimum of protecting and promoting public health through the drug regulatory framework. Furthermore, regulatory

decision making needs to become more transparent to improve the accountability and reasonableness of regulatory decisions.[14]

The price of precaution

More stringent regulatory safety requirements have increased the costs of drug development,[12,15] and yet the potential opportunity costs of stringent regulatory safety requirements go largely unnoticed when proposals for more safety regulation are made.[16] The central elements of economic evaluation are constrained resources, trade-offs, and opportunity costs: *'you can't have everything you want, you can't get something for nothing, and you should think about what you have to give up to get something you do want'*.[17] Every Euro spent on compliance with a cost-*ineffective* regulatory requirement, would therefore be better spent on cost-*effective* regulation, or not at all. As both regulatory cost-effectiveness analyses reported in this thesis (**chapters 6** and **7**) demonstrated high ICERs of safety regulation (compared to no regulation), it is probable that a non-optimal allocation of resources in the drug regulatory framework currently exists, regardless of whether the actual total costs of drug development are $800 million[18] or $34 million.[19] If the willingness to pay per QALY for drug safety regulation would be €80,000 per QALY gained, both regulatory requirements studied in **chapters 6** and **7** should be removed from the regulatory framework, and not removing them from the regulatory framework would result in both efficiency losses and opportunity costs.

Figure 1 illustrates that the costs of adverse drug reactions are low when the incidence of the adverse drug reaction is low and that in such a situation the costs of avoiding the adverse drug reaction (i.e. safety regulation) are higher than the aggregated costs invoked by the adverse drug reaction. This implies that when health effects of safety regulation are not taken into account, a safety risk should only be regulated when the costs associated with the risk are higher than the costs of avoiding the risk. However, in the current regulatory framework costs are hardly considered at all and regulatory decision making is driven by avoiding adverse drug reactions. Yet, if decision making would be based solely on costs, any health effects invoked by avoiding safety risks would be disregarded. A decision-making framework based on costs alone therefore is insufficient as well. Regulatory cost-effectiveness analysis weighs both the costs and health effects of a regulation in deciding whether safety risks should be regulated or not and therefore is a more comprehensive framework for regulatory decision-making.

Regulatory cost-effectiveness analysis would be an essential tool in establishing a shift from implicit to explicit regulatory decision making. The application of regulatory cost-effectiveness analysis would have little value, however, if its outcomes cannot be confronted

with a societal willingness to pay per QALY gained by safety regulation. Furthermore, the acceptability of drug safety risks, both in severity and magnitude, depends on several drug characteristics (**Chapter 3**). Quantitative benefit-risk assessment tools could express health gains and health losses of pharmaceuticals in terms of QALYs as well.[21-23] Therefore, quantitative benefit-risk assessment would not only aid explicit decision making in benefit-risk assessment, but could also facilitate regulatory decision making regarding safety risks as the cost-effectiveness of safety regulation would be easier to assess with net health benefit information available.

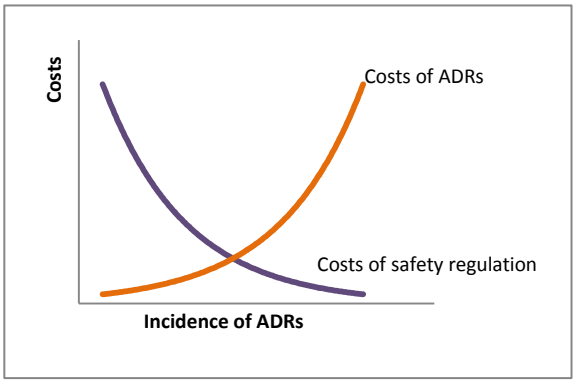

Figure 1. Relationship between the costs of safety regulation and the costs of adverse drug reactions. Total costs of regulation decrease when ADR incidence is high, whereas the costs of ADRs depend on the incidence of ADRs. For each ADR, the optimum (do the costs of ADRs require regulatory action) is determined by (a) the costs of ADRs, (b) the costs of regulation, and (c) the health gains associated with regulation (not depicted in this graph). Figure based on Pedroni (1984) and Lundkvist & Jonsson (2004).

