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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Smoking Cessation Interventions and Services

November 2021: NICE guideline NG92 (March 2018) has been updated and replaced by NG209.
The recommendations labelled [2018] or [2018, amended 2021] in the updated guideline were based on these evidence reviews.
See www.nice.org.uk/guidance/NG209 for all the current recommendations and evidence reviews.

ALEXANDRA FILBY, Research Consultant
MATTHEW TAYLOR, Director

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UNIVERSITY of York
INVESTORS IN PEOPLE

Contents

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Abbreviations

ASH	Action on Smoking and Health
CBT	Cognitive Behavioural Therapy
CHD	Coronary Heart Disease
COPD	Chronic Obstructive Pulmonary Disease
HSCIC	The Health and Social Care Information Centre
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
LC	Lung Cancer
MI	Myocardial Infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
NRT	Nicotine Replacement Therapy
PA	Prolonged Abstinence
PHAC	Public Health Advisory Committee
PHG	Public Health Guidance
PP	Point Prevalence
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
ROI	Return-on-Investment
RR	Relative Risks
SSRI	Selective Serotonin Reuptake Inhibitors

Plain Language Summary

In order to help the Public Health Advisory Committee (PHAC) to develop recommendations for smoking cessation guidance, we developed a cost-effectiveness model. The model was developed so that we could use the best-available information in order to understand how different interventions might affect the general health of a group of current smokers, as well as the impact that the intervention might have on the costs to the National Health Service (NHS), local authorities and to society as a whole.

To calculate the benefits, we used evidence from published studies that reported the quit rates for a number of interventions. We used the outputs from other studies to estimate the likelihood that smokers and non-smokers would die or develop a range of health complications, including lung cancer, myocardial infarction (also known as heart attack), coronary heart disease, chronic obstructive pulmonary disease and asthma. Because we also know the costs associated with each of these complications, it was possible to calculate the overall costs for each group of people over their remaining lifetimes.

As well as estimating costs, we measured the health benefits that people would gain by quitting smoking. This was done by combining the increases in life expectancy with increases in the patients' quality of life (by avoiding some of the conditions listed above). This allowed us to calculate a measure known as the *quality-adjusted life year* gain for a person that could potentially be achieved by quitting cigarettes.

For each intervention that we assessed, the benefits of the intervention were matched against the costs that would be incurred to deliver it. These included a range of things such as GP visits, nurse consultations, telephone calls, leaflets and medical products.

The results of the analysis showed that, in all cases, the benefits of the intervention substantially outweighed the costs, meaning that it would be beneficial to the NHS and to society as a whole to provide the interventions. This was true even when we changed some of the inputs to reflect a more pessimistic scenario. Most interventions, when compared against no intervention or a basic level of support, provided health benefits to smokers and saved public sector money by preventing disease. For example, for every £1 spent on an intervention combining bupropion with a nicotine lozenge, the NHS would save £9.10 in costs and improve health by 0.003 quality-adjusted life years. Every £1 spent on varenicline plus additional counselling, meanwhile, would save the NHS around £1.65 and improve health by 0.0004 quality-adjusted life years. However, even when therapies increase NHS costs, investing in many of them would still be cost-effective because the health benefits are sufficiently large.

As with any analysis of cost-effectiveness, there were some factors in our analysis that could be challenged, or where alternative approaches could have been taken. However, most areas that we left out of our analysis (due to being unable to find suitable evidence) would have meant that the interventions would have been even more cost-effective. For example, we did

not include any of the impacts of reducing ‘second-hand smoke’, and we assumed that quitting smoking would only affect the conditions listed above, and not any of the conditions that could potentially be avoided through quitting smoking. Had we included those factors, the benefits of each intervention would have been greater still. Because of this, we are confident that, as long as an intervention is effective at helping people to quit smoking, then there is a high likelihood that it will also be cost-effective.

Section 1: Introduction

1.1 BACKGROUND

As stated in the NICE final scope, smoking is the main cause of preventable illness and premature death in England. Smoking is linked with many health problems, including circulation problems, heart disease (coronary heart disease (CHD) and heart attacks), stroke, lung cancer and cancer in other parts of the body including the mouth, throat and oesophagus and chronic obstructive pulmonary disease (COPD) [1]. Smoking can also affect people other than the smoker themselves through passive smoking. Passive smoking can increase the risk of getting the same health conditions as smokers. Infants and children are at particular risk of passive smoking. Smoking during pregnancy can affect the unborn baby's health and leads to an increased risk of complications [1].

The Health and Social Care Information Centre (HSCIC, 2014) has published data which show that 17% of all deaths in adults aged 35 and over were caused by smoking [2]. Treating smoking-related illness is estimated to cost the National Health Service (NHS) £2 billion per year [3]. In order to reduce the number of smokers and smoking- related illness, the NHS and Local Authorities provide services such as behavioural support and pharmacological therapies to support people who want to quit smoking. In addition, many interventions to quit smoking can be privately purchased (such as nicotine replacement therapy (NRT) in various forms). Recent data have shown that the number of people using Stop Smoking Services has declined but the reasons for this are unclear [4].

There is evidence that stop smoking interventions are effective and previous work commissioned by NICE has shown that many interventions can be considered cost-effective (Public Health Guidance (PHG1 and PHG10)). The current project will update NICE's guidelines on brief advice and referral for smoking cessation (PHG1) and smoking cessation services (PHG10). The evidence for selected interventions will be updated and additional interventions will be considered. The aim of the economic model is to assess the cost-effectiveness of the interventions prioritised by the PHAC that are identified as either having more recent evidence since the last guidance or having previously not been modelled. The outcome from the economic model will help to inform the Committee's guidance decisions.

1.2 OBJECTIVES

The key questions from the NICE scope are listed below.

Key questions from NICE scope:

1. Is brief advice from a community, health or social care professional effective and cost effective?
- Do effectiveness and cost effectiveness vary according to the person delivering it or the way it is delivered (including the media and setting used)?

2. Is very brief advice from a community, health or social care professional effective and cost effective?
- Do effectiveness and cost effectiveness vary according to the person delivering it or the way it is delivered (including the media and setting used)?

3. Is behavioural support (delivered to a person or a group) effective and cost effective?
- Do effectiveness and cost effectiveness vary according to the person delivering it or the way it is delivered (including the media and setting used)?

4. Is nicotine replacement therapy (such as patch, gum, spray or licensed e-cigarettes) or bupropion, on their own or combined with behavioural support, effective and cost-effective?

5. Do effectiveness and cost effectiveness vary when over-the-counter nicotine replacement therapy is used (on its own or combined with behavioural support)?

6. How can stop smoking services and other providers use digital media effectively as part of the interventions considered in this guideline?

7. What advice and referral options are appropriate for people using consumer e-cigarettes (or similar consumer nicotine delivery systems)?

Please note that the consultation version of this report included data on the effectiveness of consumer e-cigarettes as a proxy for licensed e-cigarettes; this has now been removed.

Section 2: Methods

2.1 MODEL OVERVIEW

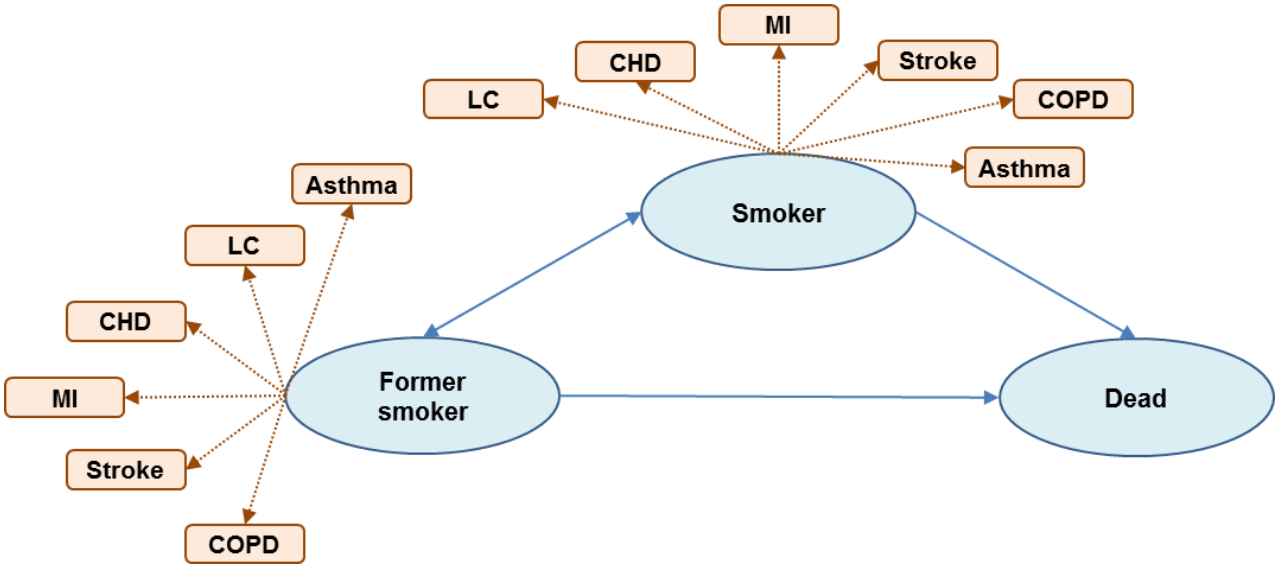
A cohort model was developed in line with the NICE methods manual [5]. The model was developed from NHS, personal social services (PSS) perspective. The model includes productivity costs and private costs and allows these results to be viewed within the main results and separately. The model allows for various time horizons to be reported, and incorporates a lifetime time horizon in order to capture all relevant costs and benefits. Discount rates of 3.5% for both costs and benefits are applied as stipulated in the NICE methods manual. The major outcome from the model is the incremental cost-effectiveness ratio (ICER), expressed as the incremental cost per quality-adjusted life year (QALY), for the comparison between therapy alternatives. Disaggregated results show both cost savings and quality of life (QOL) benefits. In addition, net monetary benefit (NMB), private intervention costs and lost productivity costs are shown.

The NICE scope outlines a number of interventions that will be updated since the previous guidance was published and those interventions that will be included in the update that were not included in previous guidance. The final interventions to be modelled were selected by the NICE team dependent on Committee input and data availability. The modelling approach adopted is based on previous modelling that has been carried out in the development of previous NICE guidance (PHG10 & PHG45). This approach takes into account long-term epidemiological data in order to capture the lifetime complications associated with five long-term smoking-related illnesses (see Section 2.2). In addition, the model has been updated to incorporate acute asthma exacerbations.

2.2 MODEL STRUCTURE

The model structure is shown in Figure 2.1. A similar model structure has been used in past cost-effectiveness models for smoking interventions (PHG10, PHG45, Taylor *et al.* 2011 [6]).

Figure 2.1: Model structure



* LC = lung cancer, CHD = coronary heart disease, MI = myocardial infarction, COPD = chronic obstructive pulmonary disease, asthma = asthma exacerbation.

In each annual cycle smokers have a probability of quitting (and becoming 'former smokers') and former smokers have a probability of relapsing. People from either the 'smoker' or 'former smoker' health state can move to the 'dead' health state. It is noted that tobacco harm reduction is out of the scope of this project.

Each cycle, smokers and former smokers have a probability of five different long-term comorbidities occurring:

- Lung cancer (LC);
- Coronary heart disease (CHD);
- Chronic obstructive pulmonary disorder (COPD);
- Myocardial infarction (MI);
- Stroke.

In addition, smokers and former smokers have a probability of experiencing an acute asthma exacerbation.

The prevalence of the five long-term comorbidities by age and smoking status is used to calculate the number of people in each health state and in each cycle, who develop one of these diseases (see Section 2.3.4). The incidence of asthma exacerbations is used to calculate the number of people by age and smoking status that develop this acute condition. Each health state has a utility value associated with it. Each comorbidity has an associated cost and disutility associated with the disease occurring. These costs and utilities are applied each cycle.

2.3 MODEL INPUTS

This section outlines the model inputs that have been used to populate the economic model and also highlights any area in which there are data gaps. Targeted searches were carried out to update the inputs from previous smoking models (PH10, PH45) and to identify new data required for the model update.

2.3.1 Effectiveness

Due to the size of the literature and due to resource constraints, a stepped approach to reviewing the evidence was taken by the review for this guidance update. The first step involved consideration of review level evidence. If the questions in the scope could not be addressed with the reviews a second step was undertaken which involved consideration of primary studies. This has meant that for most of the interventions considered only review level evidence (review of reviews and systematic reviews) was identified and analysed. Importantly, in terms of the modelling, these reviews could not provide the data in the format required to input into the economic model (i.e. quit rates) as reviews tend to report ORs and not quit rates. Previous reviews for similar guidelines would have included primary studies which would have provided the relevant data.

Due to the review approach the NICE team adopted a pragmatic approach to identify the most relevant and useful studies to include in the economic model. The approach taken was a combination of identifying the most recently published studies to better reflect the current context with results similar to the results of meta-analyses and systematic reviews and taking into account specific requests and interests of PHAC members. Given that the studies were not identified through the systematic review of all the possible studies, the approach to presenting the model results begins with a scenario/threshold analyses with the individual interventions identified by the NICE team reported as illustrative examples. The quit rates and interventions that are included in the illustrative examples are outlined in Table 2.1.

Where relapse rates are reported for less than one year, long-term relapse curves are used to adjust the rates to provide a quit rate at one year. The relapse curve that was used in this model was reported by Coleman *et al.* (2010) [7] in a Health Technology Assessment report (Graph 2.1). The Health Technology Assessment (HTA) report is used to calculate the percentage of remaining quitters from various time points to one year (e.g. the HTA reported showed that at six months 30.6% had quit, at one year 26.2% had quit). The percentage of remaining quitters was calculated (26.2/30.6=85.6%) and applied to the study data. The relapse curve was based on pooling 16 trials of NRT, bupropion and varenicline. However, it is noted here that the relapse curve may take a different shape when alternative interventions are used, or within certain subgroups. For this reason the quit rate at one year is varied by +/- 20% in sensitivity analysis. Where the trial did not report a control arm, the comparator was assumed to be 'no intervention' and the natural quit rate (2%) was applied.

Table 2.1: Intervention quit rates

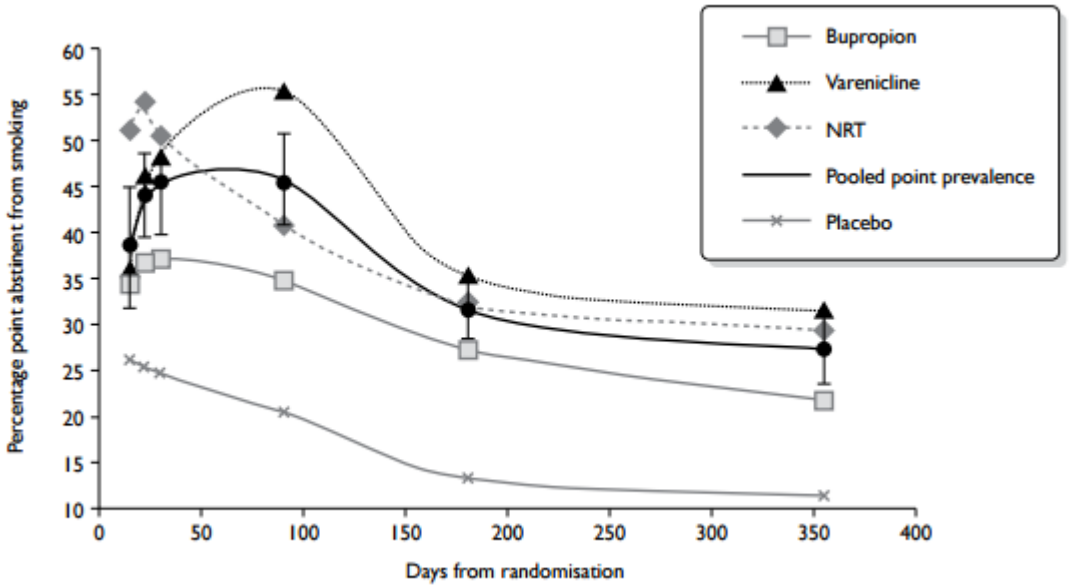
Intervention	P (quit) 12 months	Source
No intervention (background rate)	2.00%	NICE (2013)
Patch and nasal spray	27.00%	Blondal *et al.* (1999) [8]
Patch only	11.00%	Blondal *et al.* (1999) [8]
No intervention*	13.19%	Brown *et al.* (2014) [9]
NRT OTC*	8.65%	Brown *et al.* (2014) [9]
No intervention (placebo)	4.00%	Caponnetto *et al.* (2013) [10]
Placebo + counselling*	5.91%	Chengappa et al. (2014) [11]
Varenicline + counselling*	16.61%	Chengappa *et al.* (2014) [11]
Brief advice	6.60%	Heydari *et al.* (2011) [12]
Varenicline + brief advice	25.00%	Heydari *et al.* (2011) [12]
Sequence (var, bup, SSRI) (PA)	40.30%	Issa *et al.* (2013) [13]
Placebo + counselling	17.30%	Jorenby *et al.* (2006) [14]
Varenicline + counselling	30.50%	Jorenby *et al.* (2006) [14]
Usual care	10.20%	Joyce *et al.* (2008) [15]
Counselling	14.10%	Joyce *et al.* (2008) [15]
Counselling + pharmacotherapy	15.80%	Joyce *et al.* (2008) [15]
Telephone quit line	21.20%	Joyce *et al.* (2008) [15]
Placebo + counselling	15.90%	Rigotti *et al.* (2009) [16]
Varenicline + counselling	27.90%	Rigotti *et al.* (2009) [16]
Bupropion and lozenge	25.60%	Smith *et al.* (2009) [17]
Lozenge only*	14.38%	Smith *et al.* (2009) [17]
Standard care*	3.51%	Williams *et al.* (2006) [18]
Self-determination intervention*	10.10%	Williams *et al.* (2006) [18]
Minimal intervention (PA)	29.60%	Wittchen *et al.* (2010) [19]
Bupropion (PA)	29.00%	Wittchen *et al.* (2010) [19]
CBT PA)	20.90%	Wittchen *et al.* (2010) [19]
NRT (PA)	29.60%	Wittchen *et al.* (2010) [19]
Minimal intervention (PP)*	33.66%	Wittchen *et al.* (2010) [19]
Bupropion (PP)*	47.33%	Wittchen *et al.* (2010) [19]
CBT (PP)*	38.20%	Wittchen *et al.* (2010) [19]
NRT (PP)*	41.30%	Wittchen *et al.* (2010) [19]

PA prolonged abstinence.

