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# Cost-effectiveness of retreatment with varenicline after failure with or relapse after initial treatment for smoking cessation

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ABSTRACT

*Objectives.* A recent trial showed the clinical benefit of retreatment with varenicline in subjects failing on the initial treatment, or relapsing after initial success. The objective of this study was to evaluate the cost-effectiveness of retreatment with varenicline compared with other smoking cessation interventions.

*Methods.* A published Markov model was adapted to compare one quit attempt of varenicline followed by retreatment to treatment/retreatment with nicotine replacement therapy (NRT), bupropion or placebo, and with only 1 quit attempt of varenicline. Efficacy was obtained from clinical trials. Incidence of smoking-related diseases was based on published data. Cost of therapies and complications was obtained from databases and literature.

*Results.* For 1000 smokers willing to quit, varenicline retreatment saves 275,000€, 118,000€, 316,000€ and 237,000€ compared to NRT, bupropion, placebo, or one single varenicline quit attempt respectively at lifetime and from the healthcare payer perspective. The number of quality adjusted life years gained is 74, 63, 193 and 111 respectively. Sensitivity analyses showed the robustness of these findings.

*Conclusion.* This analysis suggests that in the long term, varenicline retreatment is a dominant intervention, meaning both greater health gains and greater costs saved, over other possible interventions and therefore should be considered as a standard option.



## Introduction

Smoking cessation (SC) therapies are widely available in Europe and many are reimbursed by public health care payers (Aubin et al., 2014).

Smoking cessation is aimed at preventing severe complications associated with smoking, including COPD, lung cancer, coronary heart diseases (CHD), stroke and asthma exacerbations. It is well established that the lifespan of a smoker is shorter than that of a non-smoker, with a difference of 6 to 10 years, on average, depending on the number of cigarettes smoked (Van den Bruel et al., 2004).

Varenicline, nicotine replacement therapy (NRT) and bupropion are the current standard pharmacological interventions to aid in smoking cessation. In motivated subjects, starting a treatment with one of these therapies is justified in association with behavioral counseling. However, smoking cessation is difficult and relapse is common among individuals attempting to quit (Fiore et al., 2000).

A recent trial assessing the efficacy of varenicline retreatment in subjects unsuccessful after a first attempt showed a success rate (defined as continuous abstinence from 9–52 weeks) of 20.1% (Gonzales et al., 2014).

In the current health care environment, the need to allocate public finances has increased the interest in cost-effectiveness research (Annemans et al., 2011) and reimbursement of medicines does not only require clinical effectiveness but also cost-effectiveness.

The objective of this study was to estimate the cost-effectiveness of varenicline in retreatment compared to other possible retreatment options including no treatment, and retreatment with bupropion or NRT.

## Methods

### *General aspects*

The perspective of this analysis is the healthcare payer perspective: the public health care payer (Rijksinstituut voor ziekte — en invaliditeitsverzekering/Institut National d'Assurance Maladie-Invalidité — RIZIV/INAMI) and the patient. This combined perspective follows the recommendations of the Belgian Health Technology Assessment (HTA) body KCE (Kenniscentrum—Centre d'expertise) (Cleemput et al., 2012) and gives a complete picture of smoking cessation since

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NRT is not reimbursed by the public health insurance. Given this chosen perspective only direct health care costs are included.

*Decision model*

The Two-quit BENESCO (Benefit of Smoking Cessation on Outcomes) model is based on an adaptation of the original BENESCO model, a Markov model that was developed to assess the cost-effectiveness of one quit attempt with smoking cessation interventions (Howard et al., 2008). The BENESCO model simulates the incidence of smoking-related morbidity and mortality over time and is an extension of the HECOS (Health Economic Consequences of Smoking) model that was used by the World Health Organization European Partnership Project to reduce tobacco dependence (Orme et al., 2001). BENESCO model has also been reviewed in various health technology assessments. This model has been customized for various countries, including Belgium, and the results have been widely published (Hoogendoorn et al., 2008; Fernández de Bobadilla Osorio et al., 2008; Bolin et al., 2008; Annemans et al., 2009; Igarashi et al., 2009; Bae et al., 2009; Linden et al., 2010; Athanasakis et al., 2012; Lutz et al., 2012). These analyses were also included in systematic reviews about the cost-effectiveness of varenicline (Keating and Lyseng-Williamson, 2010; Zimovetz et al., 2011; Mahmoudi et al., 2012).

The Two-quit BENESCO model follows a simulated cohort of 1000 Belgian smokers from first quit attempt through retreatment among those who were initially not successful or who relapsed, until all members of the cohort have either died or reached the age of 100 (Fig. 1). Lifetime clinical and economic outcomes of an initial quit attempt with varenicline followed by retreatment with varenicline, if the patient fails with or relapses after initial treatment (=2QA varenicline) are simulated and compared with the alternative interventions:

- 1 quit attempt with nicotine replacement therapy (NRT) followed by NRT retreatment in case of failure or relapse (=2QA NRT)
- 1 quit attempt with bupropion followed by bupropion retreatment in case of failure or relapse (=2QA bupropion)
- 1 quit attempt with placebo followed by placebo retreatment in case of failure or relapse (=2QA placebo)
- Only 1 quit attempt with varenicline followed by 1 quit attempt with placebo (1QA varenicline).

As in the initial BENESCO model, this model allows transitions to the smoking-related diseases as described in Fig. 2. A cycle length of one year was chosen because the abstinence rate is measured at 1 year in the clinical trials. Moreover, the benefits of smoking cessation interventions are apparent only up to several years after cessation, which makes a shorter cycle length not useful. All subjects entering the model are smokers, with co-morbidities according to their baseline prevalence among smokers. In the first year, subjects in the cohort receive initial smoking cessation treatment. At the end of each year, subjects transition between 3 smoking states (smoker, recent quitter, long term quitter), each of which can be further defined in terms of the presence or absence of the mentioned smoking-related diseases.