Final remarks

Dutch writer Maarten 't Hart lives in a house that is situated several meters below sea level. Although the actual risk of a flood is very low, nonetheless he keeps a rubber boat in his attic.[24] While most people living below sea level do not have rubber boats in their attics, the cost (as measured in both time and resources) of buying a rubber boat and placing it in the attic are low and its impact could be potentially lifesaving. But what if Maarten 't Hart would have thought that a rubber boat was not sufficient and would have dedicated his time and resources to build an Ark of biblical proportions? Considering the opportunity cost of building an Ark implies no time for writing beautiful books, it would make no sense to spend months or years building an Ark *when a rubber boat will suffice*.

The notion that regulating drug safety, no matter what the cost, can invoke substantial efficiency losses has been largely ignored, both by regulators and the scientific literature, and therefore was addressed in **chapters 6** and **7** of this thesis. **Chapters 2** and **3** provide possible explanations for the observations made with regard to the high ICERs for safety regulation that were identified. In conclusion, there is a need for a move to more explicit regulatory decision making with regard to the acceptability and unacceptability of drug safety risks. Regulatory cost-effectiveness analysis is the only tool that could support determining an optimum between protecting and promoting public health. Furthermore, the use of regulatory cost-effectiveness analysis, in combination with quantitative benefit-risk assessment tools, will help regulators choosing between rubber boats and Arks in shaping a more transparent drug regulatory framework.

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Summary

The European pharmaceutical market is strictly regulated. Sufficient levels of quality, safety, and efficacy will have to be demonstrated before a pharmaceutical is allowed to enter the market. Drug regulation has two aims: first, to protect public health by keeping low-quality, unsafe, or inefficacious products from entering the market, and second, to promote public health by ensuring needed drugs reach patients without unnecessary delay. There is little evidence, however, that the current drug regulatory framework is achieving its goals in a cost-effective manner. The aim of this thesis therefore was to assess the cost-effectiveness of several parts of the drug regulatory framework in order to identify whether the aims of safety-related drug regulation are met. Furthermore, several other methodological approaches were used to assess the monetary valuation of safety-related regulatory actions, as well as trade-offs made with regard to benefit-risk assessment of pharmaceuticals.

In **chapter 2**, we found that the societal valuation of safety-related drug regulation as measured in monetary terms is high. In this study, the general public as well as chronic kidney disease patients were asked how much they were willing to pay to reduce the risk of Pure Red Cell Aplasia (PRCA) in users of epoetin. The general public was willing to accept an average increase of their annual health insurance premium, which was about €1,100, of €24.40 (median €10). Chronic kidney disease patients were willing to accept an annual increase of their health insurance premium of €46.52 (median €35). Although two different PRCA risks were used in the study, as 50% of respondents were told the risk of PRCA was 4.5 per 10,000 patients, whereas the other 50% of respondents were told the PRCA risk was 45 per 10,000 patients, no significant risk magnitude effect was found. Risk perception, however, *was* found to have a significant impact on willingness to pay, illustrating that risk perception determines willingness to pay for safety-related regulatory actions rather than actual risk magnitude. Furthermore, respondents have difficulty in the interpretation of small risks. Although several limitations existed in this study, we believe the results indicate a high societal valuation of drug safety regulation, as measured in monetary terms.

Chapter 3 was dedicated to the elicitation of preferences with regard to regulatory benefit-risk assessment of pharmaceuticals. A discrete choice experiment (DCE) was used to study trade-offs that are made by regulators, academics, a pharmaceutical company, and hospital pharmacists. We found that both regulators and academics prefer drugs that are aimed at treating diseases with a high disease severity, with non-severe and infrequent adverse drug reactions, and that have no therapeutic alternatives. A substantial proportion of both the regulator and the academics group was reluctant to trade-offs large adverse drug reaction risks for substantial health benefits. This might indicate that in benefit-risk assessment, health benefits and health losses are not valued equally, which is in line with economic theory. Furthermore, we found that regulators exhibited slightly more loss aversion than

academics. The results of **chapter 3** stipulate the need for a more explicit and transparent framework for regulatory benefit-risk assessment.

