Volume 13 • Number 2 • 2010
VALUE IN HEALTH

Crossing Borders: Factors Affecting Differences in Cost-Effectiveness of Smoking Cessation Interventions between European Countries

Pepijn Vemer, MSc, Maureen P.M.H. Rutten-van Mölken, PhD

Institute for Medical Technology Assessment (iMTA), Erasmus MC, Rotterdam, The Netherlands

ABSTRACT

Objectives: Many different factors affect the transferability of cost-effectiveness results between countries. The objective is to quantify the impact of nine potential causes of variation in cost-effectiveness of pharmacological smoking cessation therapies (SCTs) between The Netherlands (reference case), Germany, Sweden, UK, Belgium, and France.

Methods: The life-time benefits of smoking cessation were calculated using the Benefits of Smoking Cessation on Outcomes model, following a cohort of smokers making an unaided quit attempt, or using nicotine replacement therapy (NRT), bupropion, or varenicline. We investigated the impact of between-country differences in nine factors—demography, smoking prevalence, mortality, epidemiology and costs of smoking-related diseases, resource use and unit costs of SCTs, utility weights and discount rates—on the incremental net monetary benefit (INMB), using a willingness-to-pay (WTP) of €20,000 per quality adjusted life year (QALY).

Results: The INMB of 1000 quit attempts with NRT versus unaided, varies from €0.39 million (Germany) to €1.47 million (France). The differences between the countries were primarily due to differences in discount rates, causing the INMB to change between −65% to +62%, incidence and mortality rates (epidemiology) of smoking-related diseases (−43% to +35%) and utility weights. Impact also depended on the WTP for a QALY and time horizon: at a low WTP or a short time horizon, the resource use and unit costs of SCTs had the highest impact on INMB.

Conclusions: Although all INMBs were positive, there were significant differences across countries. These were primarily related to choice of discount rate and epidemiology of diseases.

Keywords: bupropion, cost-effectiveness, cost-utility, incremental net monetary benefit, Markov model, nicotine replacement therapy, smoking cessation, smoking-related diseases, transferability, varenicline, Western Europe.

Introduction

An increasing number of regulatory agencies across the world require evidence on the cost-effectiveness of new pharmacotherapies. All these agencies need results that represent their own unique national or regional setting. Nevertheless, time and budget constraints limit the number of clinical trials and economic evaluations pharmaceutical companies can conduct in potential markets. In addition, there is increased acknowledgement of the limited external validity of country-specific cost-effectiveness data. In recognition of these difficulties, ISPOR initiated the Transferability of Economic Data Task Force. Their mission was to develop good research practices on the transferability of economic data in health technology assessment [1].

The Task Force advocates the use of mathematical decision-analytic models to assess setting-specific cost-effectiveness. These models synthesize and structure evidence from diverse sources, allow expanding the time horizon beyond that of a clinical trial, as well as adapting and transferring results from one setting to another [2,3]. For these reasons, models have been developed to assess the long-term cost-effectiveness of smoking cessation interventions.

A recent example is the BENESCO (Benefits of Smoking Cessation on Outcomes) model [4] which was developed by Heron Evidence Development Ltd, to support the launch of varenicline in various countries, e.g., The Netherlands [5], Sweden [6], Belgium [Annemans et al., unpubl. ms.], Germany [7], the UK [8], the Czech Republic [9], Korea [10], Japan [11], and Denmark [12]. Interesting differences in the cost-effectiveness of the various smoking cessation medications were observed [13,14], which may relate to various sources of variation, for example the incidence and prevalence of smoking and smoking-related diseases, characteristics of the population of smokers, differences in absolute and relative unit costs of medications and health-care services and many other factors.

This study was designed to unravel the factors driving differences in cost-effectiveness of pharmacological smoking cessation therapies (SCTs) between six European countries. The countries included were The Netherlands, Belgium, Germany, Sweden, the UK, and France, countries for which, at the start of the study, country-specific input data of the model were available.

Methods

The Model

The projections of the effects of smoking cessation were based on the BENESCO model [15], which is a probabilistic, updated, and improved version of the Health and Economic Consequences of Smoking model [16]. The BENESCO model simulates the consequences of smoking and the benefits of quitting in terms of smoking-related morbidity, mortality, and associated medical costs in a population. The model is structured as a Markov model (cycle length 1 year) and follows a hypothetical cohort of current smokers making a single attempt to quit smoking at the beginning of the simulation. The cohort is followed from the time of their quit attempt until all members of the cohort have died. Individuals are classified into one of three smoking states, i.e., smoker, recent quitter (abstinent 1 to 5 years after successful quit attempt), or long-term quitter. Transition probabilities between smoking states in the first year depend on cessation rates of the

Address correspondence to: Pepijn Vemer, Erasmus University, Institute for Medical Technology Assessment, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands. E-mail: vemer@bmg.eur.nl

10.1111/j.1524-4733.2009.00612.x

interventions, while the probabilities after 1 year depend on relapse rates, which in turn depend on time since quitting. The model simulates the age, gender, and smoking status-specific incidence and mortality of four major diseases for which smoking is a well-established risk factor: chronic obstructive pulmonary disease (COPD), lung cancer, coronary heart disease (CHD), and stroke. Smoking state-specific incidence and mortality rates were calculated using relative risks [17,18]. The incidence and mortality rates for recent quitters were calculated using the relative risks of former smokers versus nonsmokers, while the rates for long-term quitters were assumed to be the same as those of never smokers. Because COPD and lung cancer are chronic progressive conditions, these diseases were given hierarchical prominence over the other conditions with acute recurrent events. This means that individuals with COPD or lung cancer remain in this state until they die and cannot move to a CHD or stroke state, whereas individuals with CHD or stroke can move to the COPD or lung cancer state. As in all Markov models, states are mutually exclusive, which means that a patient cannot have two diseases at the same time. The model calculates the total number of smokers and quitters that have one of the smoking-related diseases as well as the number of deaths (due to one of the smoking-related diseases and overall) over the time horizon of the simulation. Based on these numbers, the total health-care costs associated with the different disease states and the total number of (quality adjusted) life years is calculated. The model uses three age bands: 18 to 34 years, 35 to 64 years, and 65 years and older. Subjects alive in the model at age 99 years are all assumed to die in the next cycle. It is assumed that there is no smoking-related morbidity or mortality in the 18 to 34 years age class.

SCTs

We calculate the cost-effectiveness of three frequently used pharmacological SCTs— nicotine replacement therapy (NRT), bupropion, and varenicline—and unaided cessation. NRT is the generic term for any form of smoking cessation aid which delivers a measured dose of nicotine to the person using it. Examples include the nicotine patch or nicotine gum. Bupropion is an antidepressant used to support smoking cessation [19]. Varenicline is designed to relieve symptoms of nicotine withdrawal including cigarette craving and block the reinforcing effects of continued nicotine use [20]. The 12-month continuous abstinence rates were based on a meta-analysis of available randomized controlled trials, where the SCTs were always given in combination with counselling [5]. They were 5.0% for unaided cessation, 14.8% for NRT, 17.0% for bupropion, and 22.4% for varenicline. In all analyses, we assumed that 25% of smokers undertake a single quit attempt, using one of the smoking cessation interventions, or unaided. It is this cohort that is followed over lifetime.

Factors Affecting Transferability

A total of nine factors that could potentially cause differences in cost-effectiveness between countries were investigated. Each factor consists of a group of country-specific input parameters which are varied simultaneously. Table 1 gives the most important input parameters of each of the nine factors.

The nine country-specific factors include:

F1: Demography. This includes the total number of people older than 18 years of age and the break-downs of the population by gender and age-classes.

F2: Smoking Prevalence. This refers to the percentage of smokers, nonsmokers, and former smokers in each age/gender class.

F3: All-cause mortality. Mortality in the general population is expressed as the all-cause mortality rate, which is the percentage of the total number of people in each age/gender class that dies during a single year.