PP point prevalence.

* Adjusted to one-year quit rate using relapse curve.

Graph 2.1: Relapse rate from Coleman *et al.* (2010) [7]



Studies reporting quit rates report either one or both of prolonged abstinence (PA) and point prevalence (PP) rates. PA is often considered the gold standard. However, the definition of PA varies, both in what is considered a relapse and the length of time that prolonged abstinence is measured over. PA rates are usually lower than PP, therefore this is the conservative option. PA abstinence can underestimate the effectiveness of an intervention while PP can overestimate it. PA could underestimate quit rate because it does not take into account more recent quitters that may go on to become prolonged quitters. Although these participants have quit (and may have quit for a number of months), they would not be classified as such when measuring prolonged abstinence. PP abstinence provides the number of people that have quit smoking at a given time point. In the economic model, the natural quit rate is then applied to this which is the 'net' smoking rate and accounts for people quitting and relapsing. There are difficulties in applying the relapse curve referenced in this report because it is based on point prevalence. Therefore, where a study reports PA at one year this was included in addition to PP.

Included Studies

Blondal *et al.* (1999)

Blondal *et al.* (1999) evaluated the effectiveness of using a nicotine patch for five months and a nicotine nasal spray for one year compared to using a patch alone. The study was a placebo controlled, double-blind trial carried out in a population of 237 smokers living in or around Reykjavik. The main outcome was sustained abstinence from smoking. The study concluded that both short and long-term abstinence rates showed that the most effective methods of stopping smoking was the combination of nicotine patch and nasal spray.

Brown *et al.* (2014)

Brown *et al.* (2014) investigated the 'real-world' effectiveness of e-cigarettes, over the counter nicotine replacement therapy (OTC NRT) and no intervention. The study was a retrospective analysis of a large cross-sectional survey in the English population, therefore, there was no randomisation and no control over the type of intervention received (such as the level of dosing of the e-cigarette, or the number of patches used or the length of time over which they were used). The survey population that this study investigated was any respondent who had smoked in the past 12 months and had reported making one quit attempt during that period. The main outcome measure was self-reported abstinence up to the time of the survey. The study results only show the number of people who reported not smoking. However, it is not possible to know when this was reported, meaning that respondents could have been quit for almost a year, or a day, or any time point in between. A crude assumption was applied that this was the six-month quit rate. Because the e-cigarettes used in this study were *consumer* e-cigarettes rather than licensed e-cigarettes, this was considered to be outside the scope of the guideline and were not included in the cost-effectiveness analysis.

Chengappa *et al.* (2014)

Chengappa *et al.* (2014) investigated the effectiveness of varenicline for smoking cessation in a population of clinically stable adults with bipolar disorder. Participants were recruited from an outpatient clinic in the US. The study was randomised, double-blind and placebo-controlled. Participants were assigned to either the varenicline arm in which patients receive varenicline for 12 weeks or the placebo arm. In addition, patients had 15 minutes of smoking cessation counselling at each visit (enrolment and follow-up). The study concluded that varenicline is effective for smoking cessation in bipolar patients.

Heydari *et al.* (2011)

Heydari *et al.* (2011) evaluated the efficacy of varenicline compared with no intervention. The study also included an arm reporting the effectiveness of NRT patches. However, this not included in the current report. This paper was selected to reflect the findings of the NICE effectiveness review. Participants in both arms also received brief counselling on smoking cessation via four weekly five-minute sessions. The study was conducted in a population of smokers willing to quit based in Iran. It should be noted that there are some inconsistencies in reporting in this paper. In the NRT arm the disaggregated results table in the NRT patch arm does not match the figures reported in the text. The study showed that after 12 months, the proportion of people remaining smoke-free in the varenicline group was higher than that in the group that received brief advice alone.

Issa *et al.* (2013)

Issa *et al.* (2013) [13] report the effectiveness of a smoking cessation intervention in a 'real-life setting' in Brazil. The study was not a retrospective study and was not randomised. Results were reported for four 'arms': i) varenicline monotherapy, ii) varenicline plus bupropion, iii) varenicline plus selective serotonin reuptake inhibitors (SSRI), iv) varenicline

plus bupropion plus SSRI. However, the results cannot be interpreted as separate arms of a study because the treatments were given sequentially. In brief, patients were given varenicline, if they did not quit after a given number of weeks bupropion was added and if the participants experienced mood changes SSRIs were prescribed. Although the study treats the interventions as different arms. Including them separately in the model would be biased given that there was something fundamentally different about each group (the fundamental difference being that they had or had not quit at a given time point and that previous treatments had not been successful). Therefore, the approach was taken to treat all four arms as one sequential intervention. In order to calculate this, a weighted average of the quit rates in each scenario was calculated assuming that the intervention itself is to stratify people in this way providing additional treatments when required. This was compared with no intervention in the economic model (assuming a background quit rate of 2%).

Jorenby *et al.* (2006)

Jorenby *et al.* (2006) [14] evaluated the efficacy of varenicline compared to placebo and sustained-release bupropion in the US. The study was a randomised, double-blind, placebo-controlled trial with over 1,400 participants. In all arms of the study participants received a ten-minute counselling session every week for 12 weeks, five clinic visits which included smoking cessation counselling and one phone call. The study reported seven-day abstinence point prevalence at 52 weeks. The conclusion of the study was that varenicline was the most effective smoking cessation therapy compared with both placebo and sustained-release bupropion.

Joyce *et al.* (2008)

Joyce *et al.* (2008) [15] examined whether reimbursement for provider counselling, pharmacotherapies and a telephone Quitline increased smoking cessation compared with usual care for Medicare Beneficiaries. The study was a randomised trial including 7,354 'seniors' enrolled in the Medicare Stop Smoking Program. The study consisted of four arms: 1) usual care, 2) reimbursement for provider counselling, 3) reimbursement for provider counselling with pharmacotherapy and 4) telephone counselling with telephone Quitline and nicotine patch. The study reported the proportion of participants who reported not having smoked in the last seven days at the time of the twelve-month survey and found that quit rates were highest for the telephone Quitline, followed by counselling plus pharmacotherapy, then counselling alone and the lowest quit rate was observed for usual care. This study has limited generalisability to the UK for several reasons. Firstly, the study population was Medicare beneficiaries which is not relevant to the UK NHS. Due to this context, the study was investigating the effectiveness of reimbursement for services, rather than the service itself. Participants in the study were required to make a 20% co-payment for counselling sessions. The reports suggests that the co-payment was an out of pocket expense but does not explicitly state this. In the UK NHS patients would not make a co-payment and it is not clear how this would affect the participants' behaviour and the effectiveness of the intervention. It may be that patients engage more with therapy because they have made a financial commitment or it may be that patients are more likely to drop out if they know they have to contribute towards

the payment. Both the costs and the effects of the intervention are uncertain when applying this study to the UK NHS, therefore, this study will be addressed by means of scenario analysis

Rigotti *et al.* (2009)

Rigotti *et al.* (2009) [16] investigated the efficacy of varenicline compared with placebo in a randomised, double-blind placebo-controlled trial. The patients were 714 smokers with stable cardiovascular disease. In all arms of the trial participants received a ten-minute counselling session every week for twelve weeks, seven clinic visits and five phone calls which provided additional brief smoking counselling. Participants were adults aged 35 to 75 years who had smoked an average of over ten cigarettes daily in the past year and wanted to stop smoking but had not tried to quit in the last three months. The study reported seven-day abstinence point prevalence at 52 weeks. The study concluded that varenicline is effective for smoking cessation.

Smith *et al.* (2009)

Smith *et al.* (2009) [17] carried out a study investigating the comparative effectiveness of five smoking pharmacotherapies in primary care clinics. The five interventions were as follows: 1) bupropion, 2) nicotine lozenge, 3) nicotine patch, 4) bupropion + lozenge, 5) nicotine patch + lozenge. The interventions included in the economic model are interventions two (lozenge) and four (bupropion + lozenge). The study was a randomised trial and the population was 1,346 primary care patients attending routine appointments in the US that consented to take part in the study. Seven-day point prevalence rates were reported at six months. These were 16.8% for the lozenge and 29.9% for bupropion + lozenge and were adjusted to 12-month rates using the relapse curve.

Williams *et al.* (2006)

Williams *et al.* (2006) [18] carried out a randomised trial in the US with a general population of smokers in which intention to quit was not required. The conditions consisted of a community care condition which reflected standard of care in which participants were given an information booklet, results of their cholesterol test and a list of Stop Smoking Services (contact details and costs). The intervention condition was a self-determination intervention in which participants received standard care plus counselling sessions. Counsellors were trained to support participants in making a clear an autonomous decision in whether to stop smoking. Participants were also told that they could have additional contacts with the counsellor and could schedule visits with the study doctor. In the intervention arm patients received one initial 50 minute counselling session and there were an average of 3.42 visits after this of 20 minute duration, 51% of which were in person. Forty-five percent saw a study doctor, of those, the average number of appointments was 1.3 and 33% of these were in person rather than phone. Williams *et al. r*eported point prevalence at 6 months which was adjusted to 12-month quit rate using the relapse curve.

Wittchen *et al.* (2010)

Wittchen *et al.* (2010) [19] investigated the effectiveness of a number of interventions in primary care in a randomised controlled trial in Germany. All participants received a brief (<3 minutes) face-to-face motivational intervention to quit smoking plus an information sheet. Subsequently, the four treatment arms differed: i) minimal intervention (MI) in which participants received a non-smoking diary and two brief (5 to 10 minutes) feedback sessions, ii) in the cognitive behavioural therapy (CBT) condition, the participants received the MI intervention plus a total of four (optional five) counselling sessions in which a doctor used a standardised CBT manual, iii) bupropion in which participants received the same treatment as the CBT group plus sustained release bupropion, iv) in the NRT therapy group patients received the same treatment as the CBT group plus a nicotine replacement product accordance with the participants choice. It should be noted that patients in the bupropion group and the NRT group were required to cover all expenses for the pharmacological treatment. However, in the UK, bupropion is only available via prescription and consequently it is assumed that the patient cannot privately pay for this intervention in the economic model. However, it should be noted that this may have some effect on the quit rate (i.e. are participants more likely to continue use of a treatment if they do not have to pay privately?). Wittchen *et al.* report PP at three months and PA at one year, both of which will be considered in the economic model (as shown in

Table **2.2**).

This guideline was interested in e-cigarettes as follows: an effectiveness review for licensed e-cigarettes and a descriptive review on advice and referral for 'consumer' e-cigarettes. No systematic reviews or RCT studies were found on the effectiveness of *licensed* e-cigarettes. Therefore, e-cigarettes were not included as an option in the cost-effectiveness model.

2.3.2 Costs

Comorbidity costs

Annual costs associated with each co-morbidity were identified. The costs reflect the on-going annual costs and are multiplied by the number of people with each co-morbidity each cycle.

Table 2.2: On-going annual comorbidity costs (NHS)

Parameter	Cost	Source
Stroke	£5,504	NICE CG92 Full guideline [20] Inflated from 2007/08 to 2014/15 prices using PSSRU (2015) H&CHS indices [21]
Lung cancer	£9,254	Cancer Research UK [22] Inflated from 2012/13 to 2014/15 prices using PSSRU (2015) H&CHS indices [21]
MI	£1,012	Godfrey *et al.* [23] Inflated from 2011/12 to 2014/15 prices using PSSRU (2015) H&CHS indices [21]
CHD	£1,323	British Heart Foundation. Cardiovascular Disease Statistics [24] Inflated from 2012/13 to 2014/15 prices using PSSRU (2015) H&CHS indices [21]
COPD	£546	NICE CG101 Full guideline Inflated from 2007/08 to 2014/15 prices using PSSRU (2015) H&CHS indices [21]
Asthma exacerbation	£1,231	Leaviss *et al.* (2014) [25] Inflated from 2010/11 to 2014/15 prices using PSSRU (2015) H&CHS indices [21]

PSSRU Personal Social Services Research Unit

The comorbidity cost sources were reviewed to identify if social care costs were included, and if so whether these costs could be disaggregated. It was not clear if the cost sources for stroke included social care costs. Lung cancer costs, MI costs, COPD costs and asthma costs included hospital and primary care costs. The source for CHD costs separated the costs by 'community care' and 'care provided in other settings' which may encompass social care. However, given that not all cost sources reported the disaggregated costs it was not possible to report overall costs for social care separately and, therefore, results are reported for NHS and personal social services as a whole.

Productivity costs

Productivity costs for smokers and non-smokers were included in the model. The sources used to populate these inputs aligned with the NICE return-on-investment (ROI) tool.

The excess number of days absent from work per year due to smoking was taken (2.74 days, Weng *et al.* [26]) and applied to the proportion of smokers in employment (assumed to be 58% as per the NICE ROI tool). It was assumed that people aged over the average retirement age (63 years, ONS 2013 [27]) did not incur any productivity losses. In order to calculate the cost of absenteeism from work, the number of lost days was multiplied by the average daily wage by age and gender (ONS 2015 [28]) (

Table **2.3**).

Table 2.3: Mean weekly wage ([28])

	Men	Women
16 to 24	£277.76	£224.32
25 to 34	£550.95	£421.14
35 to 44	£686.20	£452.25
45 to 54	£721.95	£430.60
55 to 64	£624.70	£355.85
65 to 74	£540.00	£295.00
75+	£540.00	£295.00

Note: Figures include both full- and part-time workers

The productivity costs associated with smoking were calculated and applied to the number of smokers at each time point within the model, in each arm of the model.

Intervention costs

The total cost of each of the included interventions, the components used to calculate the costs and the sources are summarised in Table 2.4.