Chapter 4 provided a brief overview of the most important arguments in favor of regulatory cost-effectiveness analysis and was followed by **chapter 5**, in which the application of Health Technology Assessment (HTA) in the evaluation of medical interventions is demonstrated. Four different treatment strategies for acute ischemic stroke patients were evaluated: conservative treatment, intravenous thrombolysis, intra-arterial thrombolysis, and intravenous thrombolysis followed by intra-arterial thrombolysis. This exploratory study found that the cost-effectiveness of intravenous thrombolysis followed by intra-arterial thrombolysis depends on several factors: (i) recanalization rates, (ii) the costs of treatment, and (iii) the rate of complications.

Chapter 6 and **chapter 7** demonstrated the feasibility of HTA in the economic evaluation of drug regulation. **Chapter 6** was dedicated to assessing the cost-effectiveness of thorough QT/QTc (TQT) studies. These clinical trials are aimed at assessing a pharmaceutical's QT-prolonging potential and have been implemented as a mandatory part of drug development since 2005. The cost-effectiveness of TQT studies was assessed for the US and European populations of antipsychotic users, as antipsychotics are a drug class in which QT-prolongation is a common adverse event. The incremental cost-effectiveness of the TQT-studies regulation, as compared to a scenario of no TQT-studies regulation, was about €187,000 per quality-adjusted life year gained and about €2.4 million per sudden cardiac death prevented.

In **chapter 7**, the cost-effectiveness of Periodic Safety Update Reports (PSURs) for biologicals during 1995-2009 was assessed. During this time period, PSURs identified a total of 24 urgent safety issues, of which two (swelling complications after dibotermin-alfa and systemic spread of botulinum toxin with therapeutic use) were primarily identified through PSURs. The incremental cost-effectiveness of PSUR-reporting for biologicals, as compared to no PSUR reporting, was about €343,000 per QALY gained. Extensive sensitivity analyses indicated that only two parameters could have resulted in much more favorable results: a high risk of severe complications after systemic spread of botulimun toxin, and a risk reduction of 100% after both urgent safety issues were identified.

Chapter 8 was dedicated to a general discussion of the work reported in this thesis. Both **chapter 2** and **chapter 3** indicate a high societal valuation of safety-related regulatory measures, which might explain the high incremental cost-effectiveness ratios (ICERs) we found in **chapter 6** and **chapter 7**. Nonetheless, it is argued in **chapter 8** that the potential opportunity costs of regulating small drug safety risks are often overlooked, yet, these opportunity costs could be substantial and result in higher drug prices. Developments during

the last two decades have resulted in a regulatory and societal focus on drug safety, with little regard for the potential adverse effects of this safety focus. Even though several methodological challenges exist in regulatory cost-effectiveness analysis, this thesis demonstrated the feasibility of this approach in the evaluation of the drug regulatory framework. Regulatory cost-effectiveness analysis therefore could play an important role in assessing regulatory measures, in order to determine a more efficient, and therefore more sustainable, drug regulatory framework. Furthermore, regulatory cost-effectiveness analysis is able to determine whether regulatory measures are risk proportionate, not only with regard to the risk magnitude, but also with regard to the resources required to reduce drug safety risks.