F4: Epidemiology of smoking-related diseases. The epidemiology of smoking-related diseases consists of three elements: the incidence rates, prevalence rates, and annual cause-specific mortality rates by age/gender class. We applied the disease definitions that were actually used in each country at the time of writing the reimbursement dossiers for varenicline. To identify COPD, all countries used ICD-10 codes J40–44, UK and Sweden also used J47. To identify lung cancer, all countries used C33–34, except Sweden that defined lung cancer as C34. CHD is identified in all countries as I20–25. Stroke in The Netherlands and Belgium is identified as I60–I69 plus G45, in Sweden as I61 and I63, in Germany as I60, I61, I63 and I64, and in the UK and France as I60–I64.

Given the causal relationship, there is a strong association between smoking prevalence and the epidemiology of smoking-related diseases. To enter these two factors as independent factors in the univariate analysis, we calculated the country-specific incidence, prevalence, and mortality of smoking-related diseases among nonsmokers, i.e., the country-specific baseline risk. This was done using the country-specific epidemiology and smoking prevalence, and the relative risks for smokers, former smokers, and nonsmokers used within the model. When studying the impact of the factor "epidemiology" in the univariate analysis, the Dutch baseline-risk was replaced by the country-specific baseline risk, which was then combined with the relative risks and the Dutch smoking prevalence to estimate the incidence (or prevalence or mortality) of smoking-related diseases among smokers and ex-smokers.

F5: Costs of smoking-related diseases. The model makes a distinction between the first-year costs and subsequent-year costs for lung cancer, CHD, and stroke, diseases for which high initial costs are generally followed by lower maintenance costs. As COPD does not have (much) higher initial costs, this distinction is not relevant for COPD.

F6: Resource use and F7: Unit costs of SCTs. The intervention costs of SCTs are separated into two components: the amount of resource use (i.e., medication and counselling) associated with the SCTs and the unit costs of these resources. We have investigated both these factors separately.

F8: Utility weights. The BENESCO model requires two categories of utility inputs: utility weights for the general, disease-free (developed no smoking-related disease) population, which vary by age, and the disease-specific utility weights, which vary by type of smoking-related disease. The Netherlands is the only country in our sample for which country-specific utility weights for both categories were provided. Germany, Sweden, the UK, and France all have used the provided default values within the model. Belgium has used the general population utility weights from The Netherlands and the default disease-specific utility values.

F9: Discount rates. All costs and outcomes are discounted using the country-specific values that are recommended in the national guidelines for economic evaluations. In the reference case, costs are discounted at 4%, outcomes at 1.5%.

We adopted a health-care perspective and included health-care costs that are either covered from the health-care budgets or paid for by patients. All prices and costs were inflated to 2006, using the Harmonised Indices of Consumer Prices—all items [100]. We also compensated for differences in purchasing power,

Table 1 Main country-specific input parameters for each factor potentially contributing to between-country variation in cost-effectiveness of smoking cessation interventions

	The Netherlands	Belgium	Germany	Sweden	United Kingdom	France
Population characteristics (age 18+, × mln)						
Population size	12.7	8.2	67.1	7.3	46.6	46.8
Number of smokers	3.54	2.25	18.61	1.51	12.70	11.53
As % of adult population	28%	27%	28%	21%	27%	25%
Cohort size: smokers making a quit attempt	0.88	0.56	4.65	0.38	3.17	2.88
F1: Demography						
Males, 18 to 34 years	14.1%	13.9%	13.6%	15.4%	14.4%	14.6%
Males, 35 to 64 years	27.3%	25.5%	26.5%	24.7%	25.4%	24.6%
Males, 65+ years	7.6%	8.9%	7.9%	9.0%	8.7%	8.6%
Females, 18 to 34 years	13.8%	13.7%	13.5%	14.9%	14.3%	14.4%
Females, 35 to 64 years	26.8%	25.3%	25.8%	24.0%	26.1%	25.3%
Females, 65+ years	10.4%	12.7%	12.6%	12.0%	11.1%	12.4%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Source	[21]	[22]	[23]	[24]	[25]	[26]
F2: Smoking prevalence						
Males, 18 to 34 years	32.3%	34.6%	38.7%	15.0%	32.6%	39.4%
Males, 35 to 64 years	34.1%	35.4%	36.0%	22.4%	27.7%	29.3%
Males, 65+ years	15.6%	19.2%	13.3%	15.4%	12.7%	10.2%
Females, 18 to 34 years	27.4%	26.1%	29.7%	23.0%	28.0%	31.2%
Females, 35 to 64 years	28.8%	27.8%	27.2%	26.8%	28.5%	21.8%
Females, 65+ years	12.3%	8.9%	6.4%	12.8%	26.7%	6.2%
Source	[27]	[28]	[29]	[24]	[25]	[30,31]
F3: All-cause mortality						
Males, 18 to 34 years	0.06%	0.12%	0.08%	0.07%	0.09%	0.09%
Males, 35 to 64 years	0.40%	0.54%	0.58%	0.39%	0.47%	0.55%
Males, 65+ years	5.38%	5.48%	4.89%	4.14%	4.88%	4.72%
Females, 18 to 34 years	0.03%	0.04%	0.03%	0.03%	0.04%	0.04%
Females, 35 to 64 years	0.28%	0.29%	0.29%	0.25%	0.30%	0.25%
Females, 65+ years	4.57%	4.48%	4.67%	2.85%	3.87%	3.65%
Source	[21]	[22]	[23]	[24]	[32]	[26]
F4: Epidemiology: annual incidence rate of COPD per 1,000 inhabitants						
Males, 18 to 34 years	0.17	0.16	0.00	0.02	0.00	0.03
Males, 35 to 64 years	2.08	2.31	0.10	0.74	0.15	0.17
Males, 65+ years	9.68	12.77	3.26	15.22	3.82	1.73
Females, 18 to 34 years	0.17	0.17	0.00	0.02	0.00	0.01
Females, 35 to 64 years	2.13	2.63	0.06	0.97	0.11	0.09
Females, 65+ years	6.46	12.17	2.25	9.58	1.95	2.05
Source	[33]	[33]	[29]	[34]	[35,36]	[37–42]
F4: Epidemiology: annual incidence rate of lung cancer per 1,000 inhabitants						
Males, 18 to 34 years	0.01	0.01	0.01	0.01	0.00	0.01
Males, 35 to 64 years	0.56	0.61	0.69	0.69	0.56	1.00
Males, 65+ years	4.24	5.15	5.38	4.95	4.84	4.25
Females, 18 to 34 years	0.01	0.01	0.00	0.01	0.01	0.01
Females, 35 to 64 years	0.42	0.48	0.39	0.56	0.36	0.20
Females, 65+ years	1.07	1.71	1.43	1.88	1.63	0.82
Source	[43]	[43]	[29,44–47]	[34]	[25]	[48]
F4: Epidemiology: annual incidence rate of CHD per 1,000 inhabitants, all events						
Males, 18 to 34 years	0.35	0.33	0.80	0.05	0.04	0.00
Males, 35 to 64 years	7.60	7.95	8.36	6.97	2.32	4.27
Males, 65+ years	24.35	26.26	33.15	33.84	25.58	33.42
Females, 18 to 34 years	0.06	0.05	0.60	0.02	0.01	0.00
Females, 35 to 64 years	2.37	2.54	5.29	2.32	0.53	1.21
Females, 65+ years	15.29	17.44	25.76	20.84	15.48	15.45
Source	[49]	[49]	[29,50]	[34]	[25,51]	[52]
F4: Epidemiology: annual incidence rate of CHD per 1,000 inhabitants, first event only						
Males, 18 to 34 years	0.33	0.32	0.46	0.04	0.04	0.00
Males, 35 to 64 years	5.69	5.95	4.86	4.39	1.60	3.80
Males, 65+ years	17.50	18.87	19.25	17.24	14.93	26.27
Females, 18 to 34 years	0.06	0.05	0.35	0.02	0.01	0.00
Females, 35 to 64 years	1.81	1.94	3.07	1.57	0.46	1.12
Females, 65+ years	11.42	13.04	14.96	12.11	11.27	13.42
Source	[49]	[49]	[29,50]	[34]	[25,51,53]	[52]
F4: Epidemiology: annual incidence rate of stroke per 1,000 inhabitants, all stroke events						
Males, 18 to 34 years	0.03	0.03	0.12	0.06	0.08	0.14
Males, 35 to 64 years	1.31	1.39	1.89	1.69	2.29	0.79
Males, 65+ years	11.69	12.61	17.80	14.67	13.25	9.07
Females, 18 to 34 years	0.10	0.10	0.03	0.05	0.07	0.13