Table 2.4: Intervention costs

Parameter	Total cost	Components	Source
Blondal *et al.* (1999)			
Patch only	£119.64	Cost per week for 7 patches for 20 weeks + one 15-minute GP nurse appointment	Drug costs (BNF online) [29] Nurse GP practice (PSSRU, 2015) [21]
Patch and nasal spray	£763.74	As above plus nasal spray. Assumed 25 sprays per day on average over a year	Drug costs (BNF online) [29]
Brown *et al.* (2014)			
OTC NRT	£202.60 (private)	Average price of 7-day supply from Boots. Standard patches only (not invisible patches)	www.boots.com
Chengappa *et al.* (2014)			
Placebo + counselling	£28.93	Two 15-minute sessions with GP nurse	Nurse GP practice (PSSRU, 2015) [21]
Varenicline + counselling	£220.03	As above plus varenicline. 0.5 mg for 3 days, 0.5 mg twice per day for 4 days, 11 weeks of 1mg twice daily	Drug costs (BNF online) [29]
Heydari *et al.* (2011)			
Brief advice	£19.10	All participants received 5-minute sessions of brief advice for four weeks.	Nurse GP practice (PSSRU, 2015) [21]
Varenicline + brief advice	£193.79	As above plus varenicline 0.5 mg daily for 3 days, 0.5mg twice daily for four days, 1mg twice daily for 8 weeks	Drug costs (BNF online) [29]
Issa *et al.* (2013)			
Sequential treatment	£269.18	Varenicline, bupropion and SSRI standard doses (BNF).	Nurse GP practice (PSSRU, 2015) [21]

Parameter	Total cost	Components	Source
		Percentage on each treatment. Six visits (15-minute nurse GP practice)	Drug costs (BNF online) [29]
Jorenby *et al.* (2006)			
Placebo + counselling	£189.32	10-minute counselling every week for 12 weeks, 5 clinic visits (held at weeks 13, 24, 36, 44, and 52. assumed 15 minutes), 1 7.1-minute phone call with GP	Nurse GP practice and telephone GP consultation 7.1 minutes (PSSRU, 2015) [21]
Varenicline + counselling	£353.12	As above plus varenicline 1mg twice daily for 12 week	Drug costs (BNF online) [29]
Rigotti *et al.* (2009)			
Placebo + counselling	£343.41	10-minute counselling every week for 12 weeks, 7 clinic visits (assumed 15 minutes), 6 71-minute GP phone calls	Nurse GP practice and telephone GP consultation 7.1 minutes (PSSRU, 2015) [21]
Varenicline + counselling	£507.21	As above plus varenicline 1mg twice daily for 12 week	Drug costs (BNF online) [29]
Smith *et al.* (2009)			
Lozenge only	£77.75	Lozenges for 12 weeks plus 15-minute GP nurse appointment plus 7.1-minute telephone counselling for 40.5% of patients	Drug costs (BNF online) [29] Nurse GP practice (PSSRU, 2015) [21]
Bupropion + lozenge	£78.86	As above plus bupropion over 8 weeks	Drug costs (BNF online) [29]
Williams *et al.* (2006)			
Standard care	£14.47	One 15-minute appointment (nurse GP practice)	PSSRU (2015) [21]
Self-determination	£198.96	One 50-minute session, an average of 3.42 20-minute sessions, 51% of which were in person and 49% by phone. Plus 45% saw a doctor with an average of 1.3 appointments (33% in person (11.7-minute consultation) and 67% by phone (7.1 minutes))	Advanced nurse with qualification costs – client contact GP consultation lasting 11.7 minutes with qualification costs (PSSRU, 2015) [21]
Wittchen *et al.* (2010)			
Minimal intervention	£43.40	Three 15-minute visits with nurse in GP practice	Nurse GP practice (PSSRU, 2015) [21]
CBT + MI	£268.40	MI cost plus additional 5 11.7-minute sessions with a GP or advanced nurse	Advanced nurse GP practice, GP (PSSRU, 2015) [21]
Bupropion + CBT + MI	£351.92	MI and CBT cost plus 8 weeks of bupropion	Bupropion cost and dose (BNF online) [29]
NRT + CBT + MI	£115.73	MI and CBT cost plus NRT (privately purchased)	NRT (boots.com – average cost of standard patches)

Notes: Where the comparison was 'no intervention' it was assumed there were no costs associated with the comparator arm.

2.3.3 Utilities

Utilities are applied to smokers and former smokers. In addition, the utility values associated with each of the five comorbidities are used to calculate disutilities. The disutilities are applied to the utilities of smokers and former smokers in the model when they experience a comorbidity.

It is possible to experience more than one comorbidity. When patients experience multiple comorbidities at one time, it is not clear how this affects their quality of life. For example, if people with lung cancer experience a decrement in quality of life and people with COPD also experience a decrement, would patients with both lung cancer *and* COPD experience the sum of both decrements, only the decrement associated with the most severe comorbidity, or somewhere in between? This is a complex issue which is affected both by the type of comorbidity and by the number of comorbidities experienced. Therefore, there are two methods of applying the disutility associated with multiple comorbidities in the model:

1. The disutility associated with each comorbidity is incurred;
2. Only the disutility associated with the most severe comorbidity is incurred.

Option two requires assumptions to be made about the number of people that have more than one co-morbidity given that it is not possible to determine this from the prevalence data. Therefore, option one is included in the base case and option two is explored in scenario analysis.

It should be noted that it was assumed that the asthma exacerbation disutility occurs in addition to other disutilities even in the scenario in which the most severe comorbidity is incurred is selected, because it is an acute event and is assumed to have an additional quality of life decrement for one week.

The utility inputs included in the model are shown in Table 2.5. A formal update search was carried out and the utility inputs were updated from the previous model inputs where a better data source was available. Details of the search strategy and sifting are available in Appendix A.

Table 2.5: Utility values

Parameter	Utility value	Source
Stroke	0.48	Tengs and Wallace [30]
Lung cancer	0.61	Bolin *et al.* (2009) [31]
MI	0.80	Tengs and Wallace [30]
CHD	0.76	Stevanovic [32]
COPD	0.73	Rutten-van Molken *et al.* 2006 [33]
Asthma exacerbation*	0.52	Applied for one week. Szende *et al.* [34]
Smoker	0.8486	Vogl *et al.* (2012) [35]
Former smoker	0.8669	Vogl *et al.* (2012) [35]

* Assumed that disutility is incurred for 1 week.

It is possible that the disutilities for smokers and non-smokers could be derived as a result of one, or both, of two factors:

- Non-smokers feeling better than smokers simply *because they do not smoke*;
- Non-smokers feeling better than smokers because they experience fewer co-morbidities (as already partially captured in the model).

If the latter is the greater driver of differences in quality of life, then potential double-counting will be occurring in the model. However, this approach has been used in previous models because it was felt that the former effect would be significant in isolation and, as such, the base case model allows a differentiation by smoking status.

2.3.4 Comorbidity Epidemiology

The model generates average (or 'expected') outcomes for specific baseline characteristics (i.e. the outcomes are calculated for a person of a pre-specified age and smoking status). However, results are calculated for every possible baseline characteristic, and the model then produces a 'weighted average' output, based on the known demographics of the assessed group.

The inputs required to inform the calculations of the prevalence of comorbidities by age, gender and smoking status are summarised in this section. A number of sources were searched suggested by the PHAC members, these included the Avon Longitudinal Study of Parents and Children (ALSPAC) and specific author searches of ALSPAC and the Global Burden of Disease (GBD) data base was searched. The specific data needed for the model was not identified in these searches.

Table 2.6 summarises the sources used for the prevalence of each comorbidity.

Table 2.6: Sources for prevalence of comorbidities

Prevalence	Source/notes
Stroke	Bhatnagar *et al.* (2015) [36]*
Lung cancer	Maddams *et al.* (2009) [37]*
MI	Bhatnagar *et al.* (2015) [36]*
CHD	Liu *et al.* (2002) [38]. Assumed that 12 to 15 year olds had 0% prevalence (given that the prevalence for the 16 to 24 age group was 0% (females) and 0.1% (males) and the risk reduces with age). Data were only reported as young as 16 to 24 years (0.1%)
COPD	Public Health England data set (not reported by gender). Assumed 12 to 15 year olds had 0.1% prevalence (given that the prevalence for the 16 to 24 age group 1.28% and the risk reduces with age). Data were only reported for ages as low as 16 to 24 years (1.28%)

* Studies reported prevalence for age 0-44 and this was not reported with any more granularity.

The prevalence of smoking by age and gender was extracted from the Health Survey for England (2014) [39]. Inputs for ages 12 to 15 are not reported in the survey. At this age bracket data are only reported for the question 'have you ever smoked?' However, Action on Smoking and Health (ASH) reports the prevalence of regular smoking in 2014 for children aged 11 to 15 and this input is used in the model [40]. To calculate the prevalence of non-smokers and former smokers in the 12 to 15 age bracket, the same percentage difference from current smokers was applied as in the 16 to 24 age bracket.

Table 2.7 summarises the sources used for the relative risks by smoker, non-smoker and former smoker by gender.

Table 2.7: Sources for relative risks (RR) of comorbidities

Relative risks	Source/notes
Stroke	Myint *et al.* (2008) [41]
Lung cancer	Pesch *et al.* (2012) [42]
MI	Prescott *et al.* (1998) [43]
CHD	Shields *et al.* (2013) [44]
COPD	Lokke *et al.* (2006) [45]

The data summarised above show the sources for the prevalence, by age, of each comorbidity in the general population (regardless of smoking status) (A), the relative risk of each co-morbidity by smoking status (smokers versus formers smokers (B) and smokers versus non-smokers (C)) and the prevalence of smoking (D). This can be used to calculate the prevalence of each co-morbidity for a current smoker (E), former smokers (F) and non-smokers (G), by ensuring that the following equation was satisfied:

$$(E \times D1) + (F \times D2) + (G \times D3) = A$$

Where E:F = the odds ratio, B; G:F = the odds ratio C

This can be illustrated using the example of a 60-year-old male with lung cancer. The prevalence of lung cancer is provided in Table 2.8 [37], the relative risk of lung cancer is shown in Table 2.9 [42] and the prevalence of smoking is shown in

Table **2.10** [39].

Table 2.8: Prevalence of lung cancer (males)

Age	**%**
12 to 15	0.002%
16 to 24	0.002%
25 to 34	0.002%
35 to 44	0.002%
45 to 54	0.089%
55 to 64	**0.089%**
65 to 74	0.748%
75+	0.150%

Table 2.9: Relative risk of lung cancer (males)

RR of lung cancer (men)		
Smoker	**Former**	**Non**
23.6	7.5	1

Table 2.10: Prevalence of smoking (males)

Age	Non	Former	Smoker
12 to 15*	96.34%	0.66%	3.00%
16 to 24	67.99%	5.78%	26.23%
25 to 34	53.55%	17.23%	29.22%
35 to 44	51.78%	23.18%	25.04%
45 to 54	54.31%	24.72%	20.96%
55 to 64	**45.43%**	**37.26%**	**17.30%**
65 to 74	44.80%	41.74%	13.46%
75+	41.64%	53.28%	5.08%

* From ASH report [40]

It is important to note that although the same term ('regular smoker') is used for under 16s and over 16s in the literature, regular smoking for adults (age 16+) is defined in most surveys as 1 or more cigarettes/day whereas for 12 to 15 year olds it is defined as one or more cigarettes/week. The measure for the two groups is different, but in the absence of better data these inputs were implemented in the model. This will have a very minor impact on the results given that the 12 to 15 age group is small and have a very low risk of all comorbidities.

Substitute the prevalence of smoking and the actual prevalence rate:

$$(E \times 0.17) + (F \times 0.37) + (G \times 0.45) = 0.089\%$$

Substitute the odds ratios and calculate prevalence by smoking status using the RRs:

$$(E \times 0.17) + (E \times 0.37 \times 7.5) + (E \times 0.45 \times 23.6) = 0.089\%$$

$$E = \frac{0.089\%}{(0.17 + (0.37 \times 7.5) + (0.45 \times 23.6))}$$

(E) = 0.29%
(F)= 0.09%
(G) = 0.01%

This process was repeated for each age and gender for all co-morbidities. Prevalence by smoking status is shown in Appendix B.

2.3.4.1 Asthma Exacerbation Inputs

Similarly to Leaviss *et al.* [25], mortality associated with asthma exacerbation was assumed to equal all-cause mortality (i.e. asthma exacerbations did not result in death). In addition, it was assumed that asthma exacerbations were transient in nature and resolved within one year.

In the Leaviss *et al.* HTA report, asthma exacerbation incidence rates were reported for short-term and long-term quitters Table 2.11). The incidence data for short-term quitters was

applied for 4 years after quitting in the model. However, the current model structure does not allow the incidence rates to be applied in this way and consequently the long-term rate is applied in the base case (which is not a conservative estimate but may be more accurate given the lifetime time horizon of the model). The impact of these inputs on the model results and direction of results is explored in sensitivity analysis.

Table 2.11 Incidence of asthma exacerbations

	Males		
Age	**Smokers**	**Long-term quitters**	**Short-term quitters**
12 to 15	0.08%	0.05%	0.05%
16 to 24	0.08%	0.05%	0.05%
25 to 34	0.08%	0.05%	0.05%
35 to 44	0.05%	0.05%	0.05%
45 to 54	0.05%	0.05%	0.05%
55 to 64	0.05%	0.05%	0.05%
65 to 74	0.07%	0.06%	0.06%
75+	0.07%	0.06%	0.06%
	Females		
Age	**Smokers**	**Long-term quitters**	**Short-term quitters**
12 to 15	0.08%	0.06%	0.06%
16 to 24	0.08%	0.06%	0.06%
25 to 34	0.08%	0.06%	0.06%
35 to 44	0.05%	0.05%	0.05%
45 to 54	0.05%	0.05%	0.05%
55 to 64	0.05%	0.05%	0.05%
65 to 74	0.06%	0.05%	0.06%
75+	0.06%	0.05%	0.06%

Leaviss *et al.* report the incidence rates of asthma exacerbations for smokers and long-term quitters (applied to former smokers) by age and gender. The number of people in these health states is multiplied by the relevant incidence rate to determine the number of people that experience an asthma exacerbation each year.

2.3.5 Mortality Epidemiology

The inputs required to inform the calculations of the mortality rates by age, gender and smoking status are summarised in this section.

The mortality rates from Doll *et al.* (1994) [46] were adjusted to reflect the general population mortality rates. To adjust the mortality to reflect that found in the general population the mortality per 1,000 men, by age band, was taken from the Doll study. Although a more recent paper which provides follow-up until 2011 has been produced in 2004 [47], the 1994 paper has been used because it provided annual mortality by smoking habits at age of death. The 2004 paper does not provide figures for those over 85 and for former smokers under 45 years. The Doll (2004) paper reports mortality beginning at the age of 35. In order to populate the age bands below this, an exponential distribution was applied and the mortality for the lower age groups was calculated (Table 2.12). The Doll paper was used to calculate the odds ratio for smokers versus formers smokers and smokers versus non-smokers. The ONS Life Tables

[48] provide the ‘real’ mortality for each age. The prevalence of smoking for each age and gender was taken from the Health Survey for England [39] (

Table **2.10**), for ages 12-15 this was taken from ASH [40]. Mortality calculations are shown in Appendix B.

Table 2.12: Mortality by smoking status

Age	Mortality per 1000 men		
	Non	Former	Smoker
12 to 15	0.1*	0.2*	0.3*
16 to 24	0.2*	0.3*	0.6*
25 to 34	0.6*	0.8*	1.3*
35 to 44	1.6	2.0	2.8
45 to 54	4.0	4.9	8.1
55 to 64	9.5	13.4	20.3
65 to 74	23.7	31.6	47.0
75 to 84	67.4	77.3	106.0
85+	168.6	179.7	218.7

* Extrapolated data (exponential).

The above information was used to calculate the actual mortality rates for smokers, former smokers and non-smokers, by ensuring that the same equation as described in Section 2.3.4, replacing comorbidity prevalence with mortality, was satisfied.

2.3.6 Mental Health Subgroup

The PHAC were interested in including studies investigating smoking cessation strategies in people with severe mental illness. Therefore, pragmatic searches to identify the inputs to populate the model for this sub-group were carried out. This search included searching for baseline utilities for current and previous smokers with mental health issues as well as disutilities which might be caused by smoking. Studies reporting QoL for people with mental health illnesses who are smokers were difficult to identify. The majority of studies identified only reported on different states of smokers' mental health, including prevalence of depression among smokers and no other comorbidities or did not include utilities. In total, 13 studies were identified as well as possible data sources such as the CEA Registry, PHE Toolkit and NICE website. Unfortunately, none of the studies reported utilities or disutilities; one study mentioned SF-36 scores. However, these were limited to Canadian population and only included people with Hepatitis C, therefore, study results could not be generalised [49]. The PHE toolkit did not contain any studies with utilities, the CEA registry search did not identify any results for current or ex- smokers with mental health issues. The NICE economic analysis of smoking cessation in secondary care (including mental health care setting) was also reviewed. However, its study population only included patients with schizophrenia and PTSD. The study did not provide utilities for smokers and ex- smokers with mental health issues and, as a result of this, the impact of smoking cessation on the quality of life for patients with schizophrenia was not calculated in the previous economic analysis [50].

A search for the quit rates for a mental health subgroup was focused on identifying clinical trials as well as any published studies. Fourteen studies and trials were identified as potentially relevant. However, only ten studies were used for data extraction because four

studies did not report quit rates or focused primarily on smoking reduction or prolonged abstinence rather than cessation. It has to be noted that studies which reported quit rates mainly looked at patients with severe mental health issues such as major depression, PTSD or severe depression and most of trial participants were treated at psychiatric facilities. The scope for this guideline states that 'acute, secondary and mental health services' are not covered. Therefore, many were out of scope.