Subjects are considered recent quitters if abstinent for 2–5 years after successful quit attempt and long term quitters after more than 5 years of abstinence. Health benefits of cessation are applied to all quitters, although risk of relapse remains (Feenstra et al., 2005; van Genugten et al., 2003). Furthermore all subjects who fail during first quit attempt or relapse after first quit attempt will attempt a second quit. The evaluation of treatment failure or relapse occurs at the end of each cycle.

Fig. 2 illustrates the order of the smoking-related diseases in the BENESCO model. By modeling the morbidities in this way, a patient can have, for example, one or more asthma exacerbations, followed by CHD or stroke with one or more acute events, followed by lung cancer or COPD. Death can occur at any time, and its cause is specified. If subjects have one of the two acute morbidities (CHD or stroke) they cannot develop the other. Similarly if subjects develop one of the two chronic complications (lung cancer or COPD) they cannot develop the other. Subjects can progress from an acute disease to chronic, but not the other way. If subjects progress from an acute disease to a chronic one, their acute disease is ignored from that point forward.

*Health data input*

The abstinence rates of the various smoking cessation interventions were derived from a recent Cochrane systematic review (Cahill et al., 2013) as well as from the results of the randomized clinical trial on varenicline treatment/retreatment. In the absence of efficacy data of NRT and bupropion at 52 weeks in retreatment trials, we have conservatively used the same value in the retreatment as in the first treatment for these 2 interventions. As in the initial BENESCO model, the current model does not consider the adverse events related to the SC interventions because clinical trial data do not indicate sustained comparative difference between interventions that would impact on outcomes.

The clinical data are shown in Table 1.