Table 1 Continued

	The Netherlands	Belgium	Germany	Sweden	United Kingdom	France
Females, 35 to 64 years	0.88	1.00	1.34	0.93	1.58	0.73
Females, 65+ years	11.43	12.71	11.95	13.23	12.28	6.19
Source	[54]	[54]	[29]	[34]	[25]	[55]
F4: Epidemiology: annual incidence rate of stroke per 1,000 inhabitants, first event only						
Males, 18 to 34 years	0.03	0.03	0.06	0.05	0.06	0.00
Males, 35 to 64 years	1.19	1.25	0.99	1.44	1.73	0.43
Males, 65+ years	10.53	11.36	9.29	11.29	8.74	8.15
Females, 18 to 34 years	0.10	0.10	0.02	0.04	0.05	0.00
Females, 35 to 64 years	0.80	0.91	1.07	0.80	1.17	0.43
Females, 65+ years	10.52	11.70	9.51	10.66	8.03	5.07
Source	[54]	[54]	[29]	[34]	[25]	[55]
F5: Annual costs* per patient with a smoking-related disease						
COPD	1,036	1,928	2,245	2,907	1,127	2,220
Lung Cancer						
First year	13,236	13,505	33,983	10,355	5,132	17,629
After first year	13,236	13,505	33,983	5,502	5,132	17,629
CHD						
First year	4,841	4,867	1,969	4,795	1,348	5,721
After first year	2,949	796	985	1,374	1,348	5,721
Stroke						
First year	23,119	7,685	10,741	7,056	22,006	9,641
After first year	5,229	5,439	4,618	1,884	22,006	9,641
Source	[56–59]	[57,60–63]	[29,64]	†[65,66]	[67–70]	[71]
F6: Resource use: intervention costs using different resource use across countries, but equal unit costs*						
Varenicline	391.79	304.79	294.59	391.79	381.59	294.59
Bupropion	327.81	244.81	226.60	335.51	160.30	230.61
NRT	323.35	213.94	207.00	298.79	234.56	231.05
Unaided cessation	0.00	0.00	0.00	0.00	0.00	0.00
Source	[20,72]	[73,74]	[75]	[19,76,77]	[78]	
F7: Unit costs: intervention costs using different unit costs across countries, but equal resource use*						
Varenicline	391.79	391.78	337.28	401.90	290.62	390.60
Bupropion	327.81	277.42	292.22	350.92	285.02	327.15
NRT	323.35	311.05	317.13	365.76	213.15	387.03
Unaided cessation	0.00	0.00	0.00	0.00	0.00	0.00
Source	[79,80]	[73,74]	[75]	[19,76,77]	[81]	
F8: General population utility weights						
m 18–34	0.910	0.910	0.930	0.930	0.930	0.930
m 35–64	0.910	0.910	0.877	0.877	0.877	0.877
m 65+	0.820	0.820	0.800	0.800	0.800	0.800
f 18–34	0.920	0.920	0.910	0.910	0.910	0.910
f 35–64	0.890	0.890	0.853	0.853	0.853	0.853
f 65+	0.760	0.760	0.770	0.770	0.770	0.770
Source		[82–90]				
F8: Disease-specific utility weights						
COPD	0.690	0.760	0.760	0.760	0.760	0.760
Lung cancer first year	0.610	0.610	0.610	0.610	0.610	0.610
Following years	0.500	0.500	0.500	0.500	0.500	0.500
CHD	0.710	0.760	0.760	0.760	0.760	0.760
Stroke first year	0.540	0.740	0.740	0.740	0.740	0.740
Following years	0.290	0.150	0.150	0.150	0.150	0.150
Source		[83–93]				
F9: Discount rates						
Costs	4.0%	3.0%	5.0%	3.0%	3.5%	3.0%
Outcomes	1.5%	1.5%	5.0%	3.0%	3.5%	0.0%
Source	[94]	[95]	[96]	[97]	[98]	[99]

*In 2006 Euros, accounting for differences in purchasing power; †Bolin K, Dozet A, unpubl. data.
COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; NRT, nicotine replacement therapy.

using the average exchange rates on January 2, July 3, and December 31, 2006, and 2006 purchasing power parities [100].

Analyses

The starting point of all between-country comparisons were the results of the BENESCO model populated with Dutch input data. Hence, The Netherlands was the reference case. In a series of univariate analyses we replaced the group of input parameters belonging to the same factor by its country-specific estimates. We changed one factor at a time; all other factors were kept constant at the reference values. We compared the impact of each factor on the outcomes. In the subsequent multivariate analysis, we

Table 2 Lifetime outcomes of the Benefits of Smoking Cessation on Outcomes model filled with Dutch* input data, expressed per 1000 smokers making a quit attempt

	NRT versus unaided cessation	Bupropion versus NRT	Varenicline versus bupropion
Difference in total costs (€1000)†	126.7	–40.4	–44.7
Difference in QALYs	77.4	17.7	42.8
Incremental net monetary benefit (INMB) (€1 mln)‡	1.42	0.39	0.90
Incremental cost-effectiveness ratio (ICER)	1636.7	Dominant	Dominant

*Outcomes differ from [5] because all cost inputs were updated to 2006 prices, Harmonised Indices of Consumer Prices was used; asthma exacerbations were excluded and the price of varenicline was updated.
†Intervention costs plus total costs of smoking-related diseases.
‡WTP is €20,000.
NRT, nicotine replacement therapy; QALYs, quality adjusted life years; WTP, willingness-to-pay.

consecutively enter parameters from the highest to the lowest impact. Eventually, this results in models that are filled completely with country-specific parameters. In all analyses, the time horizon is lifetime. Sensitivity analyses were done using different time horizons and different threshold values of the willingness-to-pay (WTP) for a quality adjusted life year (QALY).

Outcomes

Outcomes were presented as incremental costs, QALYs gained, incremental cost-effectiveness ratios (ICERs), and incremental net monetary benefits (INMBs). The ICER is the difference in total costs between two smoking cessation interventions, divided by the difference in total QALYs. The percentage change in the INMB of the reference case caused by each factor was our primary measure of interest. The INMB was calculated as the difference in QALYs between two interventions, times societies' WTP, for a QALY (threshold value) minus the difference in costs. The INMB was calculated with a relatively low threshold value of €20,000 per QALY. For each country, we have ranked all country-specific input parameters according to the percentage of change in INMB compared with the reference case. A rank order of 1 indicates that this factor caused the INMB to change most; a rank order of 9 indicates that this factor had the least impact on the INMB.

We present the outcomes according to a hierarchy of effectiveness of the interventions: NRT versus unaided cessation, bupropion versus NRT, and varenicline versus bupropion. The ranking was averaged over these three pair-wise comparisons.

Results

Reference Case

In Table 2, the outcomes of the reference case are given. The ICER of NRT compared with unaided cessation was about €1600 per QALY. Bupropion dominated NRT, and varenicline dominated bupropion. Using a WTP of €20,000 per QALY, the INMBs of all three comparisons were positive.

Univariate Analysis

F1: Demography. Demography influences the age and gender distribution of the cohort of smokers that is followed over lifetime. If the cohort of smokers that attempts to quit becomes older than in the reference case, the INMB and ICER worsen, for all three pair-wise comparisons of smoking-cessation interventions. This is primarily due to a decrease in QALYs that is greater for the more effective intervention because the number of people who remain disease free and survive to old age is greater for this intervention. Table 3 summarizes these effects. Replacing the age and gender distribution in the reference case by the country-specific age and gender distribution caused the INMB of NRT versus unaided cessation to change between –2.1% in Belgium and –0.4% in Sweden. The change in INMB of bupropion versus NRT varies from –1.7% in Belgium to –0.4% in Sweden. The change in INMB of varenicline versus bupropion varies from –1.8% in Belgium to –0.4% in Sweden (Fig. 1).

F2: Smoking prevalence. Like demography, smoking prevalence primarily influences the age and gender distribution of the cohort of smokers attempting to quit. When smoking prevalence among the elderly gets higher, the cohort of smokers attempting to quit becomes older and the INMB and the ICER worsen. Compared with the reference case, the change in INMB for NRT versus unaided cessation that is due to a change towards country-specific smoking prevalence varies from –6.2% in Sweden to +7.6% in France. The change in INMB for bupropion versus NRT varies from –5.1% in Sweden to +6.3% in France. The change in INMB for varenicline versus bupropion varies from –5.4% in Sweden to +6.6% in France (Fig. 1).