A pragmatic search was adopted to establish if there is a difference in risk in any of the comorbidities and if the relative risks are different for smokers and non-smokers in the mental health subgroup compared to the general population. Most of the studies identified looked at serious mental illnesses such as schizophrenia. Also, none of them looked at the risk of lung cancer. Three studies were identified for possible data extraction because they mentioned COPD, CHD, MI and stroke. One study reported that males with phobic anxiety had a link to the RR of fatal CHD and this association was not explain by the confounding factor of smoking [51]. This study suggests that there is a difference in risk (at least for CHD) in this subgroup. However, the remaining studies did not report if there is a difference in risk in any of the comorbidities and whether the relative risks are different for smokers and non-smokers. In addition, it would also be necessary to identify data on the prevalence of comorbidities in the mental health population and the prevalence of smoking in this subgroup. This was not searched for given the result of the searches. It is unlikely that these detailed data would be available and if so, the missing data in other areas would preclude inclusion of the mental health subgroup.

For these reasons, there is currently not enough data available on the mental health subgroup to populate the economic model. It should also be noted that although the mental health subgroup is not modelled separately, the current model population includes all smokers, including those with mental health issues, therefore, the utility benefits of quitting will already be captured within the general population this way. As described in Section 2.3.1, one study including a mental health subgroup is included within the general model as an illustrative example.

Section 3: Results

As stated in Section 2.3.1 the novel approach to reviewing the evidence for this guidance update has meant that for most of the interventions considered only review level evidence was identified. In terms of the modelling, these reviews could not provide the data in the format needed to input into the economic model. Given that the studies were not identified through the systematic review, the approach was taken to begin with a scenario/threshold analyses with the individual interventions identified by the NICE team reported as illustrative examples.

The results in this section are representative of the average age and gender in the general population, unless stated otherwise. The results are weighted by gender and age and an average is taken. Although the majority of the evidence for interventions is from adult populations, the age weightings applied in this model are for all smokers, including those in the 12-15 group. However, these account for only around 5% of the total population. Results are reported for a lifetime time horizon (unless stated otherwise) from the perspective of the NHS. Private costs and lost productivity costs are also reported separately in the illustrative examples (Appendix C). The net monetary benefit (NMB) is calculated using the formula:

$$NMB = (QALY_{tx} - QALY_{cx})k - (Cost_{tx} - Cost_{cx})$$

Where tx and cx refer to the treatment and comparator arms, respectively. Incremental QALYs are converted into a monetary value using k, the cost-effectiveness threshold. Our analyses all use a threshold of £20,000 per QALY.

3.1 SCENARIO ANALYSIS

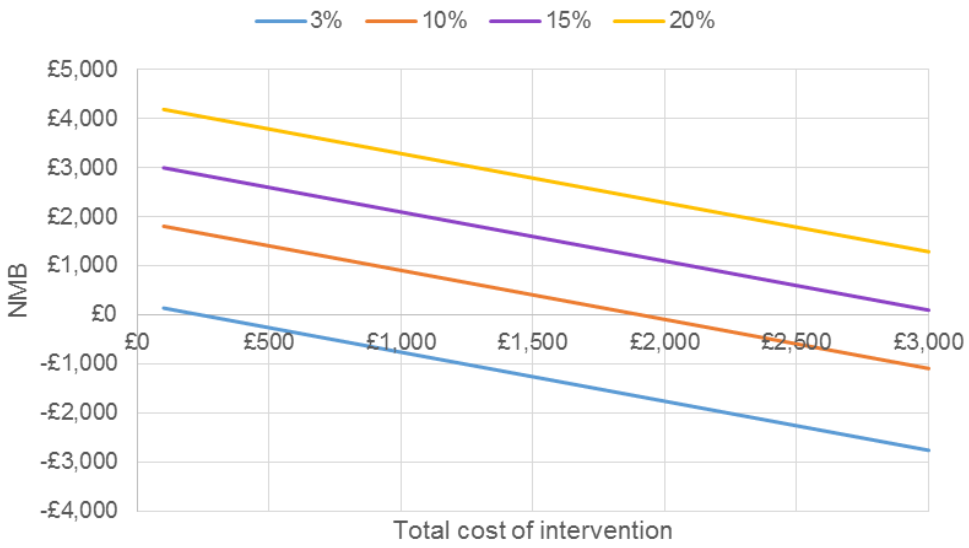
3.1.1 Quit Rate and Cost

The following two-way scenario analysis varies the quit rate associated with an intervention and the cost of the intervention. This allows a variety of scenarios to be assessed and to observe the difference of effect on the results. The following scenario analysis reports the NMB and assumes that the comparator quit rate is 2% (Graph 3.1).

Graph 3.1 shows that, as expected, as the cost if the intervention increases and as the effectiveness decreases the NMB becomes lower. It also shows that in order for an intervention to be considered not cost-effective, fairly extreme inputs are required. For example, if an intervention increases the quit rate from 2% (comparator arm) to 10% (an increase of 8%), it would have to cost over £1,900 per person before it was not considered cost-effective. The intervention costs included in the wide range of illustrative examples ranged from £19 to £763. The intervention effectiveness ranged from 9% to 47% which would all be considered cost-effective in the scenario analysis above. It is important to note that, even when the lowest quit rate identified in the effectiveness studies is combined with the most

expensive intervention cost, the intervention is still cost-effective. If the quit rate of the intervention was 13% higher than the comparator quit rate (15% purple line), the intervention could cost up to £3,000 before it would not be considered cost-effective. If the intervention was only 1% more effective than the comparator (3% blue line), it could cost around £225 before it would not be considered cost-effective. Therefore, if the difference in effectiveness is very small it would be necessary to refer back to the scenario analysis in Graph 3.1 or run the scenario through the model in order to confirm if the intervention was cost-effective.

Graph 3.1: Quit rate and cost scenario analysis



The Committee was interested in the impact of sequential interventions. However, there is a lack of evidence in this area. The cost of a sequential intervention will be higher than that of a single intervention but studies reporting quit rates of sequential interventions are scarce. This analysis can be used to identify optimistic and pessimistic scenarios. A pessimistic scenario would assume that the sequential intervention costs much more than a single intervention but has no impact upon the quit rate. This scenario analysis can be used to identify how much could be spent on a sequential intervention while still remaining cost-effective. An optimistic scenario would assume that the sequential intervention is more costly (it would not be realistic to assume it would be cheaper) and that it also improves the quit rate compared to a single intervention.

Additionally, the Committee was interested in a stepped approach to providing smoking cessation interventions in which a patient may try one approach and if this is not successful the patient would move on to another approach until a successful intervention for the patient was identified. The threshold analysis in Graph 3.1 demonstrates that if it is possible to be confident in there being moderate effectiveness (e.g. 10% compared to 2%) of just one of the interventions in the stepped approach then it would be possible to spend a little more on several interventions while still remaining cost-effective.

Similarly, the scenario analysis shows that if the intervention is moderately effective (say, 10% quit rate compared to a 2% comparator quit rate) then the amount that could be spent on an intervention before it is considered not cost-effective is far beyond the cost of any of the relatively inexpensive therapies explored in this project. Therefore, it would be possible to spend a little more money in order to access highly dependent smokers and still remain cost-effective. Moreover, if these groups are high risk groups, it may be that highly dependent smokers have more capacity to benefit, which may increase the cost-effectiveness further than in the base case shown in Graph 3.1.

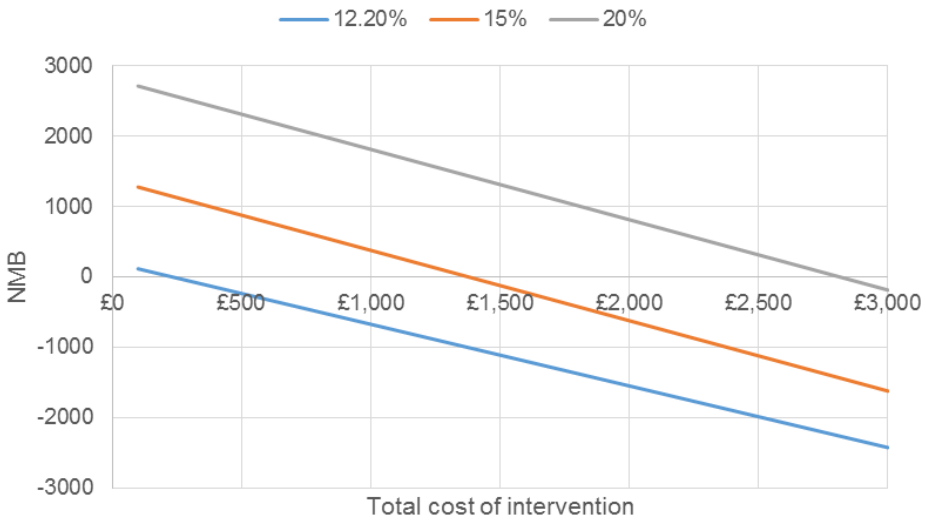
3.1.2 Examples from Selected Studies

Issa *et al.* (2013) [9] provided an example of a sequential intervention. The study showed a prolonged abstinence at one year to be 40.30% (based on a weighted average calculated by the number of people in each arm in order to consider this as a sequential intervention). The cost of the intervention was just under £270. Graph 3.3 shows that even if the intervention was half as effective with a quit rate of 20% the intervention could cost up to approximately £4,000 before it would be considered not cost-effective.

A recently published meta-regression [52] has called into question the claimed effectiveness of NRT. While the NRT evidence base may include some publication bias, the conclusion that NRT is effective is unlikely to change. Therefore, the study with the largest sample size identified in the Cochrane review (CEASE study) [53] has been identified. This study examined the effectiveness of standard (15mg) and high dose (25mg) NRT patches and varied the duration of treatment (8 or 22 weeks). The results range from a 12 month sustained success rate of 11.7% up to 15.4%. This study reports sustained success rates which is likely to result in a lower reported quit rate compared to if point prevalence at 12 months was reported. The scenario analysis in Graph 3.3 can be used to determine the expected result if NRT patches have the lowest reported efficacy. On the graph the orange line represents a 10% quit rate (slightly lower than the study reported) compared to a comparator quit rate of 2%. This graph shows that the intervention could cost just below £2,000 before the intervention is not considered cost-effective. Taking the most expensive combination of patches from the study (25mg patches for 22 weeks) the total cost of the intervention would be £227.92. Given the low price of patches (£10.36 for seven 25mg 'Invisi' patches (BNF online [29]), even the most expensive combination is far from the intervention cost threshold value at which point the direction of results changes.

Joyce *et al.* (2008) [15] carried out a study investigating the effectiveness of smoking cessation services (counselling with or without pharmacotherapy and a telephone Quitline) for Medicare beneficiaries as described in Section 2.3.1. As previously discussed, there is uncertainty around the effectiveness of the intervention in the UK given that, in the vast majority of cases, UK patients would not make co-payments for therapy. The patient population was those aged over 65. Therefore, a separate scenario analysis has been run for this population age group (Graph 3.2) and compared to the usual care quit rate in the study (10.2%). The quit rates for each intervention as reported by Joyce *et al.* at 12 months are 14.1% for counselling, 15.5% for counselling plus pharmacotherapy and 19.3% for a telephone Quitline. Graph 3.2 shows that at around 15% (near to the quit rate for counselling) the intervention could cost up to around £1,400 before it is not considered to be cost-effective and for the Quitline that resulted in a quit rate of almost 20%, the intervention could cost up to around £2,800 before the direction of results changes. Given that there is uncertainty about the effectiveness of the intervention in the UK, a more pessimistic scenario of 12.2% was implemented (a 2% increase in quit rate compared to the comparator arm) in this scenario the intervention would be cost-effective up to an intervention cost of around £200.

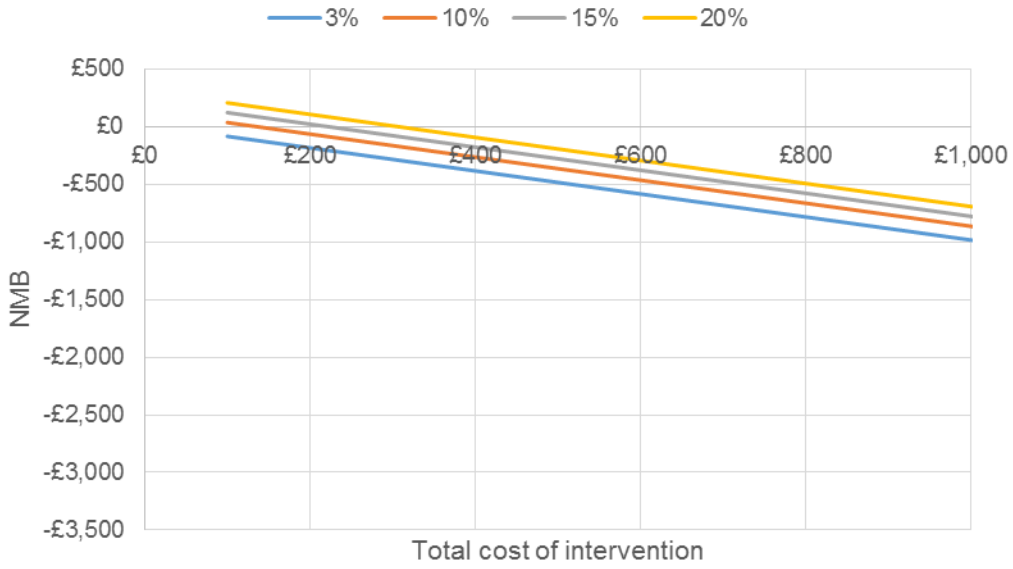
Graph 3.2: Joyce *et al.* scenario analysis



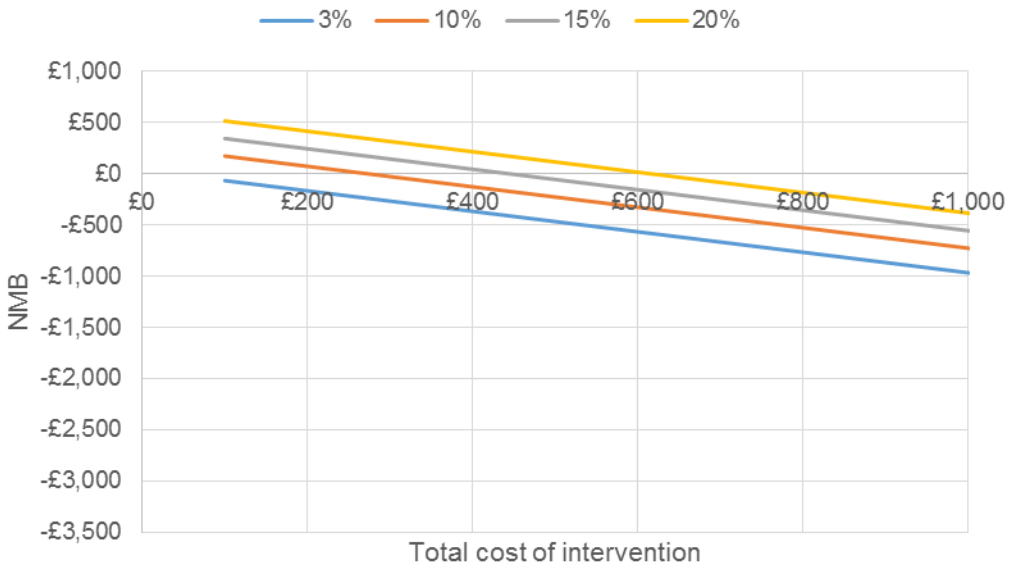
3.1.3 Scenario analysis time horizon

The Committee expressed an interest in viewing results based on different time horizons. Graph 3.3 to Graph 3.5 display the scenario analysis results at three, five and ten years.