Samenvatting

De Europese farmaceutische markt is sterk gereguleerd. Voordat een geneesmiddel op de markt mag worden gebracht, moet eerst worden aangetoond dat de kwaliteit, veiligheid en werkzaamheid van voldoende niveau zijn. Medicijnregulering heeft twee doelen: ten eerste, het *beschermen* van de volksgezondheid door ervoor te zorgen dat medicijnen van lage kwaliteit, onveilige medicijnen of niet-werkzame medicijnen niet op de markt worden gebracht. Ten tweede heeft medicijnregulering tot doel de volksgezondheid te *bevorderen* door ervoor te zorgen dat noodzakelijke medicijnen patiënten bereiken zonder onnodige vertraging. Op het moment is er echter weinig bewijs dat het huidige systeem van medicijnregulering ook daadwerkelijk deze doelen bereikt op een kosteneffectieve manier. Het doel van dit proefschrift was daarom om vast te stellen wat de kosteneffectiviteit is van verschillende onderdelen van het systeem van medicijnregulering, om te kijken of de doelen van medicijnregulering ook daadwerkelijk worden bereikt. Bovendien worden in dit proefschrift verscheidene andere methoden aangewend om zowel de monetaire waardering van veiligheid-gerelateerde medicijnregulering, als de afwegingen zoals die in de baten-risico afweging van medicijnen gemaakt worden, te onderzoeken.

In **hoofdstuk twee** stellen we vast dat de maatschappelijke waardering van veiligheid-gerelateerde medicijnregulering (gemeten in monetaire termen) hoog is. In deze studie werd zowel het algemene publiek als patiënten met chronische nieraandoeningen gevraagd naar hun betalingsbereidheid om het risico op Pure Red Cell Aplasia (PRCA) in gebruikers van epoetin te verminderen. Het algemene publiek was bereid om een gemiddelde toename van €24,40 van hun jaarlijkse zorgverzekeringspremie (die rond de €1.100 lag ten tijde van de studie) te accepteren. Hoewel twee verschillende PRCA risico's gebruikt werden in deze studie (50% van de respondenten werd verteld dat het PRCA risico 4.5 per 10.000 patiënten was, terwijl de andere 50% werd verteld dat het risico 45 per 10.000 patiënten was), vonden we geen significant effect van de risicogrootte. Risicoperceptie, echter, was wel significant van invloed op de betalingsbereidheid van respondenten. Deze bevinding illustreert dat de betalingsbereidheid voor veiligheid-gerelateerde medicijnregulering in grotere mate bepaald wordt door de risicoperceptie dan door het daadwerkelijke risico. Hoewel er verschillende beperkingen, inherent aan de gebruikte methode in deze studie, bestaan, geloven we dat deze resultaten laten zien dat de maatschappelijke waardering voor veiligheid-gerelateerde regulering, gemeten in monetaire termen, hoog is.

In **hoofdstuk drie** van dit proefschrift zijn de voorkeuren met betrekking tot de risico-baten afweging van geneesmiddelen zoals deze door reguleerders wordt gemaakt, gemeten. Hierbij werd gebruikt gemaakt van een discrete choice experiment (DCE). De voorkeuren van vier verschillende groepen zijn bestudeerd: reguleerders, academici, een farmaceut, en ziekenhuisapothekers. We vonden dat zowel reguleerders als academici voorkeuren hebben voor geneesmiddelen die tot doel hebben om ziektes met een hoge ziektelast te behandelen,

voor geneesmiddelen die niet-ernstige en in frequente bijwerkingen hebben, en voor geneesmiddelen die geen therapeutische alternatieven hebben. Een substantieel gedeelte van zowel de groep van reguleerders als ook de groep academici was niet bereid om een hoog risico op ernstige bijwerkingen uit te ruilen tegen een hoge gezondheidswinst. Deze bevinding illustreert mogelijkerwijs dat in risico-baten analyse gezondheidswinst en gezondheidsverliezen niet identiek worden gewaardeerd, maar dat gezondheidsverlies zwaarder weegt dan gezondheidswinst, wat in lijn is met economische theorie. Deze resultaten benadrukken de noodzakelijkheid van een expliciet en transparant raamwerk voor regulatoire risico-batenanalyse.