F3: All-cause mortality. In countries where the all-cause mortality rate is lower (i.e., the life expectancy is higher) than in the reference case, the INMBs of the smoking cessation interventions

Table 3 Effect of changing the reference case input values to the country-specific input values on cost-effectiveness outcomes compared with the reference case

	Effect on INMB and ICER compared with the reference case
F1: Demography	
Older cohort	Worsens
F2: Smoking prevalence	
Higher smoking prevalence among elderly	Worsens
F3: All-cause mortality	
Lower mortality	Improves
F4: Smoking-related disease epidemiology	
Higher incidence	Improves
Higher mortality	Improves
F5: Costs of smoking-related diseases	
Higher costs	Improves
F6: Resources used for SCTs	
Resource use of a more effective SCT increases more than the resource use of a less effective SCT	Worsens
F7: Unit costs of SCTs	
Unit cost of a more effective SCT increases more than the unit costs a less effective SCT	Worsens
F8: Utility weights	
Higher disease-specific utility weights	Worsens
Lower general population utility weights	Worsens
F9: Discount rates	
Higher discount rates on costs	Worsens
Higher discount rates on outcomes	Worsens

INMB, incremental net monetary benefit; ICER, incremental cost-effectiveness ratio; SCTs, smoking cessation therapies.

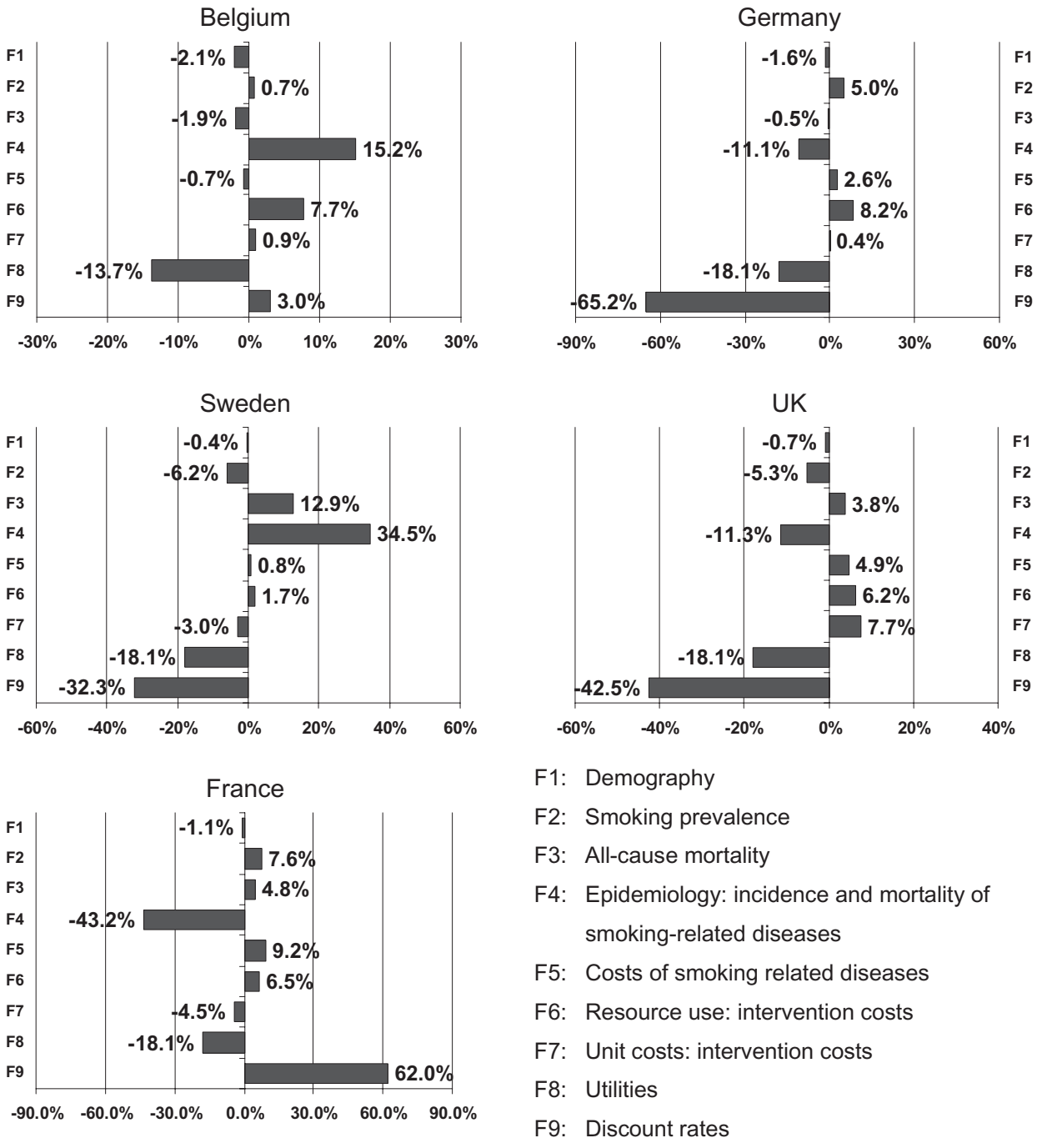

Figure 1 Relative change in incremental net monetary benefits of nicotine replacement therapy versus unaided cessation of the reference case, caused by applying each country-specific factor univariately.

are higher and the ICERs improve, primarily because of higher QALY gains. The increase in QALYs that result from a lower mortality rate is largest for the most effective treatment, because the number of people who stop smoking and remain disease free is highest for this intervention. The change in INMB for NRT versus unaided cessation because of a change in all-cause mortality varies from –1.9% in Belgium to +12.9% in Sweden. The change in INMB for bupropion versus NRT varies from –1.6% in Belgium to +10.6% in Sweden. The change in INMB for varenicline versus bupropion varies from –1.7% in Belgium to +11.3% in Sweden (Fig. 1).

F4: Epidemiology of smoking-related diseases. In countries where the incidence of all smoking-related diseases is higher than in the reference case, the INMBs and ICERs improve, because preventing more diseases results in higher QALY gains and

greater cost savings. The same holds for countries where the mortality due to smoking-related diseases is higher. Change in prevalence has only a limited effect on the INMB. The change in INMB for NRT versus unaided cessation because of a change in epidemiology varies from –43.2% in France to +34.5% in Sweden. The change in INMB for bupropion versus NRT varies from –35.6% in France to +28.5% in Sweden. The change in INMB for varenicline versus bupropion varies from –37.7% in France to +30.1% in Sweden (Fig. 1).

F5: Costs of smoking-related diseases. In countries where the health-care costs of smoking-related diseases are higher than in the reference case, the INMBs are higher and the ICERs improve, because the savings from preventing these diseases increase. This increase gets greater when the effectiveness of the smoking cessation intervention improves. The change in INMB for NRT versus unaided cessation because of a change in costs per patient with a smoking-related disease varies from –0.7% in Belgium to +9.2% in France. The change in INMB for bupropion versus NRT varies from –0.6% in Belgium to +7.6% in France. The change in INMB for varenicline versus bupropion varies from –0.6% in Belgium to +8.0% in France (Fig. 1).

F6: Resource use and F7: Unit costs of SCTs. When the intervention costs of a more effective SCT increase relatively more than the intervention costs of a less effective treatment, the INMB will go down and the cost-effectiveness will worsen. The change in INMB for NRT versus unaided cessation because of a change in the resource use component of the intervention costs varies from +1.7% in Sweden to +8.2% in Germany. The change in INMB for bupropion versus NRT varies from –8.2% in Sweden to +20.0% in the UK. The change in INMB for varenicline versus bupropion varies from –17.5% in the UK to +0.9% in Sweden.

The change in INMB for NRT versus unaided cessation because of a change in the unit cost component of the intervention costs varies from –4.5% in France to +7.7% in the UK. The change in INMB for bupropion versus NRT varies from –17.1% in the UK to +16.3% in France. The change in INMB for varenicline versus bupropion varies from –5.6% in Belgium to +6.5% in the UK (Fig. 1).