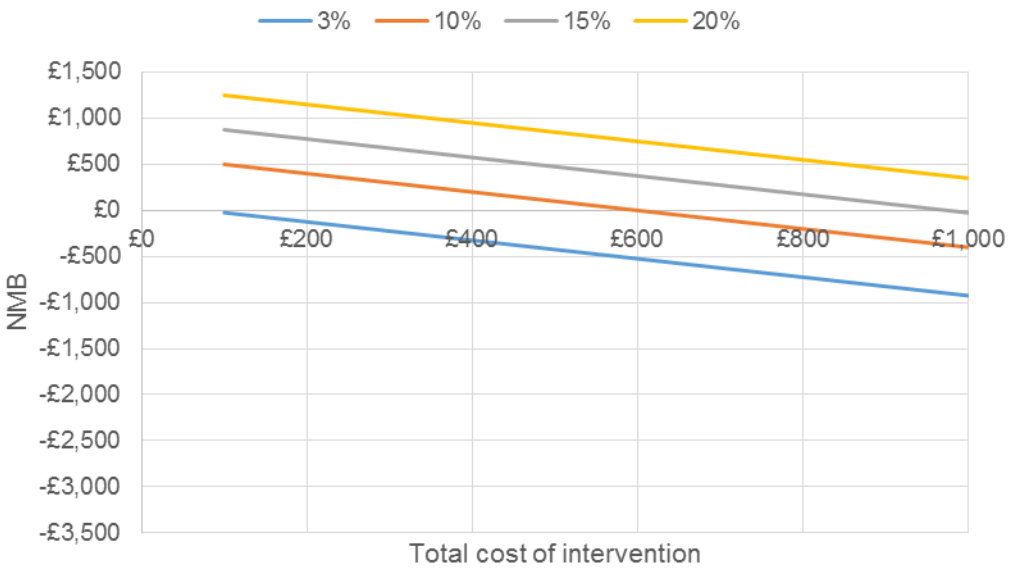
Graph 3.3: Three-year time horizon



Graph 3.4: Five-year time horizon



Graph 3.5: Ten-year time horizon



Graph 3.3 to Graph **3.5** show that as the time horizon decreases, the lines illustrating the quit rate become more compact. When there is a shorter time horizon, there is less capacity to benefit. The graphs also show that when the time horizon is shorter, the threshold price at which the intervention would be considered cost-effective decreases. This is because at a shorter time horizon the full benefits of the interventions are not being taken into account and, therefore, cost savings and QALY gains that are accrued in the long-term are not accounted for.

3.2 ILLUSTRATIVE RESULTS

The studies that have been run in the model to provide illustrative examples are outlined in Section 2.3.1. Due to the number of interventions and all the possible combinations of interventions, summary results are reported in Table 3.1 and full disaggregated results are reported in Appendix C. The results are weighted by gender and age and an average is taken. Results are reported for a lifetime time horizon from the perspective of the NHS. Numeric ICER values are reported where there are positive incremental health benefits and higher costs. If incremental health and costs are lower we report these as being 'less effective'. If the intervention generates positive incremental health and is cost saving, the intervention is reported as 'dominant'.

Table 3.1: Summary illustrative results

Intervention quit rate	Comparator quit rate	Incremental costs	Incremental QALYs	ICER
Blondal *et al.* (1999)				
Patch and nasal spray = 27.00%	No intervention = 2.00%	£3	0.26	£13
Patch only = 11.00%	No intervention = 2.00%	-£154	0.09	Dominant
Patch and nasal spray = 27.00%	Patch only = 11.00%	£158	0.17	£948
Brown *et al.* (2014)				
NRT OTC = 8.65%	No intervention = 13.19%	£138	-0.05	Less effective
Chengappa *et al.* (2014)				
Varenicline + counselling = 16.61%	Placebo + counselling = 5.91%	-£134	0.11	Dominant
Heydari *et al.* (2011)				
Varenicline + brief advice = 25.00%	Brief advice = 6.60%	-£385	0.19	Dominant
Issa *et al.* (2012)				
Sequence (varenicline, bupropion, SSRI) = 40.30%	No intervention = 2%	-£895	0.40	Dominant
Jorenby *et al.* (2006)				
Varenicline + counselling = 30.50%	Placebo + counselling = 17.30%	-£238	0.14	Dominant
Rigotti *et al.* (2009)*				
Varenicline + counselling = 27.90%	Placebo + counselling = 15.90%	-£317	0.15	Dominant
Smith *et al.* (2009)				
Bupropion and lozenge = 25.60%	No intervention = 2%	-£639	0.25	Dominant
Lozenge = 14.38%	No intervention = 2%	-£299	0.13	Dominant
Bupropion and lozenge = 25.60%	Lozenge = 14.38%	-£340	0.12	Dominant
Williams *et al.* (2006)				
Self-determination intervention = 10.10%	Standard care = 3.51%	-£16	0.07	Dominant
Wittchen *et al.* (2010)				
Bupropion (PA) = 29.00%	Minimal intervention (PA)	£243	-0.01	Less effective
CBT (PA) = 20.90%	Minimal intervention (PA)	£573	-0.09	Less effective
NRT (PA) = 29.60%	Minimal intervention (PA)	£72	0.00	Equal efficacy
Bupropion (PA) = 29.00%	CBT (PA) = 20.90%	-£330	0.08	Dominant
Bupropion (PA) = 29.00%	NRT (PA) = 29.60%	£171	-0.01	Less effective
CBT (PA) = 20.90%	NRT (PA) = 29.60%	£501	-0.09	Less effective
Bupropion (PP) = 47.33%	Minimal intervention (PP) = 33.66%	-£191	0.14	Dominant
CBT (PP) = 38.20%	Minimal intervention (PP) = 33.66%	£171	0.05	£3,620
NRT (PP) = 41.30%	Minimal intervention (PP) = 33.66%	-£160	0.08	Dominant
Bupropion (PP) = 47.33%	CBT (PP) = 38.20%	-£361	0.09	Dominant

Intervention quit rate	Comparator quit rate	Incremental costs	Incremental QALYs	ICER
Bupropion (PP) = 47.33%	NRT (PP) = 41.30%	-£31	0.06	Dominant
CBT (PP)) = 38.20%	NRT (PP) = 41.30%	£331	-0.03	Less effective

* Run for a 33 to 75 year age group as per the study population

There are a number of limitations associated with running some of the studies through the model. Chengappa *et al.* (2014) [11] investigated the effectiveness of smoking cessation interventions in a population of adults with bipolar disorder. Although the current model population includes all smokers, including those with mental health issues, the model parameters were not adjusted to account for this subgroup alone, as discussed in Section 2.3.6. A number of parameters within the model may be different for this subgroup, such as the utility (both baseline and the change from smokers to non-smokers), the cost of treating comorbidities may change and there may be mental health comorbidities specific to this subgroup that should be included if the intervention has a significant effect on mental health comorbidities, the baseline risk of comorbidities may also be different dependent on the usual lifestyle habits of people with mental illness. It is not clear how the model inputs would change and how this would impact upon the results given that almost all parameters within the model may need to be modified for this subgroup.

Rigotti *et al.* (2009) also investigated a specific patient population, those with stable cardiovascular disease aged between 35 and 75 years. Although the age of the subgroup was adjusted for this study, it was not possible to adapt the model inputs associated with CVD. Clearly in this group the baseline risk of CVD would be higher than in the general population. The current model uses the prevalence of comorbidities in the general population to calculate the prevalence of CVD in former smokers and smokers. If the baseline risk of CVD comorbidities is higher, it may be that there is more capacity to benefit when people quit smoking which would result in more costs being saved and more QALYs accrued.

Overall, the illustrative results clearly show that if an intervention is effective it is likely to save NHS costs and result in a health gain. There are some instances in which the costs are higher in the intervention arm. However, these are outweighed by the benefit of the QALYs accrued and result in an ICER below the £20,000 threshold.

One of the studies (Brown and colleagues) investigated over the counter NRT which is purchased privately [9]. This study had serious limitations in that it was not a trial but a retrospective analysis of a cross-sectional survey and there were issues with the outcome measure (discussed in more detail in Section 2.3.1). This study reported that OTC NRT was less effective than no intervention. Although the study had serious limitations it provides an example of a scenario in which intervention costs are incurred privately.

3.3 EXISTING COST-EFFECTIVENESS ANALYSES

Previous cost-effectiveness analyses of smoking cessation interventions have shown similar results to the model developed for this report (that interventions are either dominant or very cost-effective). Relevant examples have been highlighted by the PHAC and are discussed here.

Annemans *et al.* (2015) [54] evaluated the cost-effectiveness of retreatment with varenicline in participants that failed on initial treatments, or relapsed after initial success. The economic analysis compared one quit attempt with varenicline followed by varenicline retreatment with a quit attempt with NRT followed by NRT retreatment, a quit attempt with bupropion followed by bupropion retreatment, a quit attempt with placebo followed by placebo retreatment and only one quit attempt with varenicline followed by one quit attempt with placebo. Efficacy data were obtained from clinical trials which showed that varenicline was most effective at increasing smoking cessation at both first and second line treatment. The model was built from the perspective of the health care payer in Belgium. The model showed that, over a lifetime time horizon, varenicline retreatment is a dominant intervention over other interventions considered.

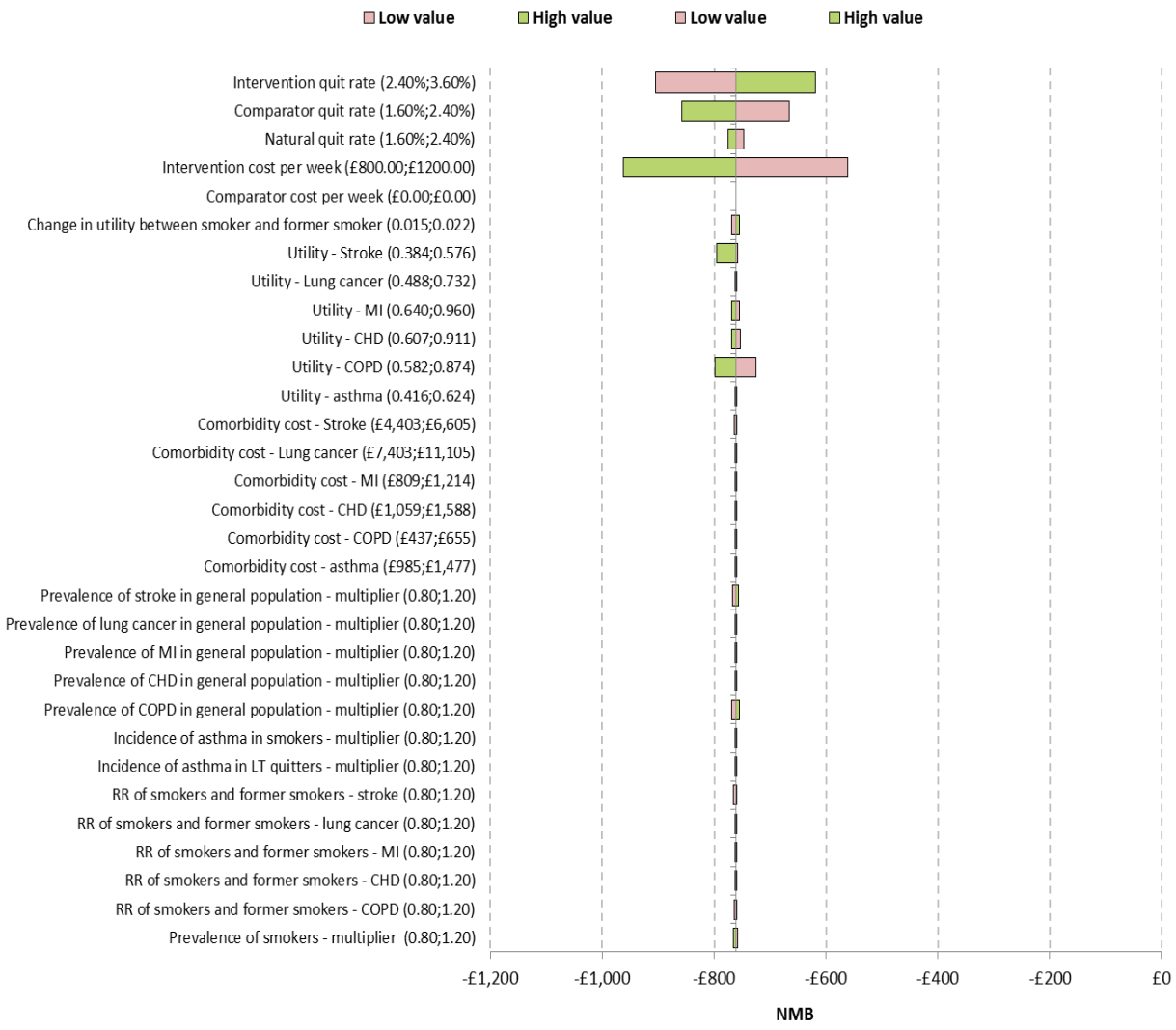
There are multiple studies that have evaluated the same or similar interventions included in the illustrative examples in this report. These studies tended to have similar results to those reported here. For example, Athanasakis *et al.* (2012) [55] used a Markov model to evaluate the cost-effectiveness of varenicline versus bupropion, NRT and unaided cessation in Greece. Varenicline had the highest quit rate. The authors found that varenicline led to additional health benefits and saved costs compared to the other smoking cessation interventions. Bauld *et al.* (2011) [56] carried out an observational study examining smoking cessation at one year of two smoking cessation services in Glasgow. One service consisted of seven weeks of group based support and the other consisted of up to 12 weeks on one-to-one counselling with pharmacists. These were compared with a 'self-quit' scenario (assumed 12 month quit rate of 1.5%). The quit rates at one year were 5.5% for the group service and 2.5% for the pharmacy service. Despite these low quit rates, the authors concluded that both services were considered to be highly cost-effective. Finally, NICE PH15 [57] concluded that several interventions targeted at disadvantaged groups (defined as individuals with mental health

problems; people who are institutionalised including those servicing a custodial sentence; some black and minority ethnic groups; homeless people; people on low incomes; lone parents and poor families and people on benefits and living in public housing) had a cost per QALY lower than the £20,000 threshold. These interventions included social marketing interventions, workplace interventions, brief interventions and proactive telephone counselling for pregnant women, recruitment in a paediatric unit, pharmacist-based interventions, free NRT and NHS Stop Smoking Services.

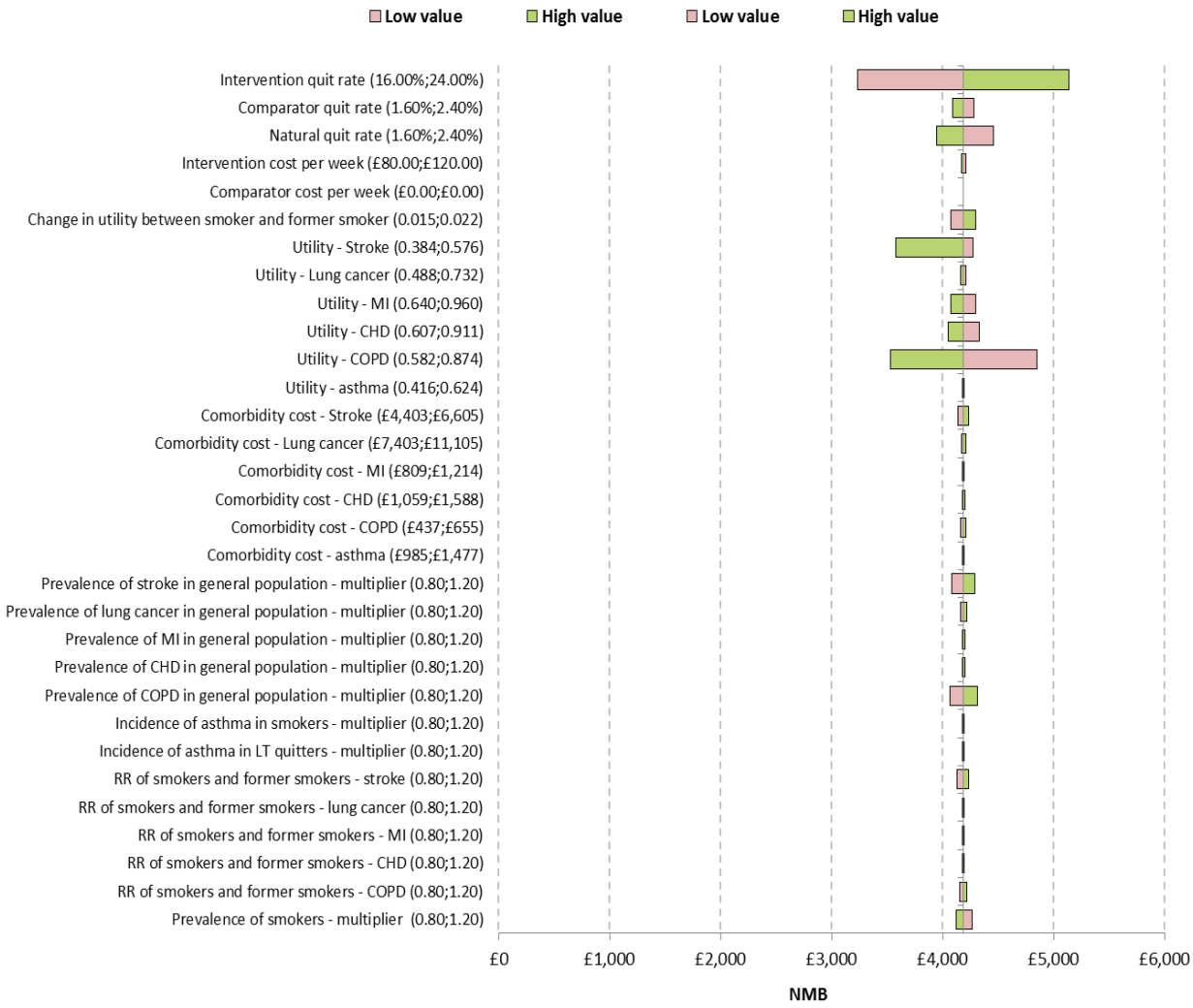
3.4 SENSITIVITY ANALYSIS

Extensive univariate sensitivity analyses have been carried out, whereby one parameter within the model is varied in isolation to assess its impact on the model's results. Tornado diagrams allow many univariate sensitivity analyses to be reported in one diagram. Presenting the univariate sensitivity analyses in a tornado diagram allows the key drivers of the model to be identified as many univariate sensitivity analyses are viewed alongside each other. Tornado diagrams in which the ranges were varied +/-20% are presented in Graph 3.6 and Graph 3.7. Graph 3.6 and Graph 3.7 shows a pessimistic (low effectiveness and high cost) and optimistic scenario (high effectiveness and low cost). These analyses are run at a lifetime time horizon for a general population and the background quit rate and the intervention quit rate is set at 2%.