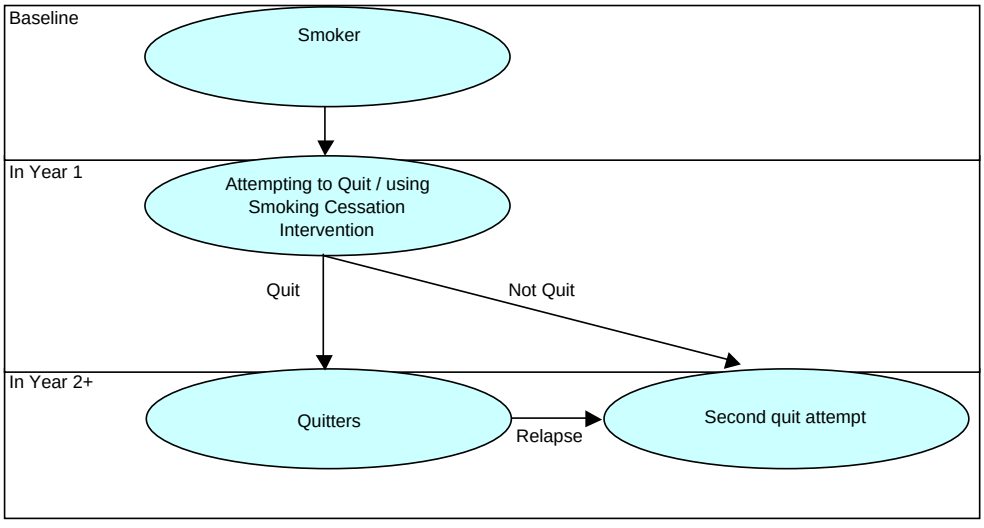


**Fig. 1.** Schematic diagram of three-stage process of quitting and relapsing to smoking.

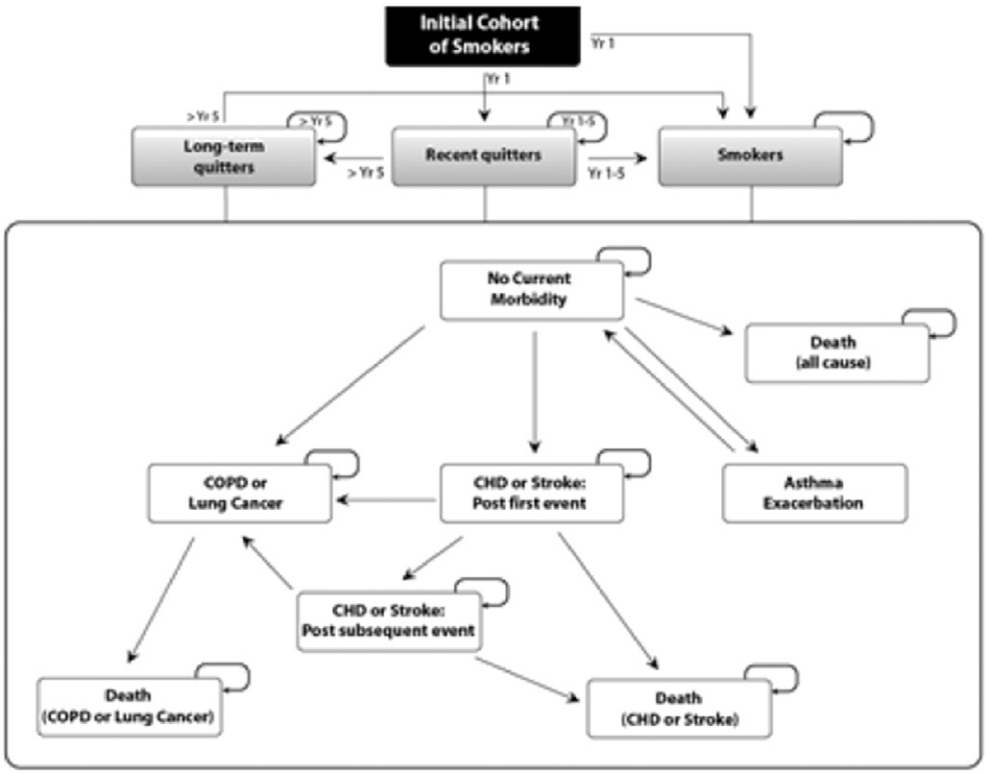


**Fig. 2.** Graphical presentation of the health economic model.

The annual relapse rate for abstinent subjects is 6% (Wetter et al., 2004), and this rate is applied to recent quitters each year in the period of 2–5 years. If after 5 years the subject is still abstinent, then the risk of relapsing to smoking is reduced to 2% annually for the next 5 years (years 6–10) (Krall et al., 2002). In the subjects that maintain abstinence through 10 years following their quit attempt, the relapse rate is reduced to 1% annually.

The hazard ratios of dying from smoking-related diseases (Thun et al., 2000) have been used as a proxy for the relative risk (RR) of the incidence and prevalence of smoking-related diseases (Howard et al., 2008; Orme et al., 2001). The RRs vary with age, gender and smoking status, as in the analysis by Thun et al. (2000) already used for the initial BENESCO model (Table 2).

The RR of smoking-related diseases for subjects who remain smokers at the end of the cycle is assumed to be the same as that of a current smoker. The RRs of a recent quitter are assumed to be equal to RRs of former smokers and RRs of long-term quitters are assumed to be equal to RRs of never-smokers. The lung cancer risk for long-term quitters has been kept equal to the risk in recent quitters over lifetime.

The transition probabilities to smoking-related diseases have been calculated, by smoking status, based on these RRs and the prevalence, incidence and mortality cases of each smoking-related disease by age and gender.

*Cost data input*

Hospitalization costs of smoking-related diseases were obtained from the Belgian TCT database (2010, tct.fgov.be). This national database provides the average cost per hospital stay for all APR-DRGs (All Patients Refined Diagnosis Related Group) paid by the public health insurance and the patient (co-payment).

The annual follow-up cost for smoking-related diseases was taken from literature (Annemans et al., 2003; Muls et al., 1998; Pacolet et al., 2011; Caekelbergh et al., 2005).

**Table 1**
Clinical input data.

| SC interventions | Efficacy (CAR 9–52 weeks) | Source | Comments |
|---|---|---|---|
| *Efficacy of smoking cessation interventions 1st line* | | | |
| Varenicline 1st line | 21.1% | Cahill et al. (2013)<br>Nides et al. (2008) | The relative effect of varenicline in comparison to placebo is 2.27 (Cahill et al.). This effect is applied to the efficacy of placebo from Nides et al. (2008) (9.3% * 2.27 = 21.1%). |
| Bupropion 1st line | 15.7% | Cahill et al. (2013)<br>Nides et al. (2008) | The relative effect of bupropion in comparison to placebo is 1.69 (Cahill et al.). This effect is applied to the efficacy of placebo from Nides et al. (2008) (9.3% * 1.69 = 15.7%). |
| NRT 1st line | 14.9% | Cahill et al. (2013)<br>Nides et al. (2008) | The relative effect of NRT in comparison to placebo is 1.60 (Cahill et al.). This effect is applied to the efficacy of placebo from Nides et al. (2008) (9.3% * 1.60 = 14.9%). |
| Placebo 1st line | 9.3% | Nides et al. (2008) | Pooled estimate of Phase III trials comparing varenicline to bupropion and placebo |
| *Efficacy of smoking cessation interventions 2nd line* | | | |
| Varenicline 2nd line | 20.1% | Gonzales et al. (2014) | CAR at 52 weeks |
| Bupropion 2nd line | 15.7% | Assumption | Assumed equivalent to 1st quit attempt |
| NRT 2nd line | 14.9% | Assumption | Idem |
| Placebo 2nd line | 3.3% | Phase IV CSR | CAR in 9–52 weeks (secondary endpoint) |

CAR = continuous abstinence rate.
CSR = clinical study report (Pfizer data on file).

**Table 2**
Relative risks for complications associated with smoking (never smokers = 1).

| Population | RR of disease | | Source |
|---|---|---|---|
| | Current smokers | Former smokers | |
| *Chronic obstructive pulmonary disease* | | | |
| Males 18–34 years | 1.0 | 1.0 | Thun et al. (2000) |
| Males 35–64 years | 10.8 | 7.8 | |
| Males 65 + years | 10.8 | 7.8 | |
| Females 18–34 years | 1.0 | 1.0 | |
| Females 35–64 years | 12.3 | 8.9 | |
| Females 65 + years | 12.3 | 8.9 | |
| *Lung cancer* | | | |
| Males 18–34 years | 1.0 | 1.0 | Thun et al. (2000) |
| Males 35–64 years | 21.3 | 8.3 | |
| Males 65 + years | 21.3 | 8.3 | |
| Females 18–34 years | 1.0 | 1.0 | |
| Females 35–64 years | 12.5 | 4.8 | |
| Females 65 + years | 12.5 | 4.8 | |
| *Coronary heart disease* | | | |
| Males 18–34 years | 1.0 | 1.0 | Thun et al. (2000) |
| Males 35–64 years | 2.6 | 1.6 | |
| Males 65 + years | 1.5 | 1.2 | |
| Females 18–34 years | 1.0 | 1.0 | |
| Females 35–64 years | 3.2 | 1.4 | |
| Females 65 + years | 1.7 | 1.4 | |
| *Stroke* | | | |
| Males 18–34 years | 1.0 | 1.0 | Thun et al. (2000) |
| Males 35–64 years | 2.4 | 1.0 | |
| Males 65 + years | 1.5 | 1.0 | |
| Females 18–34 years | 1.0 | 1.0 | |
| Females 35–64 years | 3.8 | 1.5 | |
| Females 65 + years | 1.6 | 1.2 | |
| *Asthma exacerbations* | | | |
| Males 18–34 years | 1.4 | 1.0 | Cassino et al. (1999) |
| Males 35–64 years | 1.0 | 1.0 | |
| Males 65 + years | 1.1 | 1.0 | |
| Females 18–34 years | 1.4 | 1.0 | |
| Females 35–64 years | 1.0 | 1.0 | |
| Females 65 + years | 1.1 | 1.0 | |