F8: Utilities. In countries where the utility weights of the smoking-related diseases are higher than in the reference case, the QALY gains from preventing these diseases are lower. The reduction in QALY gain is greatest for the intervention with the highest effectiveness. Thus, higher disease-specific utility weights lead to lower INMBs and a worsening of the cost-effectiveness. This applies to all five countries in our analysis, because the reference case represents the only country that has changed the model's default utility values.

If the utility weights for the general, disease-free population of a country are lower than in the reference case, the QALY gains from preventing a smoking-related disease are lower. Again, the reduction in QALY gains is greater if the treatment is more effective because more people stay disease free and their live years are thus weighted with the lower utility weights. This causes the INMBs to go down and the ICERs to worsen. The change in INMB for NRT versus unaided cessation because of a change in utility weights varies from –18.1% in Germany, Sweden, the UK, and France, to –13.7% in Belgium. The change in INMB for bupropion versus NRT varies from –14.9% in Germany, Sweden, the UK and France, to –11.3% in Belgium. The change in INMB for varenicline versus bupropion varies from –15.8% in Germany, Sweden, the UK, and France, to –12.0% in Belgium (Fig. 1).

F9: Discount rates. In countries where the costs and outcomes are discounted more than in the reference case, the INMBs and the ICERs worsen because the cost savings and QALY gains of smoking cessation that occur far into the future are reduced. The change in INMB for NRT versus unaided cessation because of a change towards country-specific discount rates varies from –65.2% in Germany to +62.0% in Sweden. The change in INMB for bupropion versus NRT varies from –53.7% in Germany to +51.1% in Sweden. The change in INMB for varenicline versus bupropion varies from –56.9% in Germany to +54.1% in Sweden (Fig. 1).

Ranking of Impact on INMB

The ranking of factors according to their impact on the INMB of NRT versus unaided cessation is largely similar for the comparisons bupropion versus NRT and varenicline versus bupropion. Table 4 shows the rank order when averaged over all three pairwise treatment comparisons. The first row shows the rank orders after averaging the impact of each factor over all countries. When substituting the reference case input univariately by country-specific input, F9: discount rates had the biggest impact on the cost-effectiveness. This is followed by F4: epidemiology and F8: utility weights. The least important factor in terms of its effect on the INMB is F1: demography, i.e., the age/gender distribution of the cohort of smokers making a quit attempt.

Sensitivity Analysis: Impact of Using a Different Time Horizon

A shorter time horizon changes the importance of the various causes of variability in cost-effectiveness between countries. The importance of the three factors with the largest long-term impact, i.e., F9: discount rates, F8: utility weights, and F3: all-cause mortality decreases. Using a time span of 2 or 10 years, the two most important factors become the two factors determining the costs of smoking cessation treatment: F6: resources used and F7: unit costs. These factors become so important because a time horizon of 2 and 10 years is insufficient to capture the full gains in QALYs and savings in costs that result from the prevention of smoking-related diseases. In other words, time has been insufficient to fully get the returns on the investments in SCT.

Sensitivity Analysis: Impact of Using a Different Threshold Value

Using different threshold values to calculate the NMB also changes the rank order of the factors. When the threshold value increases, the factors with a large influence on the QALYs, i.e., all-cause mortality, smoking prevalence, and demography, become more important. When the threshold value decreases, factors with a large influence on costs become more important. This includes resources used for the smoking cessation treatments, unit costs, and costs of smoking-related diseases. The discount rates remain important, irrespective of the threshold value. For threshold values of €5000 or higher, discounting is the single most important factor. Using a threshold value of €1000 or lower, the discount rate becomes the fourth most important factor. For a threshold value of €1000 or lower, the most important factor is the resources used to deliver SCT, followed by costs of smoking-related disease.

Multivariate Analysis

In the multivariate analysis, we enter all country-specific input parameters at the same time. Table 5 shows how the INMB differs between countries when fully accounting for all known between-country differences.

Table 4 Univariate ranking of factors according to the percentage change in incremental net monetary benefit, averaged over the three pair-wise comparisons of smoking cessation therapies, using a threshold value €20,000 per quality adjusted life year and a lifetime horizon, unless otherwise stated

	F9 Discount rates	F4 Epidemiology	F8 Utility weights	F6 Resource use	F7 Unit costs	F2 Smoking prevalence	F3 All-cause mortality	F5 Costs of smoking-related diseases	F1 Demography
Rank order averaged over all countries									
	1	2	3	4	5	6	7	8	9
Rank order for each country									
Belgium	5	1	2	4	3	8	7	9	6
Germany	1	3	2	5	6	4	9	7	8
Sweden	2	1	3	6	7	5	4	8	9
United Kingdom	1	5	2	3	4	6	8	7	9
France	1	2	3	8	5	6	7	4	9
Rank order averaged over all countries at different time horizons									
2 years	7	4	5	2	1	6	9	3	8
10 years	5	3	4	1	2	7	9	6	8
Lifetime	1	2	3	4	5	6	7	8	9
Rank order averaged over all countries at different threshold values									
€100	4	5	9	1	2	6	7	3	8
€500	4	5	7	1	2	6	8	3	9
€1,000	4	5	6	1	2	7	8	3	9
€5,000	1	2	5	3	4	7	8	6	9
€10,000	1	2	3	4	5	7	8	6	9
€20,000	1	2	3	4	5	6	7	8	9
€50,000	1	2	3	6	7	4	5	8	9
€100,000	1	2	3	7	6	5	4	9	8

In Belgium, the decrease in INMB due to higher disease-specific utilities is offset by an increase in the INMB because of a higher incidence of all smoking-related diseases. As a result, the INMBs increase, except for varenicline versus buproprion because the difference in unit costs between the two SCTs is greater than in The Netherlands.

In Germany, the INMBs of all three pair-wise comparisons decrease primarily because of the relatively high discount rate for costs and outcomes. Other causes are a lower incidence of COPD, higher disease-specific utility values and lower general population utility values.

In Sweden, the INMB is also lower than in the reference case for all pair-wise comparisons, because of higher utility weights for the smoking-related diseases and because QALYs were discounted at 3.5% instead of 1.5%. This decrease offsets the increase in INMB caused by lower all-cause mortality rates and higher incidence rates for all smoking-related diseases in most age/gender classes.

Table 5 Incremental Net Monetary Benefit (INMB) per 1000 smokers undertaking a quit attempt, using a threshold of €20,000 per quality adjusted life year, for three pair-wise smoking cessation therapy comparisons, influenced by all nine identified factors

	INMB (x€1 mln)		
	NRT versus unaided cessation	Bupropion versus NRT	Varenicline versus bupropion
The Netherlands	1.42	0.39	0.90
Belgium	1.46	0.45	0.86
Germany	0.39	0.17	0.32
Sweden	1.29	0.22	0.82
UK	0.95	0.25	0.54
France	1.47	0.64	1.01

NRT, nicotine replacement therapy.

In the UK, the INMB of all three pair-wise comparisons is lower than in the reference case, primarily because of a higher discount rate (3%) for outcomes, higher utility weights for the smoking-related diseases and a lower incidence of COPD.

In France, lower smoking-related disease mortality, higher disease-specific utility values, and lower general population utility values cause the INMB of all three pair-wise comparisons to decrease. Nevertheless, the effect of no discounting (0%) on outcomes has such a large effect that the INMB is higher than in the reference case.

Figure 2 shows the differences between countries in terms of ICERs for NRT versus unaided cessation. Incremental costs per QALYs gained in the reference case were estimated to be €1600, represented by the dotted line. This ICER improved for Belgium (BE), Sweden (SE), and the UK; it worsened for Germany (DE) and France (FR). Note that the ICER in Sweden and the UK improved whereas the INMB decreased. In France, the ICER worsened whereas the INMB improved. This is due to the valuation of the QALY gains with €20,000 per QALY, as a result of which a decrease in QALYs, as in the UK, has a much greater impact on the INMB than on the ICER.