Graph 3.6: Tornado diagram – effectiveness 3%, cost, £1,000



Graph 3.7: Tornado diagram – effectiveness 20%, cost £100



The tornado diagrams show that the key drivers of the models results are the utility for COPD, the quit rates and in the intervention cost when the cost is higher. In these comparisons, none of the parameters have enough of an impact to change the direction of results within the range varied. The utility associated with COPD has a larger impact on the results than the other co-morbidities because COPD is more prevalent. As discussed in Section 2.3.4.1 the long-term rate of asthma was applied to former smokers each year from quitting rather than applying the short-term rate for four years post-quit and the long term rate thereafter. The tornado diagrams demonstrate that this input has very little impact on the results.

3.4.1 Utility Scenario Analysis

In this scenario only the disutility associated with the most severe comorbidity that the person experiences is incurred (discussed in Section 2.3.3). Table 3.2 shows a pessimistic (low effectiveness and high cost) and optimistic scenario (high effectiveness and low cost). These analyses are run at a lifetime time horizon for a general population and the background quit rate and the intervention quit rate is set at 2%. Scenario one is run with a quit rate of 3% and an intervention cost of £1,000 and scenario 2 is run with a quit rate of 20% and an intervention cost of £100.

Table 3.2: Disutility scenario analysis results

	Scenario 1 (pessimistic)		Scenario 2 (optimistic)	
	Base case	**Highest disutility only**	**Base case**	**Highest disutility only**
Incremental costs	-£970	-£970	-£447	-£447
Incremental QALYs	0.0104	0.0098	0.1870	0.1772
ICER	£93,328	£98,499	Dominant	Dominant
NMB	-£762	-£773	£4,187	£3,991

* Changes at three decimal places.

The impact upon the result is as expected, the incremental QALYs are slightly lower, given that there is less capacity to benefit when only the utility associated with the comorbidity with the largest impact on QOL is included. The change is very small because the prevalence of each condition is low and the probability of having more than one comorbidity is lower still.

Section 4: Discussion

The economic evaluation has demonstrated that all of the smoking cessation interventions covered in this report are highly likely to be cost-effective. Scenario analysis shows the threshold at which the cost of the intervention would change the direction of results to not being considered cost-effective. Smoking cessation interventions are relatively inexpensive while providing long-term benefits for those who quit smoking. A number of illustrative examples have been included in the report, when the intervention more effective compared to the comparator the majority of interventions were dominant. Three interventions from two studies ([8]) that were slightly more expensive were not dominant but were still cost-effective (ICER = £13 (patch and nasal spray vs no intervention), £948 (patch and nasal spray vs patch only)). One further intervention ([19]) was not dominant because the effectiveness of the treatment and comparator were very similar (33.66% vs 38.20% (PP)), the ICER was £3,620 (CBT versus minimal intervention). It should be noted, however, that these results are presented from an NHS and PSS perspective. If the analysis was taken from a local authority perspective, the majority of cost-savings would not accrue to the local authority given that the costs saved are mostly NHS hospital costs, although there would be substantial gains through avoiding productivity losses. These losses were avoided whenever the intervention was cost-effective, and were typically between 6% and 8% of the net monetary benefit. This means that for every £100 benefit accruing to the NHS, a further £6 to £8 in productivity losses were avoided. Similarly, if the analysis was taken from purely an NHS perspective, all interventions would be 'dominant' given that the local authority pays for the smoking cessation services while the NHS reaps the benefits.

As with any economic evaluation, there are a number of limitations inherent within the model. The model structure, resource constraints and a lack of data made it impossible to categorise former smokers as achieving either 'recent' or 'long-term' abstinence and the impact of this on our findings is unclear. If, at some point after permanently stopping smoking, the probability of developing some or all of the model co-morbidities returns to that of non-smokers, the model will have overestimated the numbers of people with co-morbidities and, hence, co-morbidity costs, resulting in an underestimation of each interventions' cost effectiveness. For the same reasons the model was not adjusted to model a sub-group of patients with severe mental illness or a group of patients with CVD at baseline.

The model does not explicitly include multiple quit attempts beyond the initial intervention in the first year. However, the incorporation of a background 'net' quit rate into the model addresses this limitation. Sensitivity analysis showed that this input has some impact on the results but would need to change significantly in order for the direction of results to change.

Model estimates for the effectiveness of interventions were taken from the best sources available as identified by the NICE team given the difficulties with extracting quit rates from systematic reviews and meta-analyses. Given, that the studies were not selected in the usual way, the studies were used as illustrative examples and scenario analyses were reported.

There is a great deal of heterogeneity between studies and, as such; head-to-head comparisons of different treatments between studies were not made and should not be inferred from the results in this report. Further, the quit rates for most studies were drawn from single arm studies or from comparisons against 'usual care'. 'Usual care' can vary considerably from setting-to-setting and is often poorly defined. This means that the exact relative efficacy of each intervention might not necessarily be generalizable to the real world setting. However, sensitivity analysis demonstrated that the results would remain robust to even large changes in the quit rate inputs, so this is unlikely to affect the model's conclusions.

It should be noted that the following potential benefits associated with smoking cessation were *not* included in the analysis:

- Reduction in other smoking-related diseases (apart from the five long-term co-morbidities and asthma exacerbations);
- Improved recovery from other healthcare interventions such as surgery;
- Impact on other people's smoking behaviour;
- Second-hand smoke;
- Level of tobacco consumption.

The exclusion of these factors (due to a lack of reliable data and resource limitations) suggests that the current analysis may be underestimating the real benefits of quitting smoking. Given that the conclusion of this report is that effective smoking cessation interventions are highly likely to be cost-effective, or even be more effective *and* cost-saving, then included the benefits mentioned above would not alter decision making.

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56. Bauld L, Boyd KA, Briggs AH, Chesterman J, Ferguson J, Judge K, *et al.* One-year outcomes and a cost-effectiveness analysis for smokers accessing group-based and pharmacy-led cessation services. Nicotine Tob Res. 2011;13(2):135-45.
57. Supplementary economic analysis on interventions to reduce health inequalities. matrix: NICE; 2008. Available from: https://www.nice.org.uk/guidance/ph15/evidence/supplementary-economic-analysis-371205469.

APPENDIX A

Utility Search Strategy

A literature search was designed to identify studies reporting utility data for smokers, former smokers, and the following morbidities: stroke, lung cancer, chronic obstructive pulmonary disorder, coronary heart disease and myocardial infarction.

The search approach was pragmatic and targeted, reflecting that these searches were designed to provide inputs for the economic model. The searches were not designed to be exhaustive, as would be required for a systematic review. They aimed to target studies most likely to be relevant, whilst retrieving a volume of records manageable within the timescales and resources of the project. This targeted approach was especially necessary given the very large volumes of literature associated with the conditions of interest.

Searches to identify utility data in these populations had been undertaken to inform an earlier version of this model in 2012. Full details of this search were not available and therefore new strategies were constructed, date limited from 2012 to present in order to capture any utility data published subsequently.

In order to maintain precision, the search was largely restricted to databases specifically for utility studies, or economic evaluations such as cost-utility studies:

- NHS Economic Evaluation Database [NHS EED] (Cochrane Library, Wiley);
- ScHARRHud (http://scharrhud1.sheffield.ac.uk/public/);
- CEA Registry (http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx).

These resources, whilst specific to the relevant study types, do not contain any records for publications published later than 2014. In order to identify post 2014 literature a supplementary search of MEDLINE (Ovid SP) was also undertaken. The MEDLINE strategy is provided in Figure A.1. It combines a highly focused population search (searches free text terms in the title field only and focused subject headings) with the YHEC precision maximising HSUV search filter. A manuscript describing the development and testing of this filter has recently been submitted by YHEC for journal publication and has been presented at several international conferences (HTAi 2015[1], 2015 Cochrane Colloquium[2] and Mosaic Conference 2016[3]).

The MEDLINE strategy excluded animal studies using a standard algorithm. The strategy also excluded some publication types which were unlikely to yield study reports: editorials, news items and letters. The search was limited to studies published in English language from 2015 to date.

Full strategies (including search dates) for all sources searched are included overleaf.

[1] Arber *et al.* Sensitivity of a search filter designed to identify studies reporting health state utility values. Poster presented at: Global Efforts in Knowledge Transfer; HTA to Health Policy and Practice. HTAi 12th Annual Meeting; 2015 June 15-1; Oslo.

[2] Arber *et al.* Sensitivity of a search filter designed to identify studies reporting health state utility values. Poster presented at: Filtering the Information Overload for Better Decisions. 23rd Cochrane Colloquium; 2015 October 3-7; Vienna.

[3] Glanville *et al.* Sensitivity of a search filter designed to identify studies reporting health state utility values. Paper presented at: Mosaic 2016; May 18; Toronto.

Figure A.1: Search strategy for Ovid MEDLINE(R) In-Process & Other Non-indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

1	(smok* or exsmok* or nonsmok* or tobacco* or cigarette* or cigar* or pipe or pipes).ti. (109590)
2	exp *"Tobacco Use"/ (70751)
3	exp *"Tobacco Use Cessation"/ (17442)
4	exp *"Tobacco Use Cessation Products"/ (1437)
5	(stroke or strokes or apoplex* or cva or cvas or cerebrovascular accident* or vascular accident* or brain vasc* or cerebral vasc*).ti. (82837)
6	((brain* or cerebr* or cerebell* or vertebrobasilar or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj3 (ischemi* or ischaemi* or infarct* or thrombo* or emboli*)).ti. (32302)
7	((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli*) adj3 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).ti. (14674)
8	exp *Stroke/ (80406)
9	((lung or lungs or pulmonary or bronchial or bronchogenic or bronchus or bronchoalveolar or alveolar) adj3 (cancer* or tumor* or tumour* or neoplasm* or blastoma* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncol*)).ti. (115229)
10	exp *Lung Neoplasms/ (153885)
11	((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or heart) adj3 infarct*).ti. (82118)
12	((ischemi* or ischaemi*) adj3 (myocardium or myocardial or heart)).ti. (27766)
13	((acute or occlusion* or disease* or thrombos* or syndrome or acute) adj3 coronary).ti. (65715)
14	(cardiac arrest* or heart attack*).ti. (12856)
15	(CHD or CAD or ischaemic heart disease* or ischemic heart disease* or coronary aneurysm* or coronary syndrome* or coronary occlusion* or coronary stenosis or coronary restenosis or coronary thrombos* or coronary vasospasm or angina or chest pain*).ti. (54841)
16	exp *Coronary Disease/ (154643)
17	(COPD or COAD or COBD or AECB or emphysema* or chronic bronchit*).ti. (29947)
18	(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti. (26711)
19	exp *Pulmonary Disease, Chronic Obstructive/ (35708)
20	exp *Myocardial Infarction/ (117599)
21	or/1-20 (810886)
22	Quality-Adjusted Life Years/ (8828)
23	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (7324)
24	(quality adjusted or adjusted life year$).ti,ab,kf. (11303)
25	(illness state$1 or health state$1).ti,ab,kf. (4868)
26	(hui or hui1 or hui2 or hui3).ti,ab,kf. (1144)
27	(multiattribute$ or multi attribute$).ti,ab,kf. (652)
28	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (10881)
29	(utilities or disutil$).ti,ab,kf. (5469)
30	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. (6764)
31	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. (2287)
32	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (17524)
33	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (3302)
34	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (1497)
35	or/22-34 (54355)
36	21 and 35 (3482)
37	exp animals/ not humans/ (4314726)
38	(news or comment or editorial or letter or case reports).pt. or case report.ti. (3376255)
39	36 not (37 or 38) (3389)
40	limit 39 to (english language and yr="2015 -Current") (588)

Searching a number of databases produces a degree of duplication in the results. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms. Where result format did not facilitate loading into EndNote, Word documents or Excel spreadsheets were used as appropriate.

Literature Search Results

The searches identified 899 records (Table A.1). Following deduplication 827 records were assessed for relevance.

Table A.1: Literature search results

Resource	Records identified
Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE®	588
NHS EED	237
ScHARRHud	68
CEA Registry	9
TOTAL	**899**
TOTAL after deduplication	**827**

1. Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Database coverage dates: 1946 to current
Search date: 09/09/16
Retrieved records: 588
Search strategy:

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1 (smok* or exsmok* or nonsmok* or tobacco* or cigarette* or cigar* or pipe or pipes).ti. (109590)
2 exp *"Tobacco Use"/ (70751)
3 exp *"Tobacco Use Cessation"/ (17442)
4 exp *"Tobacco Use Cessation Products"/ (1437)
5 (stroke or strokes or apoplex* or cva or cvas or cerebrovascular accident* or vascular accident* or brain vasc* or cerebral vasc*).ti. (82837)
6 ((brain* or cerebr* or cerebell* or vertebrobasilar or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj3 (ischemi* or ischaemi* or infarct* or thrombo* or emboli*)).ti. (32302)
7 ((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli*) adj3 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).ti. (14674)
8 exp *Stroke/ (80406)
9 ((lung or lungs or pulmonary or bronchial or bronchogenic or bronchus or bronchoalveolar or alveolar) adj3 (cancer* or tumor* or tumour* or neoplasm* or blastoma* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncol*)).ti. (115229)
10 exp *Lung Neoplasms/ (153885)
11 ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or heart) adj3 infarct*).ti. (82118)
12 ((ischemi* or ischaemi*) adj3 (myocardium or myocardial or heart)).ti. (27766)
13 ((acute or occlusion* or disease* or thrombos* or syndrome or acute) adj3 coronary).ti. (65715)
14 (cardiac arrest* or heart attack*).ti. (12856)
15 (CHD or CAD or ischaemic heart disease* or ischemic heart disease* or coronary aneurysm* or coronary syndrome* or coronary occlusion* or coronary stenosis or coronary restenosis or coronary thrombos* or coronary vasospasm or angina or chest pain*).ti. (54841)
16 exp *Coronary Disease/ (154643)
17 (COPD or COAD or COBD or AECB or emphysema* or chronic bronchit*).ti. (29947)
18 (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti. (26711)

19	exp *Pulmonary Disease, Chronic Obstructive/ (35708)
20	exp *Myocardial Infarction/ (117599)
21	or/1-20 (810886)
22	Quality-Adjusted Life Years/ (8828)
23	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (7324)
24	(quality adjusted or adjusted life year$).ti,ab,kf. (11303)
25	(illness state$1 or health state$1).ti,ab,kf. (4868)
26	(hui or hui1 or hui2 or hui3).ti,ab,kf. (1144)
27	(multiattribute$ or multi attribute$).ti,ab,kf. (652)
28	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (10881)
29	(utilities or disutil$).ti,ab,kf. (5469)
30	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. (6764)
31	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. (2287)
32	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (17524)
33	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (3302)
34	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (1497)
35	or/22-34 (54355)
36	21 and 35 (3482)
37	exp animals/ not humans/ (4314726)
38	(news or comment or editorial or letter or case reports).pt. or case report.ti. (3376255)
39	36 not (37 or 38) (3389)
40	limit 39 to (english language and yr="2015 -Current") (588)

2. Database: NHS Economic Evaluation Database

Database coverage dates: Issue 2 of 4, April 2015, searches for database content undertaken up to 31 December 2014.
Search date: 08/09/16
Retrieved records: 237
Search strategy:

ID	Search Hits
#1	smok* or exsmok* or nonsmok* or tobacco* or cigarette* or cigar* or pipe or pipes 24218
#2	MeSH descriptor: [Tobacco Use] explode all trees 5898
#3	MeSH descriptor: [Tobacco Use Cessation] explode all trees 3610
#4	MeSH descriptor: [Tobacco Use Cessation Products] explode all trees 317
#5	(stroke or strokes or apoplex* or cva or cvas or cerebrovascular next accident* or vascular next accident* or brain next vasc* or cerebral next vasc*) 45220
#6	(brain* or cerebr* or cerebell* or vertebrobasilar or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal next ganglia) near/3 (ischemi* or ischaemi* or infarct* or thrombo* or emboli*) 8011
#7	(brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraventricular or infratentorial or supratentorial or basal next gangli*) near/3 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) 5319
#8	MeSH descriptor: [Stroke] explode all trees 6752
#9	(lung or lungs or pulmonary or bronchial or bronchogenic or bronchus or bronchoalveolar or alveolar) near/3 (cancer* or tumor* or tumour* or neoplasm* or blastoma* or carcinoma* or adenocarcinoma* or sarcoma* or malignan* or oncol*) 12167
#10	MeSH descriptor: [Lung Neoplasms] explode all trees 5604
#11	(myocardial or myocardium or subendocardial or transmural or cardiac or cardial or heart) near/3 infarct* 23254
#12	(ischemi* or ischaemi*) near/3 (myocardium or myocardial or heart) 8578
#13	(acute or occlusion* or disease* or thrombos* or syndrome or acute) near/3 coronary 23084
#14	MI or STEMI or NSTEMI or cardiac next arrest* or heart next attack* 14943

#15	CHD or CAD or ischaemic next heart next disease* or ischemic next heart next disease* or coronary next aneurysm* or coronary next syndrome* or coronary next occlusion* or coronary next stenosis or coronary next restenosis or coronary next thrombos* or coronary next vasospasm or angina or chest next pain* 23118
#16	MeSH descriptor: [Coronary Disease] explode all trees 11195
#17	[mh "Myocardial Infarction"] 9593
#18	COPD or COAD or COBD or AECB or emphysema* or chronic next bronchit* 11942
#19	obstruct* near/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) 11790
#20	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees 3182
#21	{or #1-#20} 142862
#22	[mh ^"Quality-Adjusted Life Years"] 4126
#23	[mh ^"Value of Life"] 146
#24	qaly* or qald* or qale* or qtime* 4601
#25	"quality adjusted" or (adjusted next life next year*) 7531
#26	"disability adjusted life" 366
#27	daly? 281
#28	(index near/3 wellbeing) or (quality near/3 wellbeing) or qwb 227
#29	multiattribute* or (multi next attribute*) 75
#30	utility near/3 (score? or scoring or valu* or measur* or evaluat* or scale? or instrument? or weight or weights or weighting or information or data or unit or units or health* or life or estimat* or elicit* or disease* or mean or cost* or expenditure? or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculat* or range* or increment* or state or states or status) 7238
#31	utilities 1618
#32	disutili* 206
#33	HSUV or HSUVs 4
#34	health? next year? next equivalent? 1
#35	hye or hyes 58
#36	hui or hui1 or hui2 or hui3 3024
#37	illness next state? or health next state? 1456
#38	"euro qual" or "euro qual5d" or "euro qol5d" or "eq-5d" or "eq5-d" or eq5d or euroqual or euroqol or euroqual5d or euroqol5d 3396
#39	"eq-sdq" or eqsdq 0
#40	short next form* or shortform* 6564
#41	sf36* or (sf next 36*) or "sf thirtysix" or "sf thirty six" 6071
#42	sf6 or "sf 6" or sf6d or "sf 6d" or "sf six" or sfsix or sf8 or "sf 8" or "sf eight" or sfeight 395
#43	sf12 or "sf 12" or "sf twelve" or sftwelve 995
#44	sf16 or "sf 16" or "sf sixteen" or sfsixteen 7
#45	sf20 or "sf 20" or "sf twenty" or sftwenty 67
#46	15D or "15-D" or "15 dimension" 369
#47	(standard next gamble*) or sg 6683
#48	(time next trade next off?) or (time next tradeoff?) or tto or timetradeoff? 106
#49	{or #22-#48} 31494
#50	#49 and #21 6381
#51	#50 Publication Year from 2012 to 2016, in Economic Evaluations 237

3. Database: ScHARRHUD

Database coverage dates: Not provided
Search date: 02/09/16
Retrieved records: 68
Search strategy:

(smok* OR exsmok* OR nonsmok* OR tobacco* OR cigarette* OR cigar* OR pipe OR pipes) AND 2012 > 2016:YR
(stroke OR strokes OR apoplex* OR cva OR cvas OR cerebrovascular accident* OR vascular accident* OR brain vasc* OR cerebral vasc*) AND 2012 > 2016:YR
((brain* OR cerebr* OR cerebell* OR vertebrobasilar OR hemispher* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR MCA OR anterior circulation OR posterior circulation OR basal ganglia) AND (ischemi* OR ischaemi* OR infarct* OR thrombo* OR emboli*)) AND 2012 > 2016:YR
((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli*) AND (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)) AND 2012 > 2016:YR
((lung OR lungs OR pulmonary OR bronchial OR bronchogenic OR bronchus OR bronchoalveolar OR alveolar) AND (cancer* OR tumor* OR tumour* OR neoplasm* OR blastoma* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR malignan* OR oncol*)) AND 2012 > 2016:YR
((myocardial OR myocardium OR subendocardial OR transmural OR cardiac OR cardial OR heart) AND infarct*) AND 2012 > 2016:YR
((ischemi* OR ischaemi*) AND (myocardium OR myocardial OR heart)) AND 2012 > 2016:YR
((acute OR occlusion* OR disease* OR thrombos* OR syndrome OR acute) AND coronary) AND 2012 > 2016:YR
(MI OR STEMI OR NSTEMI OR cardiac arrest* OR heart attack*) AND 2012 > 2016:YR
(CHD OR CAD OR ischaemic heart disease* OR ischemic heart disease* OR coronary aneurysm* OR coronary syndrome* OR coronary occlusion* OR coronary stenosis OR coronary restenosis OR coronary thrombos* OR coronary vasospasm OR angina OR chest pain*) AND 2012 > 2016:YR
(COPD OR COAD OR COBD OR AECB OR emphysema* OR chronic bronchit*) AND 2012 > 2016:YR
(obstruct* AND (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)) AND 2012 > 2016:YR
(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12) = 68

4. Database: CEA Registry

Database coverage dates: Not provided
Search date: 06/10/16
Retrieved records: 9
Search strategy:

The following terms were searched using the Basic search function to identify studying reporting utility weights:
“COPD”
“Chronic obstructive pulmonary disease”
“Lung Cancer”
“CHD”
“Coronary heart disease”
“Coronary artery disease”
“MI”
“Myocardial infarction”
“Stroke”
“Smoking”
“Smokers”
“Cigarettes”
“Former smoker”
“Quit”
“Smoking cessation”

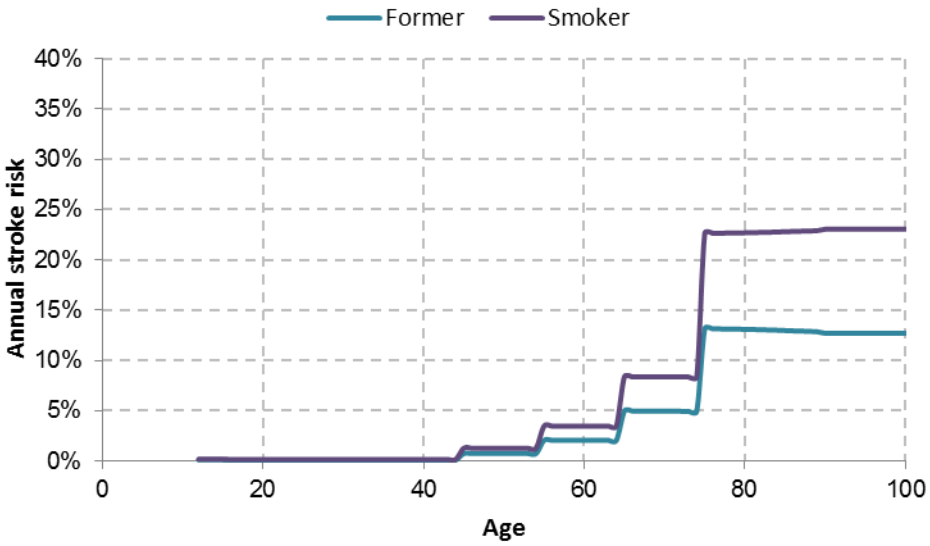
CEA Registry presents only the first 100 records retrieved for any one search. These 100 records for each search were manually screened by the searcher and only potentially relevant records retrieved. From the records presented, 9 articles were downloaded and after further deduplication, 2 articles were reviewed for data extraction.

APPENDIX B

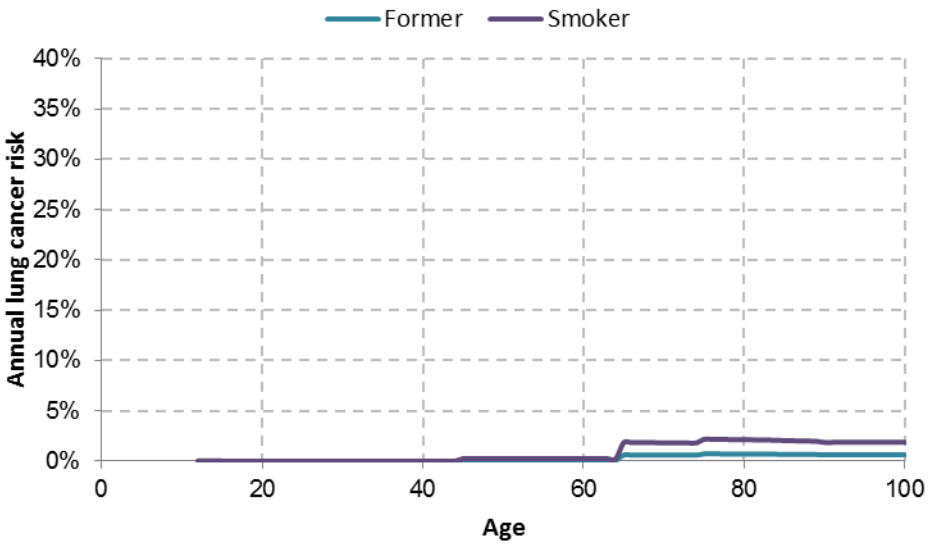
Epidemiology and Mortality Calculations

Comorbidity Calculations

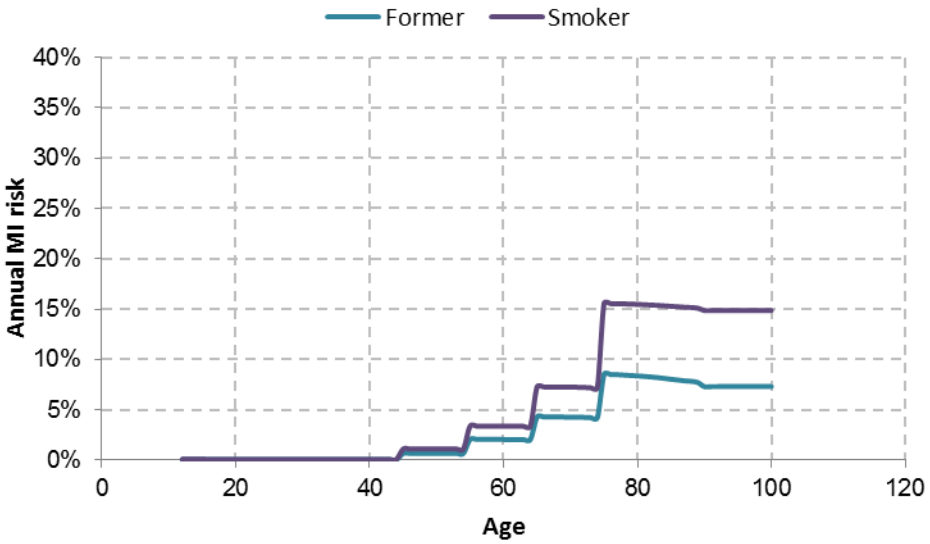
Graph B.1: Prevalence of stroke by smoking status



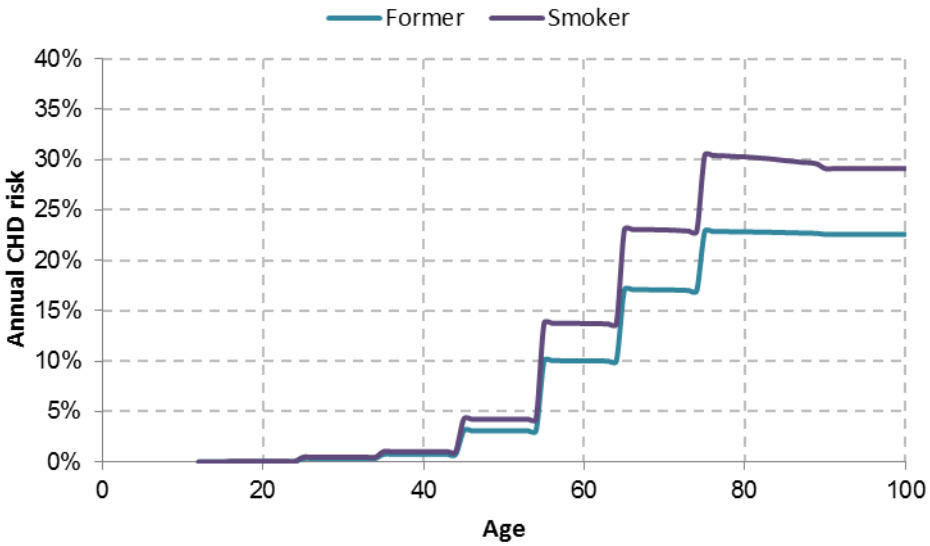
Graph B.2: Prevalence of lung cancer by smoking status



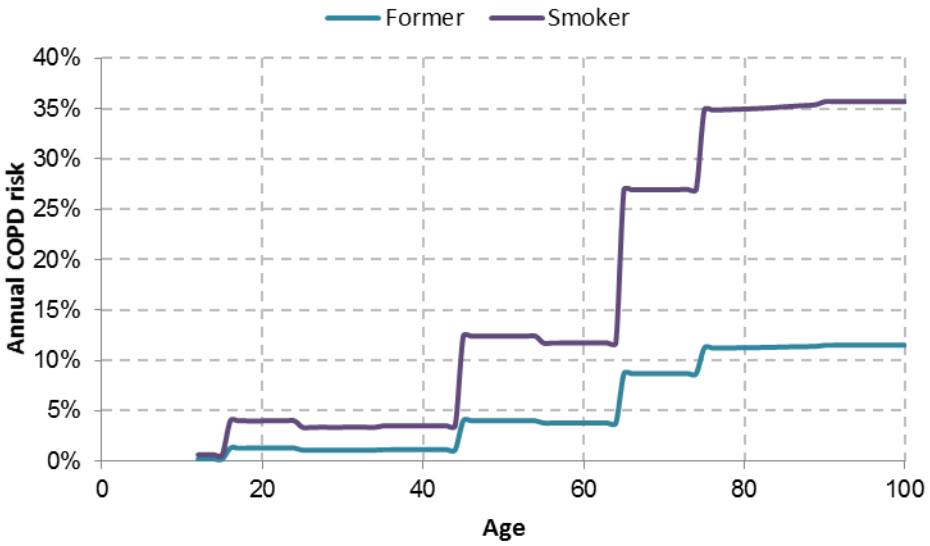
Graph B.3: Prevalence of MI by smoking status



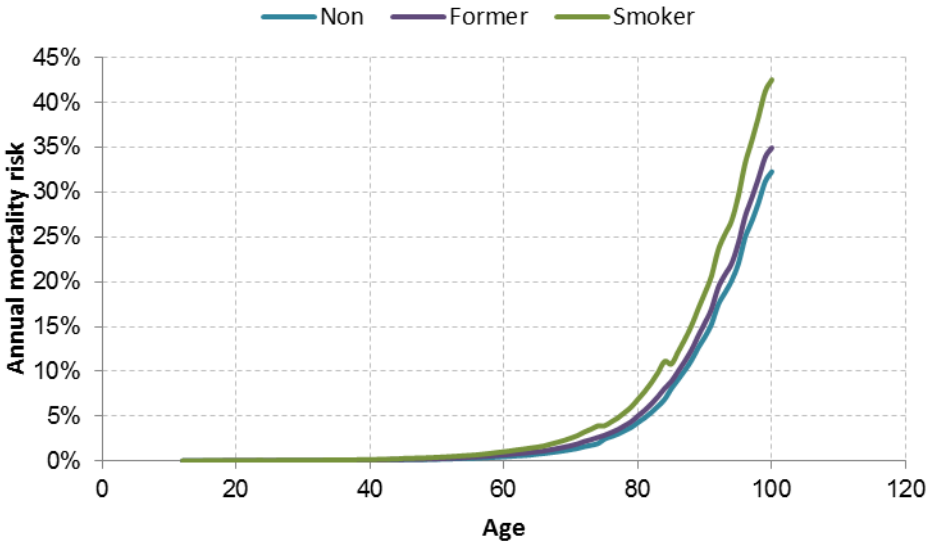
Graph B.4: Prevalence of CHD by smoking status