Drug costs were taken from the RIZIV/INAMI database for reimbursed drugs (www.riziv.fgov.be) , and from the CBIP (Centre Belge d'Information Pharmacothérapeutique) for non-reimbursed drugs, in 2013. The mean daily cost of the NRTs was estimated based on a mean daily intake from the 'Fiche de Transparence June 2008' on the CBIP website (www.cbip.be). A mean treatment duration of 12 weeks was applied.

Cost inputs and their sources were validated through discussion with a group of Belgian clinicians during an Advisory Board: in particular, agreement was reached on data source for average daily intake and duration of the smoking cessation interventions.

All costs from years prior to 2013 were inflated with the health index of December 2013 (www.mineco.fgov.be). Discount rates of 3% and 1.5% were applied to future costs and health benefits, consistent with Belgian guidelines (Cleemput et al., 2012).

Cost data are reported in Table 3.

### *Utilities*

To calculate QALYs (Quality Adjusted Life Years), the BENESCO model utilizes utility weights for smoking-related diseases. For COPD and lung cancer, utility weights were applied for the first year and for subsequent years. For CHD, stroke, and asthma exacerbations, each initial and subsequent event leads to a utility decrease in only the cycle that the event occurs (Table 4).

The baseline utility values for the general population and the utility weights for the smoking-related diseases were the same as those reported in the Belgian customization of initial BENESCO model (Annemans et al., 2009).

### *Sensitivity analysis*

One-way univariate sensitivity analyses and a probabilistic sensitivity analysis (PSA) were performed. The latter included uncertainty around effectiveness, costs of complications, and utilities. Time horizon, population characteristics and model settings were kept constant. Probability distributions are selected based on the specific parameter type according to standard practice (Gray et al., 2010).

The parameters along with the distribution used are shown in the Technical Appendix A.

### *Model validation*

Quality assurance was conducted for all structural changes made to the original BENESCO model, as well as for scenario testing and face validity checks of model results.

**Table 3**
Cost data.

| Cost of therapy | | | |
|---|---|---|---|
| Therapy | Cost per quit attempt (€) | Source | Comments |
| Varenicline (Champix) | 246.81 | www.cbip.be<br>www.inami.fgov.be | Based on public price of titration pack (2 weeks) and 10 week pack |
| NRT | 230.77 | | Based on a weighted daily cost of 2.75€ times 84 days |
| Bupropion (Zyban) | 170.40 | www.cbip.be<br>www.inami.fgov.be | Based on public price of 2 packs of 18 days and 1 pack of 50 days |
| **Cost of smoking-related diseases** | | | |
| Diseases | Cost 1st year (€) | Follow-up cost per year (€) | Source |
| Stroke | 16,501€ (8,651€ hospital stay + 7,850€ for 1st year follow-up) | 4,419€ | Acute: mean APR-DRG 045/046 (inflated year 2010) (www.tct.fgov.be)<br>Follow-up: Annemans et al. (2003), inflated |
| CHD (myocardial infarction & angina) | 8,487€ (4,395€ hospital stay + 4,091€ for 1st year follow-up) | 2,148€ | Acute: mean APR-DRG 190 (MI) & 202 (angina), inflated year 2010 (www.tct.fgov.be)<br>Follow-up: Annemans et al. (2003), inflated |
| Asthma exacerbations | 2,861€ | | Acute: APR-DRG 141, inflated year 2010 http://www.tct.fgov.be |
| COPD | 2,186€ | 2,186€ | Mean annual cost Caekelbergh et al. (2005), inflated |
| Lung cancer | 10,765€ | 10,765€ | Mean annual cost Pacolet et al. (2011) |

**Table 4**
Utilities associated with smoking- related diseases.

| Smoking-related diseases | Utility first year | Utility subsequent years | Source |
|---|---|---|---|
| Chronic obstructive pulmonary disease | 0.76 | 0.76 | (Mannino et al. (2003); Spencer et al. (2005)) |
| Lung cancer | 0.61 | 0.50 | Trippoli et al. (2001) |
| | For first event | For subsequent event | |
| Coronary heart disease | 0.76 | 0.76 | Hay and Sterling (2005) |
| Stroke | 0.74 | 0.15 | (Duncan et al. (2000); Gage et al. (1998); Tengs and Lin (2003)) |
| Asthma exacerbation | 0.52 | 0.52 | Szende et al. (2004) |

This validation process was conducted by PAREXEL-HERON, developer of the initial BENESCO model and this Two-quit update.

## Results

The base case results are shown in Table 5. When compared to other treatment/retreatment interventions, varenicline retreatment (2QA) provides both the greatest health benefits (QALYs gained) as well as cost savings in the long term. For 1000 smokers willing to quit smoking, 2QA varenicline saves respectively 275,000€, 118,000€, 316,000€ and 237,000€ as compared to two courses of NRT (2QA), bupropion (2QA), placebo (2 QA placebo) or one single varenicline (1QA varenicline) treatment at lifetime. The number of QALYs gained is 74, 63, 193 and 111 respectively.