In **hoofdstuk vier** worden de belangrijkste argumenten voor de toepassing van kosteneffectiviteitsanalyse voor het evalueren van medicijnregulering, beknopt uiteengezet. In **hoofdstuk vijf** wordt de toepassing van Health Technology Assessment (HTA) bij de evaluatie van een medische interventie gedemonstreerd. Vier behandelstrategieën voor patiënten met een beroerte werden geëvalueerd: conservatieve behandeling, intraveneuze trombolyse, intra-arteriële trombolyse, en intraveneuze trombolyse gevolgd door intra-arteriële trombolyse. In deze exploratieve studie vonden we dat de kosteneffectiviteit van intraveneuze trombolyse gevolgd door intra-arteriële trombolyse afhangt van (i) bij hoeveel procent van de patiënten recanalizatie wordt bereikt, (ii) de behandelkosten, en (iii) het aantal patiënten met complicaties.

Hoofdstuk zes en **hoofdstuk zeven** wordt de haalbaarheid van het toepassen van HTA bij de economische evaluatie van medicijnregulering gedemonstreerd. In hoofdstuk zes werd de kosteneffectiviteit van thorough QT/QTc studies gedemonstreerd. Deze klinische trials hebben tot doel te onderzoeken of een geneesmiddel het QT interval (van het hart), een risicofactor voor het optreden van plotselinge hartdood, verlengt. Deze studies zijn sinds 2005 een verplicht onderdeel van het ontwikkelingsprogramma voor nieuwe geneesmiddelen. Uit **hoofdstuk zes** blijkt dat de incrementele kosteneffectiviteit van deze studies ongeveer €187.000 per voor kwaliteit gecorrigeerd levensjaar is en ongeveer €2.4 miljoen per voorkomen plotselinge hartdood.

In **hoofdstuk zeven** is de kosteneffectiviteit van Periodieke Veiligheid Update Rapporten voor biotechnologie geneesmiddelen gedurende 1995-2009 onderzocht. Tijdens deze periode resulteerden de periodieke veiligheidsrapporten in de detectie van twee uit een totaal van 24 verschillende urgente veiligheidsproblemen voor biotechnologie geneesmiddelen. De incrementele kosteneffectiviteit van periodieke veiligheidsrapporten voor deze groep geneesmiddelen was ongeveer €343.000 per voor kwaliteit gecorrigeerd levensjaar. Sensitiviteitsanalyses wezen uit dat slechts twee parameters een grote invloed hadden op de uitkomsten: het risico op zeer ernstige complicaties bij het therapeutisch gebruikt van

botuline toxine en de risicoreductie die volgt nadat een ernstig veiligheidsprobleem is ontdekt.

Hoofdstuk acht bestaat uit een algemene discussie van het werk dat in dit proefschrift gerapporteerd wordt. Zowel **hoofdstuk twee** als **hoofdstuk drie** laten een hoge maatschappelijke waardering zien voor veiligheid-gerelateerde medicijnregulering. Deze bevinding verklaart mogelijk de hoge incrementele kosteneffectiviteitsratio's die we vonden in hoofdstuk zes en hoofdstuk zeven. Desalniettemin wordt in **hoofdstuk acht** beargumenteerd dat de potentiele opportuniteitskosten die het gevolg kunnen zijn van het reguleren van (zeer) kleine veiligheidsrisico's, vaak niet worden meegenomen, terwijl deze opportuniteitskosten zowel substantieel kunnen zijn en ook kunnen resulteren in hogere medicijnkosten. Het bepalen van de kosteneffectiviteit van medicijnregulering zou daarom een belangrijke rol kunnen spelen in het ontwerpen van een meer efficiënt en dus een duurzamer raamwerk van medicijnregulering. Bovendien is deze methode in staat om te bepalen of medicijnregulering proportioneel is gezien het veiligheidsrisico en gezien de kosten die verbonden zijn aan het reduceren van deze veiligheidsrisico's.

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Curriculum Vitae

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