Graph B.5: Prevalence of COPD by smoking status



Graph B.6: Mortality by smoking status



APPENDIX C

Disaggregated Results

Blondal *et al.* (1999)

Intervention: Patch and nasal spray
Comparator: No intervention (background rate)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£764	£0	£764
Stroke	£4,937	£5,262	-£325
Lung cancer	£862	£991	-£129
MI	£676	£725	-£50
CHD	£2,675	£2,761	-£85
COPD	£1,087	£1,258	-£171
Asthma exacerbations	£13.20	£13.41	-£0.21
Total costs	**£11,014**	**£11,010**	**£3**
QALYs	**15.33**	**15.07**	**0.26**
ICER			**£13**
Net monetary benefit			**£5,191**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,162**	**-£1,523**	**£360**

Intervention: Patch
Comparator: No intervention (background rate)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£120	£0	£120
Stroke	£5,145	£5,262	-£117
Lung cancer	£944	£991	-£46
MI	£708	£725	-£18
CHD	£2,730	£2,761	-£31
COPD	£1,197	£1,258	-£62
Asthma exacerbations	£13.33	£13.41	-£0.07
Total costs	**£10,856**	**£11,010**	**-£154**
QALYs	**15.16**	**15.07**	**0.09**
ICER			**Dominant**
Net monetary benefit			**£2,024**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,393**	**-£1,523**	**£130**

Intervention: Patch and nasal spray
Comparator: Patch

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£764	£120	£644
Stroke	£4,937	£5,145	-£208
Lung cancer	£862	£944	-£82
MI	£676	£708	-£32
CHD	£2,675	£2,730	-£54
COPD	£1,087	£1,197	-£110
Asthma exacerbations	£13.20	£13.33	-£0.13
Total costs	**£11,014**	**£10,856**	**£158**
QALYs	**15.33**	**15.16**	**0.17**
ICER			**£948**
Net monetary benefit			**£3,167**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,162**	**-£1,393**	**£231**

Brown *et al.* (2014)

Intervention: NRT OTC
Comparator: No intervention (from study)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£0	£0	£0
Stroke	£5,175	£5,116	£59
Lung cancer	£956	£933	£23
MI	£712	£703	£9
CHD	£2,738	£2,723	£15
COPD	£1,213	£1,182	£31
Asthma exacerbations	£13.35	£13.32	£0.04
Total costs	**£10,808**	**£10,670**	**£138**
QALYs	**15.14**	**15.19**	**-0.05**
ICER			**Less effective**
Net monetary benefit			**-£1,081**
Intervention costs (private)	**£203**	**£0**	**£203**
Lost productivity costs	**-£1,427**	**-£1,361**	**-£65**

Chengappa *et al.* (2014)

Intervention: Varenicline + counselling
Comparator: Placebo + counselling

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£220	£29	£191
Stroke	£5,072	£5,211	-£139
Lung cancer	£915	£970	-£55
MI	£696	£718	-£21
CHD	£2,711	£2,747	-£36
COPD	£1,158	£1,232	-£73
Asthma exacerbations	£13.29	£13.38	-£0.09
Total costs	**£10,786**	**£10,920**	**-£134**
QALYs	**15.22**	**15.11**	**0.11**
ICER			**Dominant**
Net monetary benefit			**£2,358**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,312**	**-£1,466**	**£154**

Heydari *et al.* (2011)

Intervention: Varenicline + brief advice
Comparator: Brief advice

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£194	£19	£175
Stroke	£4,963	£5,202	-£239
Lung cancer	£872	£967	-£95
MI	£680	£716	-£37
CHD	£2,682	£2,745	-£63
COPD	£1,101	£1,227	-£126
Asthma exacerbations	£13.22	£13.37	-£0.15
Total costs	**£10,505**	**£10,890**	**-£385**
QALYs	**15.31**	**15.12**	**0.19**
ICER			**Dominant**
Net monetary benefit			**£4,208**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,191**	**-£1,456**	**£265**

Issa *et al.* (2012)

Treatment: Sequence (varenicline, bupropion, SSRI)
Comparator: No intervention (background rate)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£269	£0	£269
Stroke	£4,763	£5,262	-£498
Lung cancer	£793	£991	-£197
MI	£649	£725	-£76
CHD	£2,630	£2,761	-£130
COPD	£996	£1,258	-£262
Asthma exacerbations	£13.09	£13.41	-£0.31
Total costs	**£10,115**	**£11,010**	**-£895**
QALYs	**15.47**	**15.07**	**0.40**
ICER			**Dominant**
Net monetary benefit			**£8,853**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£970**	**-£1,523**	**£552**

Jorenby *et al.* (2006)

Intervention: Varenicline + counselling
Comparator: Placebo + counselling

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£353	£189	£164
Stroke	£4,891	£5,063	-£172
Lung cancer	£844	£912	-£68
MI	£669	£695	-£26
CHD	£2,664	£2,709	-£45
COPD	£1,063	£1,154	-£90
Asthma exacerbations	£13.17	£13.28	-£0.11
Total costs	**£10,497**	**£10,734**	**-£238**
QALYs	**15.37**	**15.23**	**0.14**
ICER			**Dominant**
Net monetary benefit			**£2,980**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,112**	**-£1,302**	**£190**

Rigotti *et al.* (2009)

Intervention: Varenicline + counselling
Comparator: Placebo + counselling

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£507	£343	£164
Stroke	£6,202	£6,407	-£205
Lung cancer	£1,134	£1,220	-£85
MI	£861	£893	-£32
CHD	£3,405	£3,461	-£56
COPD	£1,312	£1,415	-£103
Asthma exacerbations	£11.58	£11.60	-£0.01
Total costs	**£13,434**	**£13,750**	**-£317**
QALYs	**13.70**	**13.55**	**0.15**
ICER			**Dominant**
Net monetary benefit			**£3,324**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£915**	**-£1,045**	**£131**

Smith *et al.* (2009)

Intervention: Bupropion and lozenge
Comparator: No intervention (background rate)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£79	£0	£79
Stroke	£4,955	£5,262	-£307
Lung cancer	£869	£991	-£122
MI	£679	£725	-£47
CHD	£2,680	£2,761	-£80
COPD	£1,097	£1,258	-£162
Asthma exacerbations	£13.21	£13.41	-£0.19
Total costs	**£10,371**	**£11,010**	**-£639**
QALYs	**15.31**	**15.07**	**0.25**
ICER			**Dominant**
Net monetary benefit			**£5,543**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,182**	**-£1,523**	**£340**

Intervention: Lozenge
Comparator: No intervention (background rate)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£78	£0	£78
Stroke	£5,101	£5,262	-£161
Lung cancer	£927	£991	-£64
MI	£701	£725	-£25
CHD	£2,718	£2,761	-£42
COPD	£1,174	£1,258	-£85
Asthma exacerbations	£13.31	£13.41	-£0.10
Total costs	**£10,711**	**£11,010**	**-£299**
QALYs	**15.20**	**15.07**	**0.13**
ICER			**Dominant**
Net monetary benefit			**£2,872**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,344**	**-£1,523**	**£179**

Intervention: Bupropion and lozenge
Comparator: Lozenge

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£79	£78	£1
Stroke	£4,955	£5,101	-£146
Lung cancer	£869	£927	-£58
MI	£679	£701	-£22
CHD	£2,680	£2,718	-£38
COPD	£1,097	£1,174	-£77
Asthma exacerbations	£13.21	£13.31	-£0.09
Total costs	**£10,371**	**£10,711**	**-£340**
QALYs	**15.31**	**15.20**	**0.12**
ICER			**Dominant**
Net monetary benefit			**£2,671**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,182**	**-£1,344**	**£162**

Williams *et al.* (2006)

Intervention: Self-determination intervention
Comparator: Standard care (from study)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£199	£14	£184
Stroke	£5,156	£5,242	-£86
Lung cancer	£949	£983	-£34
MI	£709	£722	-£13
CHD	£2,733	£2,755	-£22
COPD	£1,203	£1,248	-£45
Asthma exacerbations	£13.34	£13.39	-£0.05
Total costs	**£10,963**	**£10,979**	**-£16**
QALYs	**15.15**	**15.09**	**0.07**
ICER			**Dominant**
Net monetary benefit			**£1,386**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,406**	**-£1,501**	**£95**

Wittchen *et al.* (2010)

Intervention: Bupropion (PA)
Comparator: Minimal intervention (PA)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£268	£43	£225
Stroke	£4,911	£4,903	£8
Lung cancer	£852	£848	£3
MI	£672	£671	£1
CHD	£2,669	£2,667	£2
COPD	£1,073	£1,069	£4
Asthma exacerbations	£13.19	£13.18	£0.00
Total costs	**£10,458**	**£10,214**	**£243**
QALYs	**15.35**	**15.36**	**-0.01**
ICER			**Less effective**
Net monetary benefit			**-£368**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,133**	**-£1,125**	**-£9**

Intervention: CBT (PA)
Comparator: Minimal intervention (PA)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£352	£43	£309
Stroke	£5,016	£4,903	£113
Lung cancer	£893	£848	£45
MI	£688	£671	£17
CHD	£2,696	£2,667	£30
COPD	£1,129	£1,069	£60
Asthma exacerbations	£13.25	£13.18	£0.07
Total costs	**£10,787**	**£10,214**	**£573**
QALYs	**15.27**	**15.36**	**-0.09**
ICER			**Less effective**
Net monetary benefit			**-£2,381**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,250**	**-£1,125**	**-£125**

Intervention: NRT (PA)
Comparator: Minimal intervention (PA)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£116	£43	£72
Stroke	£4,903	£4,903	£0
Lung cancer	£848	£848	£0
MI	£671	£671	£0
CHD	£2,667	£2,667	£0
COPD	£1,069	£1,069	£0
Asthma exacerbations	£13.18	£13.18	£0.00
Total costs	**£10,287**	**£10,214**	**£72**
QALYs	**15.36**	**15.36**	**0.00**
ICER			**Equal efficacy**
Net monetary benefit			**-£72**
Intervention costs (private)	**£122**	**£0**	**£122**
Lost productivity costs	**-£1,125**	**-£1,125**	**£0**

Intervention: Bupropion (PA)
Comparator: CBT (PA)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£268	£352	-£84
Stroke	£4,911	£5,016	-£105
Lung cancer	£852	£893	-£42
MI	£672	£688	-£16
CHD	£2,669	£2,696	-£28
COPD	£1,073	£1,129	-£56
Asthma exacerbations	£13.19	£13.25	-£0.07
Total costs	**£10,458**	**£10,787**	**-£330**
QALYs	**15.35**	**15.27**	**0.08**
ICER			**Dominant**
Net monetary benefit			**£2,013**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,133**	**-£1,250**	**£117**

Intervention: Bupropion (PA)
Comparator: NRT (PA)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£268	£116	£153
Stroke	£4,911	£4,903	£8
Lung cancer	£852	£848	£3
MI	£672	£671	£1
CHD	£2,669	£2,667	£2
COPD	£1,073	£1,069	£4
Asthma exacerbations	£13.19	£13.18	£0.00
Total costs	**£10,458**	**£10,287**	**£171**
QALYs	**15.35**	**15.36**	**-0.01**
ICER			**Less effective**
Net monetary benefit			**-£296**
Intervention costs (private)	**£0**	**£122**	**-£122**
Lost productivity costs	**-£1,133**	**-£1,125**	**-£9**

Intervention: CBT (PA)
Comparator: NRT (PA)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£352	£116	£236
Stroke	£5,016	£4,903	£113
Lung cancer	£893	£848	£45
MI	£688	£671	£17
CHD	£2,696	£2,667	£30
COPD	£1,129	£1,069	£60
Asthma exacerbations	£13.25	£13.18	£0.07
Total costs	**£10,787**	**£10,287**	**£501**
QALYs	**15.27**	**15.36**	**-0.09**
ICER			**Less effective**
Net monetary benefit			**-£2,308**
Intervention costs (private)	**£0**	**£122**	**-£122**
Lost productivity costs	**-£1,250**	**-£1,125**	**-£125**

Intervention: Bupropion (PP)
Comparator: Minimal intervention (PP)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£268	£43	£225
Stroke	£4,672	£4,850	-£178
Lung cancer	£757	£828	-£70
MI	£636	£663	-£27
CHD	£2,606	£2,653	-£47
COPD	£948	£1,042	-£94
Asthma exacerbations	£13.04	£13.15	-£0.11
Total costs	**£9,900**	**£10,091**	**-£191**
QALYs	**15.54**	**15.40**	**0.14**
ICER			**Dominant**
Net monetary benefit			**£3,030**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£869**	**-£1,066**	**£197**

Intervention: CBT (PP)
Comparator: Minimal intervention (PP)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£352	£43	£309
Stroke	£4,791	£4,850	-£59
Lung cancer	£804	£828	-£23
MI	£654	£663	-£9
CHD	£2,637	£2,653	-£15
COPD	£1,010	£1,042	-£31
Asthma exacerbations	£13.11	£13.15	-£0.04
Total costs	**£10,262**	**£10,091**	**£171**
QALYs	**15.45**	**15.40**	**0.05**
ICER			**£3,620**
Net monetary benefit			**£772**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£1,001**	**-£1,066**	**£65**

Intervention: NRT (PP)
Comparator: Minimal intervention (PP)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£116	£43	£72
Stroke	£4,750	£4,850	-£99
Lung cancer	£788	£828	-£39
MI	£647	£663	-£15
CHD	£2,627	£2,653	-£26
COPD	£989	£1,042	-£52
Asthma exacerbations	£13.08	£13.15	-£0.06
Total costs	**£9,931**	**£10,091**	**-£160**
QALYs	**15.48**	**15.40**	**0.08**
ICER			**Dominant**
Net monetary benefit			**£1,747**
Intervention costs (private)	**£122**	**£0**	**£122**
Lost productivity costs	**-£956**	**-£1,066**	**£110**

Intervention: Bupropion (PP)
Comparator: CBT (PP)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£268	£352	-£84
Stroke	£4,672	£4,791	-£119
Lung cancer	£757	£804	-£47
MI	£636	£654	-£18
CHD	£2,606	£2,637	-£31
COPD	£948	£1,010	-£63
Asthma exacerbations	£13.04	£13.11	-£0.07
Total costs	**£9,900**	**£10,262**	**-£361**
QALYs	**15.54**	**15.45**	**0.09**
ICER			**Dominant**
Net monetary benefit			**£2,258**
Intervention costs (private)	**£0**	**£0**	**£0**
Lost productivity costs	**-£869**	**-£1,001**	**£132**

Intervention: Bupropion (PP)
Comparator: NRT (PP)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£268	£116	£153
Stroke	£4,672	£4,750	-£78
Lung cancer	£757	£788	-£31
MI	£636	£647	-£12
CHD	£2,606	£2,627	-£21
COPD	£948	£989	-£41
Asthma exacerbations	£13.04	£13.08	-£0.05
Total costs	**£9,900**	**£9,931**	**-£31**
QALYs	**15.54**	**15.48**	**0.06**
ICER			**Dominant**
Net monetary benefit			**£1,283**
Intervention costs (private)	**£0**	**£122**	**-£122**
Lost productivity costs	**-£869**	**-£956**	**£87**

Intervention: CBT (PP)
Comparator: NRT (PP)

Discounted per patient results	Intervention	Comparator	Incremental
Intervention costs	£352	£116	£236
Stroke	£4,791	£4,750	£40
Lung cancer	£804	£788	£16
MI	£654	£647	£6
CHD	£2,637	£2,627	£11
COPD	£1,010	£989	£21
Asthma exacerbations	£13.11	£13.08	£0.03
Total costs	**£10,262**	**£9,931**	**£331**
QALYs	**15.45**	**15.48**	**-0.03**
ICER			**Less effective**
Net monetary benefit			**-£975**
Intervention costs (private)	**£0**	**£122**	**-£122**
Lost productivity costs	**-£1,001**	**-£956**	**-£45**