In univariate sensitivity analyses, discount rates (from 0% up to 5% on both costs and effects), cost of NRT and relative risk for smoking-related diseases in long term quitters were the most influential parameters, though changes did not affect the conclusions. The probabilistic sensitivity analysis illustrated in Fig. 3 provides evidence for the robustness of the model results.

## Discussion

The current analysis assesses the cost-effectiveness of a quit attempt with varenicline followed by a retreatment with varenicline in the motivated smoker who failed or relapsed after at least one year since initial treatment. This intervention has been compared with: (1) 1 quit attempt with NRT followed by retreatment with NRT, (2) 1 quit attempt with bupropion followed by retreatment with bupropion, (3) 1 quit attempt with placebo followed by retreatment with placebo, and (4) only 1 quit attempt with varenicline.

The effectiveness of varenicline treatment/retreatment translates into benefits of reduced incidence of smoking-related diseases and deaths, and increased cumulative Life Years and Quality Adjusted Life Years. These gains are most impacted by avoiding morbidity, especially due to a predicted reduction of COPD incidence, and avoiding mortality, primarily due to COPD and lung cancer. The decreased incidence of smoking-related diseases translates into additional health care savings, which largely offset the cost associated with varenicline treatment.

The model outcomes suggest net saving and net health benefits for 2QA varenicline over lifetime, making it a cost-saving intervention. This finding results from the higher efficacy of varenicline compared to the other smoking cessation interventions.

This analysis is the first one to consider adaptation of the BENESCO model with a second quit attempt. The initial BENESCO model has been customized for many countries, leading to similar outcomes based on same comparators and time horizon (Keating and Lyseng-Williamson, 2010; Zimovetz et al., 2011; Mahmoudi et al., 2012). We might expect similar conclusions when considering 2QA varenicline in other settings. However, this needs to be further confirmed.

The study limitations should be noted. First, only the efficacy of the smoking cessation interventions is considered, with no consideration of the impact of possible adverse events. However, the earlier mentioned meta-analysis of available published data has shown that the likelihood of adverse events associated with varenicline, NRT and bupropion is very limited (Cahill et al., 2013) and consequently their impact on utilities and costs should be minimal. The good cardiovascular and neuropsychiatric safety profile of varenicline has also recently been confirmed in clinical trials (Ware et al., 2013; Gibbons and Mann, 2013; Mills et al., 2014).

Secondly, similar to the initial BENESCO model, this model only includes 5 smoking-related diseases keeping co-morbidities to a minimum. Modeling all the possible multiple-disease risks and scenarios would not only greatly increase the complexity of the model but would also increase the quantity of data required. This more simplified model is a conservative approach because it captures only five smoking-related diseases with a high impact to the healthcare system, and does not vary the risks of other diseases based on subjects' morbidity history. Thirdly, all RRs for smoking-related diseases, as derived from Thun et al. (2000) have been kept constant for each smoking status. This may be perceived, in some cases, as a simplification of reality. As such, the model considers that long term quitters (namely quitter for more than 5 years) benefit from constant former smokers' RR for lung cancer as from year 6 until their death. Peto et al. (2000) described a more progressive decrease in the risk of lung cancer as the time of abstinence increases. Yet, comparing our input values with the values referred in Peto et al. (2000), our outcomes are more conservative. This assumption has also been tested in the deterministic and probabilistic sensitivity analyses.

Other published studies have examined the cost-effectiveness of varenicline for smoking cessation in the Belgian population, using the same model as the one on which the current one is built (Annemans et al., 2009; Bolin et al., 2009; Knight et al., 2012; Wilson et al., 2010). The key way in which these studies differ from the present analysis is the number of quit attempts over the subjects' lifetime: previous studies only considered one quit attempt, while the present analysis considers up to two quit attempts with the same intervention.

The published studies also differ from the current analysis in terms of the clinical data sources used, in particular the efficacy data of the interventions. Annemans and colleagues (2009) obtained 52 week

**Table 5**
Results.

| Costs (000€) | 2QA varenicline compared with | | | |
|---|---|---|---|---|
| | 2QA NRT | 2QA bupropion | 2QA placebo | 1QA varenicline |
| COPD cost | −160 | −137 | −416 | −239 |
| Lung cancer cost | −28 | −24 | −74 | −42 |
| CHD cost | −63 | −54 | −165 | −94 |
| Stroke cost | −43 | −37 | −112 | −64 |
| Total difference in smoking-related disease cost | −295 | −251 | −766 | −440 |
| Total difference incl. drug cost | −275 | −118 | −316 | −237 |
| Effects | | | | |
| QALYs | 74 | 63 | 193 | 111 |
| LYs | 56 | 48 | 146 | 84 |

QA: quit attempt; COPD: chronic obstructive pulmonary disease; CHD: coronary heart disease (myocardial infarction and angina); NRT: nicotine replacement therapy; QALY: quality-adjusted life year; and LY: life year.