Discussion

Many factors should be taken into account when transferring cost-effectiveness results across countries and settings and there are many interactions between these factors. This stresses the importance of carefully considering whether foreign results can be applied and adapted to its own setting. In this paper, we systematically investigated the impact of nine groups of country-specific model input parameters (factors) on the cross-country variability in long-term cost-effectiveness of pharmacological smoking cessation interventions. An earlier article [13] has already shown that outcomes from cost-effectiveness studies on SCTs differ considerably between countries, but causes were not

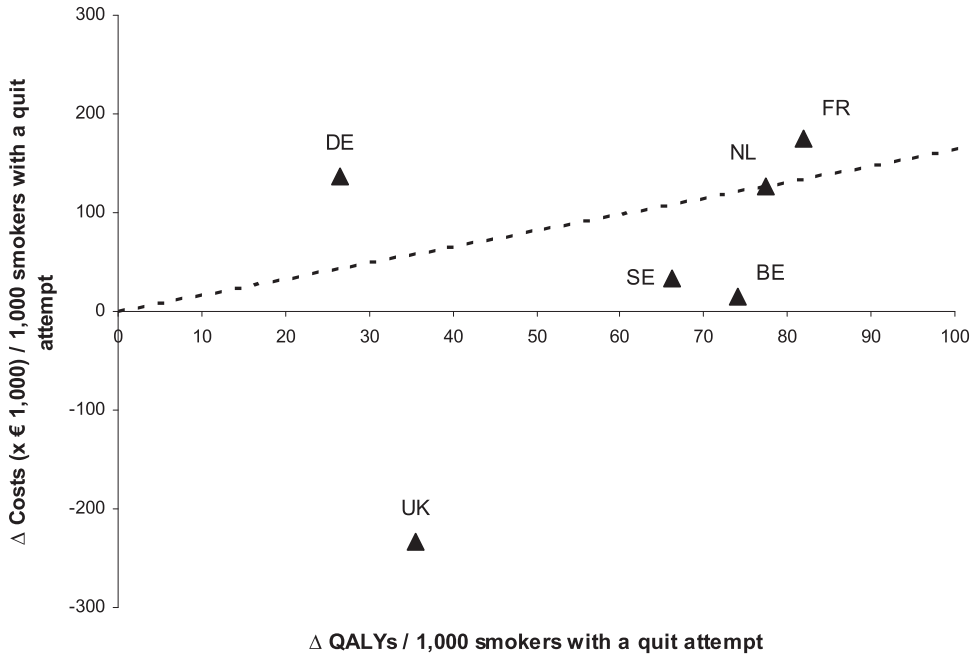

Figure 2 Cost effectiveness per 1000 smokers with a quit attempt of nicotine replacement therapy versus unaided cessation influenced by all nine identified factors. Dotted line shows all points with the same incremental cost-effectiveness ratios (ICER) as NL (€1,637 / QALY). ICERs: BE = €207 / QALY; GE = €5184 / QALY; SE = €495 / QALY; UK = -/-€6,566 / QALY; FR = €2125 / QALY.

unravelled. Among the factors that we have investigated, the choice of discount rate was the factor contributing the most to the between-country differences in cost-effectiveness, followed by the incidence and mortality of smoking-related diseases and the utility values used to calculate QALYs.

It is important to note that the importance of a factor in terms of its impact on the INMB depends on the WTP for a QALY. At a WTP of €20,000 per QALY, the impact of between-country differences in the cost parameters is relatively low, because the changes in the INMB are largely driven by factors affecting the QALYs. At lower values of the WTP for a QALY, the costs of SCTs, in terms of both the unit costs and resource use, as well as the costs of smoking-related diseases, become much more important. Irrespective of the WTP for a QALY, the impact of differences between countries in demography and all-cause mortality in the INMBs is small, because the differences between the countries investigated were relatively small and do not greatly alter the cohort of smokers undertaking a quit attempt.

Despite the differences between countries, all pair-wise treatment comparisons in our study showed that the more effective smoking cessation treatments were also cost-effective, and in some case even cost-saving. INMBs were positive and ICERs were consistently below €5300 per QALY gained. Hence, there are strong health economic arguments to support these treatments across all countries.

It is further relevant to note the differences between the changes in the ICERs and the changes in the INMBs compared with the reference case, which stresses the importance of the threshold value for a QALY in decision-making. Using the change in INMB instead of the change in ICER as a measure of the importance of a country-specific factor gives relatively greater weight to changes in QALYs. We have seen that the larger emphasis on QALYs in the INMB also affects the relative importance of a factor. For example, applying the Swedish discount rates (3% for costs and outcomes) causes both the incremental costs and QALYs gained to decrease. This leads to a change in ICER of −3% and thus a slight improvement of cost-effectiveness, whereas the INMB is a significant 32% lower.

In each country, we have used the same base-case estimates of the 12-month continuous abstinence rates [5]. This is based on the assumption that the pure biological effect of a drug can be expected to be the same, irrespective of the country. Otherwise we have used as many country-specific estimates of model input parameters as available. Some of the input data were very difficult to compare across countries. For example, smoking prevalence data may differ, because countries use different definitions and methods to determine the number of current smokers, like including only daily smokers or also including irregular smokers. In The Netherlands for example, a smoker is defined as somebody that has smoked in the 7 days before being asked [101], while in Belgium, people are asked whether they have smoked 100 cigarettes during their lives and whether they consider themselves a smoker or not [102]. In addition, the epidemiological data on smoking-related diseases are difficult to compare across countries. Different countries also used different definitions of the four diseases included in the model, especially with respect to COPD and CHD. For example, COPD was identified with ICD-10 code J40–44 in The Netherlands, but as J40–44 plus J47 in Sweden. Such a difference in definition could potentially be a source of the difference in reported epidemiology and its associated costs between countries. Furthermore, not all countries distinguish between the first-year costs of lung cancer, CHD and stroke and the costs of these diseases in later years, often because these data are not available. Such differences complicate the comparison of cost-effectiveness between countries. Nevertheless, we have deliberately chosen to use the definitions of the smoking-related diseases and the associated cost that were actually applied at the time of writing the country-specific reimburse-

ment dossiers for varenicline. By doing so, we highlight best the differences between countries and the influence of these differences on cost-effectiveness and cost-benefit estimates as they drive actual decision-making.

Despite its large influence on the outcomes, in only one of our six countries, The Netherlands, country-specific utility weights were available. This lack of country-specific utility data is probably due to the difficulty to collect these data and the assumption that utility values for a specific health state will probably not differ much between countries. Nevertheless, as this study shows, it is worthwhile to invest more time and resources in finding country-specific utility weights, because their impact on the INMB is large, especially at higher levels of the threshold value of a QALY.

The Transferability of Economic Data Task Force from ISPOR states on their webpage [103] that one of the most important questions to be answered with regard to transferability is "[w]hich elements of economic data vary most from setting to setting?" The results from this study suggest that it is not only important to see which factors vary, but also how much this variation in factors causes variation in cost-effectiveness. The factors that cause the most variation in cost-effectiveness do not necessarily have to be the same as the factors that vary most themselves. For example, the unit costs of the smoking cessation drugs differ considerably between countries, but the impact on the cost-effectiveness is limited when adopting a lifetime time horizon. We spent considerable time and effort on identifying data sources, adjusting input data to fit into the model and especially assessing the comparability of input parameters between countries. Based on this observation, we wholeheartedly agree with the concluding remark of the Task Force that "those developing national guidelines for economic evaluations should think carefully about the need for local data or methods, since this increases the burden on those undertaking studies in multiple jurisdictions." The results of our study underline that, when studying the cost-effectiveness of smoking cessation, there is a need for local data even for countries within a similar region of the world.

Source of financial support: The study was sponsored by an unrestricted grant from Pfizer.