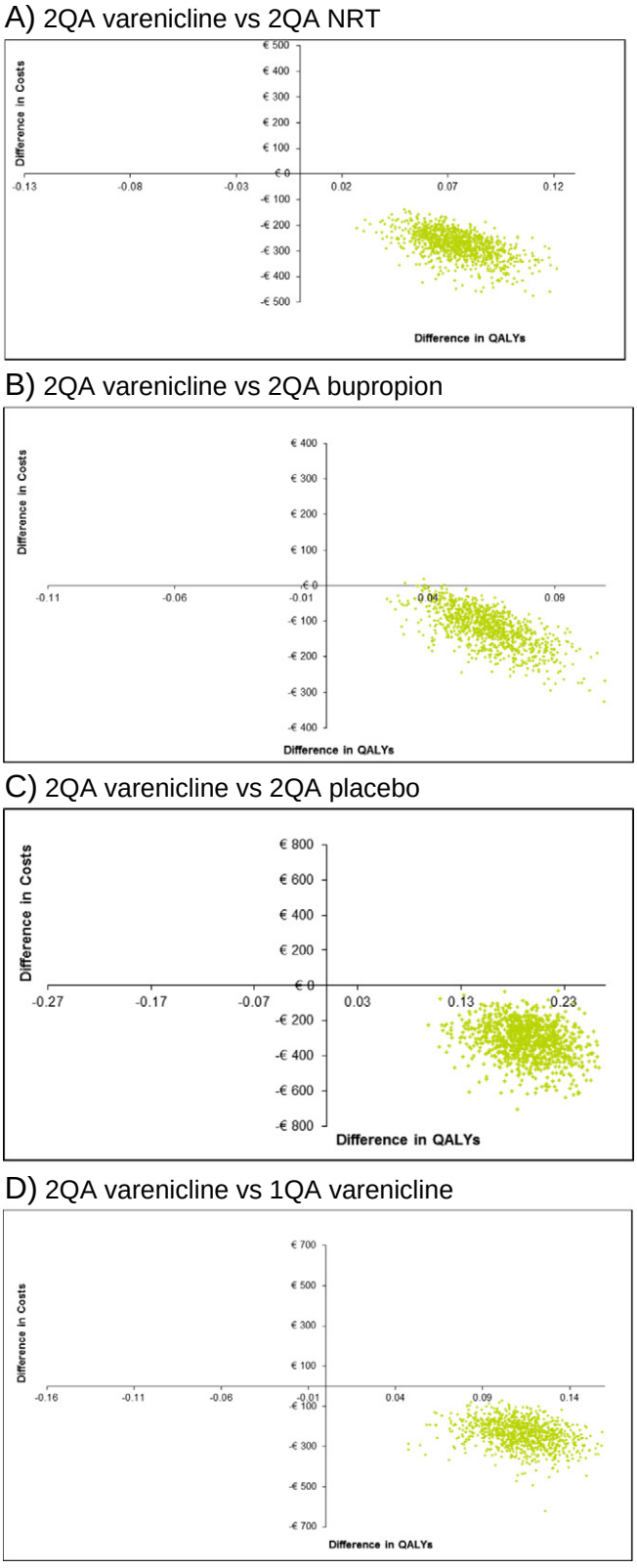


**Fig. 3.** Probabilistic sensitivity analysis based on 1000 replications.

abstinence rates for varenicline, bupropion, and placebo from pooling the results of two comparative trials (Gonzales et al., 2006; Jorenby et al., 2006). Bolin and colleagues (2009) derived efficacy data from a single randomized open-label trial that compared varenicline to NRT (Aubin et al., 2008). Knight et al. (2012) derived efficacy data from an RCT that compared a standard course of treatment with an additional 12 week maintenance course (Tonstad et al., 2006). The current study used efficacy data from a large systematic review and meta-analysis that considered 267 studies (not all for the interventions considered in the current analysis) to derive the first quit attempt efficacies of all SC interventions (Cahill et al., 2013). These studies all provide similar cost-effectiveness results, namely that varenicline dominates NRT, bupropion and placebo, meaning it is less costly and more effective over time. These findings are expected given the greater efficacy in quitting of varenicline over the other smoking cessation interventions.

Models are always a simple reflection of reality and subject to uncertainties. In order to assess the uncertainty in the current model parameters, a PSA was performed where the parameters such as the effectiveness of the smoking cessation interventions, the treatment costs of diseases, and the utilities associated with each health state were varied according to established distributions (Gray et al., 2010). For every treatment comparison, the PSA results confirmed that varenicline significantly dominated, meaning it was less costly and more effective than the comparator. The same conclusion was drawn based on one way sensitivity/scenario analyses on discount rate (from 0% up to 5% on both costs and effects), cost of NRT and relative risk for smoking-related diseases in long term quitters.

A final comment may be related to the perspective of the study which did not take into account the productivity-related costs, likely leading to an underestimation of the economic benefits of 2QA varenicline.

## Conclusion

Tobacco dependence is a chronic condition and successfully quitting smoking is extremely difficult. This Two-quit BENESCO model demonstrates that retreatment with varenicline in case of failure with or relapse after initial treatment is a cost-saving option versus no retreatment and versus other retreatment interventions. It supports the conclusion that fully supporting smokers in their attempts to quit smoking is an economically justified strategy.

## Conflict of interest

PAREXEL-HERON received funding from Pfizer to develop the model. Lieven Annemans was a paid consultant to Pfizer in connection with the development of this manuscript. Prof. K. Nackaerts reports funding and nonfinancial support from Pfizer during the conduct of varenicline clinical studies and personal fees from Pfizer (Belgium) outside the submitted work, for serving as an advisory board member and for lectures. Prof. P. Bartsch reports funding from Pfizer (Belgium) outside the submitted work, for serving as an advisory board member. Sophie Marbaix is a Pfizer Belgium/Luxembourg employee.

All authors have reviewed and approved the final content of this manuscript.

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We would like to thank the vendor, PAREXEL-HERON, that updated, validated, ran and described the model used in this analysis.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pmedr.2015.03.004.

## References


Annemans, L., Lamotte, M., Levy, E., et al., 2003. Cost effectiveness analysis of clopidogrel versus aspirin in patients with atherothrombosis based on the CAPRIE trial. J. Med. Econ. 6, 55–68.

Annemans, L., Nackaerts, K., Bartsch, P., et al., 2009. Cost-effectiveness of varenicline in Belgium, compared with bupropion, nicotine replacement therapy, brief counselling and unaided smoking cessation: a BENESCO Markov cost-effectiveness analysis. Clin. Drug Investig. 1, 655–665.

Annemans, L., Cleemput, I., Hulstaert, F., Simoens, S., 2011. Stimulating pharmaceutical innovation in the EU. Expert Rev. Pharmacoecon. Outcomes Res. 11 (3), 235–239.

Athanasakis, K., Igoumenidis, M., Karampli, E., Vitsou, E., Sykara, G., Kyriopoulos, J., 2012. Cost-effectiveness of varenicline versus bupropion, nicotine-replacement therapy, and unaided cessation in Greece. Clin. Ther. 34 (8), 1803–1814 (Aug).

Aubin, H.J., Bobak, A., Britton, R., et al., 2008. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 63, 717–724.

Aubin, H.J., Luquiens, A., Berlin, I., 2014. Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. Br. J. Clin. Pharmacol. 77 (2), 324–336.

Bae, J.Y., Kim, C.H., Lee, E.K., 2009. Evaluation of cost-utility of varenicline compared with existing smoking cessation therapies in South Korea. Value Health 12 (Suppl. 3), S70–S73 (Nov–Dec).

Bolin, K., Mörk, A.C., Willers, S., Lindgren, B., 2008. Varenicline as compared to bupropion in smoking-cessation therapy — cost-utility results for Sweden 2003. Respir. Med. 102, 699–710.

Bolin, K., Wilson, K., Benhaddi, H., et al., 2009. Cost-effectiveness of varenicline compared with nicotine patches for smoking cessation — results from four European countries. Eur. J. Pub. Health 19 (6), 650–654.

Caekelbergh, K., Spaepen, E., Annemans, L., 2005. Management of COPD in Belgium: a real life cost of illness [poster]. ISPOR 8th Annual European Congress, 2005 Nov 6–8, Florence.

Cahill, K., Stevens, S., Perera, R., Lancaster, T., 2013. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst. Rev. http://dx.doi.org/10.1002/14651858.CD009329 (Issue 5. Art. No: CD009329).

Cassino, C., Ito, K., Bader, I., et al., 1999. Cigarette smoking and ozone-associated emergency department use for asthma by adults in New York City. Am. J. Respir. Crit. Care Med. 159 (6), 1773–1779.

Centre Belge d'Information Pharmacothérapeutique (CBIP-BCFI). Available from URL: http://www.cbip.be (online. Accessed October 2013).

Cleemput, I., Neyt, M., Van de Sande, S., Thiry, N., 2012. Belgian guidelines for economic evaluations and budget impact analyses: second edition. KCE Reports 183C 2012.

Duncan, P.W., Lai, S.M., Keighley, J., 2000. Defining post-stroke recovery: implications for design and interpretation of drug trials. Neuropharmacology 39 (5), 835–841.

Feenstra, T.L., Hamberg-van Reenen, H.H., Hoogenveen, R.T., Rutten-van Molken, M.P., 2005. Cost-effectiveness of face-to-face smoking cessation interventions: a dynamic modeling study. Value Health 8 (3), 178–190.

Fernández de Bobadilla Osorio, J., Sánchez-Maestre, C., Brosa Riestra, M., Arroyo, O., Sanz de Burgoa, V., Wilson, K., 2008. Cost effectiveness analysis of varenicline (Champix) for the treatment of smoking in Spain. An. Med. Interna 25 (7), 342–348 (Jul, Spanish).

Fiore, M.C., Bailey, W.C., Cohen, S.J., et al., 2000. Treating tobacco use and dependence. Clinical Practice Guideline. US Department of Health and Human Services, Public Health Service, Rockville (MD) (June).

Gage, B.F., Cardinalli, A.B., Owens, D.K., 1998. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. Stroke 29 (6), 1083–1091.

Gibbons, R.D., Mann, J.J., 2013. Varenicline, smoking cessation, and neuropsychiatric adverse events. Am. J. Psychiatry 170 (12), 1460–1467 (Dec 1).

Gonzales, D., Rennard, S.I., Nides, M., et al., 2006. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 296, 47–55.

Gonzales, D., Hajek, P., Pliamm, L., et al., 2014. Re-treatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. Clin. Pharmacol. Ther. 96 (3), 390–396. http://dx.doi.org/10.1038/clpt.2014.124 (Epub 2014 Jun 9).

Gray, C., Clarke, P., Wolstenholme, J., Wordsworth, S., 2010. Applied Methods of Cost-effectiveness Analysis in Healthcare. Oxford University Press.

Hay, J.W., Sterling, K.L., 2005. Cost effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. Pharmacoeconomics 23 (2) (133-14).

Hoogendoorn, M., Welsing, P., Rutten-van Mölken, M.P.M.H., 2008. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. Curr. Med. Res. Opin. 24 (1), 51–61 (Jan).

Howard, P., Knight, C., Boler, A., Baker, C., 2008. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO simulation model: application to a population of US adult smokers. Pharmacoeconomics 26 (6), 497–511.

Igarashi, A., Takuma, H., Fukuda, T., et al., 2009. Cost-utility analysis of varenicline, an oral smoking-cessation drug, in Japan. Pharmacoeconomics 27 (3), 247–261.

Institut National d'Assurance Maladie-Invalidité/Rijksinstituut voor ziekte- en invaliditeitsverzekering (RIZIV-INAMI). URL: http://www.riziv.fgov.be (Accessed October 2013).

Jorenby, D.E., Hays, J.T., Rigotti, N.A., et al., 2006. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 296, 56–63.

Keating, G.M., Lyseng-Williamson, 2010. Varenicline. A pharmacoeconomic review of its use as an aid to smoking cessation. Pharmacoeconomics 28 (3), 231–254.