References

1 Drummond M, Barbieri M, Cook JR, et al. Transferability of economic evaluations across jurisdictions, in International Society for Pharmacoeconomic and Outcomes Research (ISPOR)—13th International Meeting. 2008; Toronto, Ontario, Canada.
2 Weinstein M, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—Modeling Studies. Value Health 2003;6:9–17.
3 Weinstein M. Recent developments in decision-analytic modelling for economic evaluation. Pharmacoeconomics 2006;24: 1043–53.
4 Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO Simulation model: application to a population of US adult smokers. Pharmacoeconomics 2008;26:497–511.
5 Hoogendoorn M, Welsing P, Rutten-van Mölken MPMH. Cost-effectiveness of varenicline compared with bupropion, NRT and nortriptyline for smoking cessation in the Netherlands. Curr Med Res Opin 2008;24:51–61.
6 Bolin K, Mörk A, Willers S, Lindgren B. Varenicline as compared to bupropion in smokingcessation therapy—cost–utility results for Sweden. Respir Med 2008;102:699–710.
7 Rasch A, Greiner W. Gesundheitsökonomisches Modell der Raucherentwöhnung mit Vareniclin. Suchtmedizin in Forschung und Praxis. 2008;11:47–55.
8 Hind D, Tappenden P, Peters J, Kenjegalieva K. Varenicline for Smoking Cessation: A Single Technology Appraisal. Sheffield, UK: ScHARR, University of Sheffield, 2007.
9 Skoupá J, Doležal T, Hájek P, Kovář P. Long term cost-effectiveness and cost-utility analysis for smoking cessation in Czech Republic, in International Society for Pharmacoeconomic and Outcomes Research (ISPOR)—13th International Meeting. 2008; Toronto, Ontario, Canada.
10 Bae J, Song HJ, Joe KH, et al. A long term cost-effectiveness analysis model for smoking cessation in Korea, in International Society for Pharmacoeconomic and Outcomes Research (ISPOR)—13th International Meeting. 2008; Toronto, Ontario, Canada.
11 Igarashi A, Takuma H, Fukuda T, Tsutani K. Cost-utility analysis of varenicline, an oral smoking cessation drug, in Japan. Pharmacoeconomics 2009;27:247–61.
12 Poulsen P, Dollerup J, Keiding H. The cost-effectiveness of varenicline in smoking cessation in Denmark. 2008; ISPOR 11th Annual European Congress Athens.
13 Cornuz J, Gilbert A, Pinget C, et al. Cost-effectiveness of pharmacotherapies for nicotine dependence in primary care settings: a multinational comparison. Tob Control 2006;15:152–9.
14 Rutten-van Mölken MPMH, Hoogendoorn M, Rasch A, Bolin K. Cost-effectiveness of varenicline for smoking cessation in five European countries, in Meeting of the Society for Research on Nicotine and Tobacco. 2007; Madrid, Spain.
15 O'Regan C, Baker C, Marchant N. The cost-effectiveness of the novel presciption therapy varenicline in Scotland, in Meeting of the Society for Research on Nicotine and Tobacco. 2006.
16 Orme M, Hogue SL, Kennedy LM, et al. Development of the health and economic consequences of smoking interactive model. Tob Control 2001;10:55–61.
17 Thun M, Apicella LF, Henley SJ. Smoking vs other risk factors as the cause of smoking-attributable deaths: confounding in the courtroom. J Am Med Assoc 2000;284:706–12.
18 Feenstra T, van Genugten ML, Hoogenveen RT, et al. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 2001;164:590–6.
19 Hughes J, Stead L, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2007;(1):CD000031.
20 Jorenby D, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-released bupropion for smoking cessation: a randomized controlled trial. J Am Med Assoc 2006;296:56–63.
21 Statistics Netherlands (CBS). Available from: http://www.cbs.nl [Accessed September 2, 2008].
22 Nationaal Instituut voor Statistiek. Available from: http://statbel.fgov.be/ [Accessed November 19, 2007].
23 Statistisches Bundesamt Deutschland. Leben in Deutschland—Mikrozensus 2005. 2006; Available from: http://www.destatis.de/presse/deutsch/pk/2006/mikrozensus2005_tabellenanhang.pdf#search=%22%22durchschnittliches%20Alter%20des%20Rauchbeginns%22%22 [Accessed August 14, 2007].
24 Statistics Sweden (SCB). Available from: http://www.scb.se/default____2154.asp [Accessed August 31, 2007].
25 Office for National Statistics (ONS). Available from: http://www.statistics.gov.uk/ [Accessed March 31, 2007].
26 Beaumel C, Daguet F, Richet-Mastain L, Vatan M. La situation démographique en 2004. 2006; Available from: http://www.insee.fr/fr/ppp/ir/accueil.asp?page=SD2004/dd/sd2004_nais.htm [Accessed February 9, 2007].
27 Zeegers T, Segaar D, Willemsen M. Roken de Harde Feiten: Volwassen 2004. Den Haag: STIVORO-voor een rookvrije toekomst, 2004.
28 Demarest S, Drieskens S, Gisle L, et al. Health Interview Survey, Belgium. 2004; Available from: http://www.iph.fgov.be/EPIDEMIO/hisia/index.htm [Accessed November 19, 2007].