Knight, C., Marbaix, S., Annemans, L., et al., 2012. The cost-effectiveness of an extended course (12 + 12 weeks) of varenicline plus brief counselling compared with other reimbursed smoking cessation interventions in Belgium, from a public payer perspective. Acta Clin. Belg. 67 (6).

Krall, E.A., Garvey, A.J., Garcia, R.I., 2002. Smoking relapse after 2 years of abstinence: findings from the VA Normative Aging Study. Nicotine Tob. Res. 4 (1), 95–100.

Linden, K., Jormanainen, V., Linna, M., Sintonen, H., Wilson, K., Kotomäki, T., 2010. Cost effectiveness of varenicline versus bupropion and unaided cessation for smoking cessation in a cohort of Finnish adult smokers. Curr. Med. Res. Opin. 26 (3), 549–560 (Mar).

Lutz, M.A., Lovato, P., Cuesta, G., 2012. Cost-effectiveness analysis of varenicline versus existing smoking cessation strategies in Central America and the Caribbean using the BENESCO model. Hosp. Pract. 40 (1), 24–34 (Feb).

Mahmoudi, M., Coleman, C.I., Sobieraj, D.M., 2012. Systematic review of the cost-effectiveness of varenicline vs. bupropion for smoking cessation. Int. J. Clin. Pract. 66 (2), 171–182 (February).

Mannino, D.M., Buist, A.S., Petty, T.L., Enright, P.L., Redd, S.C., 2003. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow-up study. Thorax 58 (5), 388–393.

Mills, E.J., Thorlund, K., Eapen, S., Wu, P., Prochaska, J.J., 2014. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation 129 (1), 28–41. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.003961 (Jan 7, Epub 2013 Dec 9).

Muls, E., Van Ganse, E., Closon, M.C., 1998. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: comparison between Belgium and the United States of a projected risk model. Atherosclerosis 137, S111–S116 (Suppl.).

Nides, M., Elbert, D., et al., 2008. Varenicline versus bupropion SR or placebo for smoking cessation: a pooled analysis. Am. J. Health Behav. 32 (6), 664–675.

Orme, M.E., Hogue, S.L., Kennedy, L.M., Paine, A.C., Godfrey, C., 2001. Development of the health and economic consequences of smoking interactive model. Tob. Control. 10 (1), 55–61 (Mar).

Pacolet, J., De Coninck, A., Hedebouw, G., et al., 2011. De medische en niet-medische kosten van kankerpatiënten. HIVA report (Available from URL: http://hiva.kuleuven.be/nl/publicaties/publicatie_detail.php?id=3312).

Peto, R., Darby, S., Deo, H., Silcocks, P., Whitley, E., Doll, R., 2000. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ. 321 (7257), 323–329 (Aug 5).

Spencer, M., Briggs, A.H., Grossman, R.F., Rance, L., 2005. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics 23 (6), 619–637.

Szende, A., Svensson, K., Stahl, E., Meszaros, A., Berta, G.Y., 2004. Psychometric and utility-based measures of health status of asthmatic patients with different disease control level. Pharmacoeconomics 22 (8), 537–547.

Technische Cel — Cellule technique TCT, T. Banque de données nationales 2010. Available from URL: https://tct.fgov.be/webetct/etct-web/ (online. Accessed October 2013).

Tengs, T.O., Lin, T.H., 2003. A meta-analysis of quality-of-life estimates for stroke. Pharmacoeconomics 21 (3), 191–200.

Thun, M.J., Apicella, L.F., Henley, S.J., 2000. Smoking vs other risk factors as the cause of smoking-attributable deaths: confounding in the courtroom. JAMA 284, 706–712.

Tonstad, S., Tonnesen, P., Hajek, P., Williams, K.E., Billing, C.B., Reeves, K.R., 2006. Varenicline Phase 3 study Group, Effect of maintenance therapy with varenicline on smoking cessation : a randomized controlled trial. JAMA 296 (1), 64–71 (Jul 5).

Trippoli, S., Vaiani, M., Lucioni, C., Messori, A., 2001. 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 19 (8), 855–863.

Van den Bruel, A., Cleemput, I., Van Linden, A., et al., 2004. Effectiviteit en kosten-effectiviteit van behandlingen voor rookstop. Report KCE (Available from: http://www.kce.fgov.be).

van Genugten, M.L., Hoogenveen, R.T., Mulder, I., et al., 2003. Future burden and costs of smoking-related disease in the Netherlands: a dynamic modeling approach. Value Health 6 (4), 494–499.

Ware, J.H., Vetrovec, G.W., Miller, A.B., et al., 2013. Cardiovascular safety of varenicline: patient-level meta-analysis of randomized, blinded, placebo-controlled trials. Am. J. Ther. 20 (3), 235–246. http://dx.doi.org/10.1097/MJT.0b013e31828d455b (May–June).

Wetter, D.W., Cofta-Gunn, L., Fouladi, R.T., et al., 2004. Late relapse/sustained abstinence among former smokers: a longitudinal study. Prev. Med. 39 (6), 1156–1163.

Wilson, K., Hettle, R., Marbaix, S., et al., 2010. An economic evaluation based on a randomized placebo-controlled trial of varenicline in smokers with cardiovascular disease: results for Belgium, Spain, Portugal, and Italy. Eur. J. Prev. Cardiol. 19 (5), 1173–1183.

Zimovetz, E.A., Wilson, K., Samuel, M., et al., 2011. A review of cost-effectiveness of varenicline and comparison of cost-effectiveness of treatments for major smoking-related morbidities. J. Eval. Clin. Pract. 17 (2), 288–297.