29 Statistisches Bundesamt Deutschland. Gesundheitsberichterstattung des Bundes. 2006. Available from: http://www.gbe.bund.de/ [Accessed August 14, 2007].
30 Auvray LDS, Le Fur P. L'état de Santé de la population en France en 2006. Indicateurs associé à la loi relative à la politique de santé publique, in Baromètre Santé 2005—premiers résultats. INPES, 2006. Available from: http://www.sante.gouv.fr/drees/santepop2006/santepop2006.htm [Accessed February 9, 2007].
31 Dumesnil S, Le Fur P, Auvray L. Santé, Soins et Protection sociale en 2000, in Série Résultats. Nancy: CREDES, 2001.
32 GAD. UK Interim Life Tables 2002–4. 2006. Available from: http://www.gad.gov.uk/ [Accessed March 31, 2007].
33 Poos M. COPD: Prevalentie, Incidentie, Ziekenhuisopnamen en Sterfte naar Leeftijd en Geslacht, in Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, 2006.
34 Swedish National Board of Health and Welfare. Available from: http://www.socialstyrelsen.se/en/ [Accessed August 31, 2007].
35 Lung and Asthma Information Agency. 2006. Available from: http://www.laia.ac.uk/ [Accessed December 4, 2006].
36 Soriano J, Maier WC, Egger P, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax 2000; 55:789–94.
37 Detournay B, Pribil C, Fournier M, et al. The SCOPE Study: healthcare consumption related to patients with COPD in France. Value Health 2004;7:168–74.
38 Benard E, Detournay B, Neukirch F, et al. Prévalence de la Bronchopneumopathie Chronique Obstructive (BPCO): estimation pour la France. La Lettre du Pneumologue 2005;8:158–63.
39 Pham Q, Gimenez M, Myre M, et al. Contribution à l'épidémiologie de la bronchite chronique chez les travailleurs du bâtiment. Bull Physio-patho Resp 1972;8:769–95.
40 Perdrizet S, Amphoux M, Liard R. Pathologie respiratoire en médecine du travail: évaluation de trois modes de recueil des données et recherche des facteurs de risque. Rev Mal Respir 1984;1:99–103.
41 Neukirch F, Cooreman J, Liard R, et al. Occupational exposure to bad weather, dusts and chemical fumes and respiratory abnormalities in 404 men at work (abstract). Am Rev Respir Dis 1986;133:A357.
42 Neukirch F, Perdrizet S. La bronchite chronique. Evolution, prévention. Rev Mal Respir 1988;5:331–46.
43 Poos M. Longkanker naar Leeftijd en Geslacht, in Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, 2005.
44 Schmidtmann I, Husmann G, Krtschil A, Seebauer G. Krebs in Rheinland-Pfalz, Inzidenz und Mortalität im Jahr 2002. Mainz: Krebsregister Rheinland-Pfaltz, 2004.
45 Epidemiologisches Krebsregister Saarland. 2004. Available from: http://www.krebsregister.saarland.de/ [Accessed August 14, 2007].
46 Batzler WU, Giersiepen K, Hentschel S, et al. Krebs in Deutschland 2003–2004, Häufigkeiten und Trends. Berlin: Robert Koch Institut, 2008.
47 Robert Koch-Institut. Dachdokumentation Krebs. 2006. Available from: http://www.rki.de [Accessed August 14, 2007].
48 Institut national de la santé et de la recherche médicale. Réseau français des registres du cancer. 2003; Available from: http://www.invs.sante.fr/publications/2003/rapport_cancer_2003/index.html [Accessed February 9, 2007].
49 Poos M. Coronaire Hartziekten: Prevalentie, Incidentie, Ziekenhuisopnamen en Sterfte Naar Leeftijd en Geslacht, in Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM, 2006.
50 Kohler M, Ziese T. Telefonischer Gesundheitssurvey des Robert Koch-Instituts zu chronischen Krankheiten und ihren Bedingungen. Berlin: Robert Koch Institut, 2004.
51 British Heart Foundation. 2006. Available from: http://www.bhf.org.uk/ [Accessed December 4, 2006].
52 Fender M, Arveiller D, Facello A, et al. Vers une diminution de l'infarctus du myocarde dans le Bas Rhin. Ann Cardiol Angéiol 1994;43:373–79.
53 Volmink J, Newton JN, Hicks NR, et al. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. Heart 1998;80:40–4.
54 Poos M. Beroerte: Prevalentie, Incidentie, Ziekenhuisopnamen en Sterfte naar Leeftijd en Geslacht, in Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid 2004. Bilthoven: RIVM, 2004.
55 Wolfe D, Giroud M, Kolominsky-Rabas P, et al. Variations in stroke incidence and survival in 3 areas of Europe. Stroke 2000;31:2074–9.
56 Hoogendoorn M, Feenstra TL, Rutten-van Molken MP. [Projections of future resource use and the costs of asthma and COPD in the Netherlands] Dutch. Ned Tijdschr Geneeskd 2006;150:1243–50.
57 Slobbe L, Kommer GJ, Smit JM, et al. Kosten van Ziekten in Nederland 2003. Bilthoven: RIVM, 2006.
58 Suryapranata H, Ottervanger JP, Nibbering E, et al. Long term outcome and cost-effectiveness of stenting versus balloon angioplasty for acute myocardial infarction. Heart 2001;85:667–71.
59 Struijs J, van Genugten ML, Evers SM, et al. Future costs of stroke in the Netherlands: the impact of stroke services. Int J Technol Assess Health Care 2006;22:518–24.
60 Caekelbergh K, Annemans L, Spaepen E. Management of COPD in Belgium: A real life cost study. Value Health 2005;8:214.
61 Singh B, Golden R. The uninsured patient. Am J Med 2006;119: 166.e1–5.
62 Muls E, van Ganse E, Closon MC. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: comparison between Belgium and the United States of a projected risk model. Atherosclerosis 1998;137(Suppl.):S111–16.
63 TCT. TCT database. Available from: https://tct.fgov.be [Accessed November 19, 2007].
64 Nowak D, Dietrich ES, Oberender P, et al. [Cost-of-illness Study for the Treatment of COPD in Germany] German. Pneumologie 2004;58:837–44.
65 Läkemedelsstatistik AB, Medical Index Sweden. Stockholm: Läkemedelsstatistik AB, 2002.
66 Ghatnekar O, Persson U, Glader EI, et al. Cost of stroke in Sweden: an incidence estimate. Int J Technol Assess Health Care 2004;20:375–80.
67 Halpin D. Health economics of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2006;3:227–33.
68 Curtis L, Netten A. Unit Costs of Health and Social Care 2005. Kent, UK: PSSRU, University of Kent, 2005.
69 McMurray J, Hart W, Rhodes G. An evaluation of the cost of heart failure to the National Health Service in the UK. Br J Med Ec 1993;6:99–110.
70 Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. Pharmacoeconomics 2003; 21(Suppl. 1):43–50.
71 Fournier M, Tonnel A-B, Housset B, et al. Impact économique de la BPCO en France: Étude SCOPE (Economic impact of COPD in France: The SCOPE study). Rev Mal Respir 2005; 22:247–55.
72 Gonzalez D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic aceylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. J Am Med Assoc 2006;296:47–55.
73 RIZIV/INAMI database. Available from: http://www.riziv.be [Accessed November 19, 2007].
74 Geneesmiddelen Reportorium. Available from: http://www.cbip.be [Accessed November 19, 2007].
75 Kassenärztliche Bundesvereinigung. Einheitlicher Bewertungsmaßstab. 2006; Available from: http://www.kbv.de/ebm2000plus/EBMGesamt.htm [Accessed August 14, 2007].
76 European Medicines Agency. Summary of Product Characteristics. London: EMEA, 2006.
77 Willers S. [Smoking cessation treatment-recommendations for Skåne, Sweden] (Swedish) in Bakgrundsmaterial till Skånelistans rekommendationer. Lund: Lund University, 2007.

78 NHS Clinical Knowledge Summaries (formerly PRODIGY). Available from: http://cks.library.nhs.uk/home [Accessed March 31, 2007].
79 Feenstra T, van Baal PH, Hoogenveen RT, et al. Cost-Effectiveness of Interventions to Reduce Tobacco Smoking in the Netherlands. An Application of the RIVM Chronic Disease Model. Bilthoven: RIVM, 2006.
80 CVZ. Medicijnkosten. 2006; Available from: http://www.medicijnkosten.nl [Accessed September 2, 2008].
81 NHS Business Services Authority. Available from: http://www.ppa.org.uk [Accessed March 31, 2007].
82 van Baal P, Hoeymans N, Hoogenveen RT, et al. Disability weights for comorbidity and their influence on health-adjusted life expectancy. Popul Health Metr 2006;4:1.
83 Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics 2005;23:619–37.
84 Mannino D, Buist AS, Petty TL, et al. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax 2003;58:388–93.
85 Trippoli S, Vaiani M, Lucioni C, Messori A. Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life Study Group of the Master 2 Project in Pharmacoeconomics. Pharmacoeconomics 2001;19:855–63.
86 Hay J, Sterling KL. Cost effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. Pharmacoeconomics 2005;23:133–41.
87 Duncan P, Lai SM, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. Neuropharmacology 2000;39:835–41.
88 Tengs T, Lin TH. A meta-analysis of quality-of-life estimates for stroke. Pharmacoeconomics 2003;21:191–200.
89 Szende A, Svensson K, Stahl E, et al. Psychometric and utility-based measures of health status of asthmatic patients with different disease control level. Pharmacoeconomics 2004;22:537–47.
90 Gage B, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. Stroke 1998;29:1083–91.
91 Stouthard M, Essink-Bot ML, Bonsel GJ, et al. Disability Weights for Diseases in the Netherlands. Rotterdam: Department of Public Health, Erasmus University Rotterdam, 1997.
92 Feenstra T, Hamberg-van Reenen HH, Hoogenveen RT, et al. Cost-effectiveness of face-to-face smoking cessation interventions: a dynamic modeling study. Value Health 2005;8:178–90.
93 McNamara R, Lima JA, Whelton PK, et al. Echocardiographic identification of cardiovasular sources of emboli to guide clinical management of stroke: a cost-effectiveness analysis. Ann Intern Med 1997;127:775–87.
94 Rodenburg–van Dieten HEM. Richtlijnen voor farmacoeconomisch onderzoek. Evaluatie en Actualisatie. Diemen: CVZ, 2008.
95 Cleemput I, van Wilder Ph, Vrijens F, Huybrechts M, Ramaekers D. Richtlijnen voor farmacoeconomische evaluaties in België. Health Technology Assessment (HTA). Brussels: Federaal Kenniscentrum voor de Gezondheidszorg (KCE), 2008.
96 Hannoveraner Konsensus Gruppe. Deutsche Empfehlungen zur gesundheitsökonomischen Evaluation—Revidierte Fassung des Hannoveraner Konsens. Gesundheitsökonomie und Qualitätssicherung 1999;4:A62–5.
97 Edling A, Stenberg AM. General Guidelines for Economic Evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2). Solna: Pharmaceutical Benefits Board (LFN), 2003.
98 NICE. Guide to the Methods of Technology Appraisal. London: NICE, 2004.
99 Lévy É, De Pouvourville G. French Guidelines for the Economics Evaluation of Health Care Technologies. Paris: Collège des Économistes de la Santé, 2004.
100 OECD.stat. Available from: http://www.oecd.org/statsportal/ [Accessed September 2, 2008].
101 STIVORO. Available from: http://www.stivoro.nl [Accessed September 2, 2008].
102 Bayingana K, Demarest S, Gisle L, et al. Gezondheidsenquête België. Brussel: Wetenschappelijk Instituut Volksgezondheid, 2004.
103 The Transferability of Economic Data Task Force. Available from: http://www.ispor.org/councils/transferability.asp [Accessed September 2, 2008].