National Institute for Health and Care Excellence

Draft for consultation

Tobacco: preventing uptake, promoting quitting and treating dependence

[R] Economic Modelling Report: Relapse Prevention

NICE guideline NGxx

Model

October 2020

Draft for Consultation

These evidence reviews were developed by the NICE Economic and Methodological Unit

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List of abbreviations

BNF	British National Formulary
HSCIC	The Health and Social Care Information Centre
ICER	Incremental cost-effectiveness ratio
LSSS	Local stop smoking services
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NRT	Nicotine replacement therapies
OTC	Over the counter
PHAC	Public Health Advisory Committee
PSSRU	Personal Social Services Research Unit
RCT	Randomised controlled trial
RR	Relative risk

Plain Language Summary

Tobacco smoking can have a harmful impact on people's health. People who smoke are more likely to suffer from long-term health conditions including lung cancer, coronary heart disease (CHD), myocardial infarction (MI), stroke, chronic obstructive pulmonary disease (COPD) and asthma. Interventions which promote quitting are usually beneficial to the National Health Service (NHS) as they can decrease the occurrence of smoking related diseases, thereby improving health and reducing the associated NHS treatment costs.

However, a large proportion of the people who successfully quit smoking will relapse, with many returning to smoking within 12-months. Therefore, interventions which prevent smoking relapse may be beneficial to the NHS as they could reduce smoking uptake in people who had previously quit and consequently reduce the prevalence of smoking related diseases. There are currently no specific relapse prevention interventions recommended by NICE for use in the NHS, or in local authority funded local stop smoking services (LSSS).

We conducted cost-effectiveness modelling to help the Public Health Advisory Committee (PHAC) develop recommendations on smoking relapse prevention. The analysis adapted an economic model used for the current tobacco guidelines on smoking. The adapted model allowed populations to enter as non-smokers rather than current smokers, and therefore could model relapses prevented rather than successful quit attempts. The adapted economic model uses the best-available information in order to understand how different relapse prevention interventions might affect the general health of people who would otherwise return to smoking, as well as the impact interventions might have on the costs to the NHS.

The analysis evaluated the cost-effectiveness of six interventions to prevent smoking relapse: Low intensity behavioural support which included booklets and leaflets, text messages and online materials on the benefits, triggers and methods to prevent smoking relapse; high intensity behavioural support including individual, group and telephone support sessions; short acting NRT products in the form of NRT gum and NRT inhalators; bupropion; varenicline; and combination therapy with NRT gum plus bupropion.

We used evidence from NICE reviews, based on clinical trials, to calculate how effective the interventions were at preventing smoking relapse. Specifically, we used the evidence to calculate the total number people who continued not to smoke across 12-months when receiving one of the interventions. All of the people included in the primary economic analysis had successfully quit smoking using a public sector funded smoking cessation intervention.

Once we had calculated the number of smokers/ non-smokers at 12-months, the relapse prevention model estimated the likelihood that people who did / did not smoke would die or develop a range of health complications, including lung cancer, CHD, COPD, MI, stroke and asthma. Because we also know the NHS treatment costs associated with each of these complications, it was possible to calculate the costs per smoker and non-smoker over their remaining lifetime. The model also measures health benefits for people who don't relapse back to smoking by combining the increase in life expectancy with increases in quality of life that would be achieved by avoiding the previously listed health complications. This allowed us to calculate a measure known as the quality-adjusted life year (QALY) gain for each person that could be achieved if they didn't relapse.

For each intervention, the overall health benefits in terms of QALYs and NHS treatment costs avoided, were calculated. These lifetime health benefits and NHS treatment cost avoided were compared to the upfront costs of the intervention. Interventions were considered cost-effective if their incremental cost-effectiveness ratio (ICER) (the ratio of NHS treatment saving plus upfront intervention costs to QALYs gained) was less than £20,000, the predefined cost-effectiveness threshold used by NICE.

The results indicated that several relapse prevention interventions were cost-effective. High intensity behavioural support cost the NHS £248 per person but achieved 0.02 QALYs per person, and was cost-effective as the resultant ICER was equal to £12,700 which is less than the £20,000 threshold. Short acting NRT, bupropion and varenicline were all cost-effective as they increased health (QALYs) and saved the NHS money, even when including the upfront intervention costs. Finally, combination therapy with NRT plus bupropion resulted in NHS costs of £36 and 0.02 QALYs per person, and was cost-effective with an ICER equal to £1,463. Low intensity behavioural support was the only not cost-effective intervention. This was because the intervention was not effective in preventing smoking relapse when compared with the relevant control.

For each of the interventions, we also conducted a comprehensive scenario analysis where we changed some of the models' key input parameter values and checked whether the results remained the same. The most important parameter in the economic model was the intervention effectiveness. We changed the effectiveness parameters from the average (mean) values reported in the NICE review, to the value of the lower 95% confidence interval. When we used the lower effectiveness value varenicline remained cost-effective. However, high intensity behavioural support, NRT, bupropion and combination therapy with NRT + bupropion were no longer cost-effective.

We also conducted an analysis called probabilistic sensitivity analysis (PSA) where we estimate the probability of each intervention being cost-effective given the evidence that was available to inform the model. We found that the probability of varenicline and bupropion being cost-effective was very high, equal to 98% and 94%, respectively. The probability of cost-effectiveness for high intensity behavioural support was equal to 56%, indicating high levels of uncertainty as the intervention was not cost-effective 44% of the time. There were similarly high levels of uncertainty for NRT, which was cost-effective in 57% of PSA iterations, but increased confidence for NRT + bupropion which was cost-effective in 74% of PSA iterations.

The results of our analysis show that, in people who have quit smoking using an NHS smoking cessation intervention, varenicline and bupropion are highly likely to be beneficial to the NHS, when used to prevent smoking relapse. NRT + bupropion is likely to be beneficial to the NHS but there is some uncertainty in these results. High intensity behavioural support and NRT could be beneficial to the NHS but we are very uncertain about the cost-effectiveness results for these interventions, mainly because of uncertainty in each intervention's effectiveness. Low intensity behavioural support was neither effective or cost-effective and would not be beneficial to for use in the NHS.

Finally, we conducted analyses for two relapse prevention interventions in people who had previously quit smoking without any help from NHS interventions. We found that both NRT gum and low intensity behavioural support were cost-effective in preventing smoking relapse for this population, saving the NHS money and resulting in improved health (additional QALYs).

As with any cost-effectiveness analysis, there were some factors that could be challenged, or alternative approaches that could have been taken. However, most areas that we left out of our analysis (for example due to being unable to find suitable evidence) are not likely to have influenced the results. For example, the model only includes health impacts on six smoking related conditions, and there are many other conditions that could potentially be avoided through quitting smoking. In addition, we didn't include effects of passive smoking, which have a detrimental health impact on other people. If we had included additional diseases and the impact of passive smoking in the model, greater benefits would have been attached to quitting smoking. This would have only reinforced our findings, that interventions which are effective in preventing relapse are highly likely to be cost-effective.

Introduction

Background

As stated in the NICE final scope, smoking is the main cause of preventable illness and premature death in England. However, many of those that successfully quit smoking eventually relapse over time (1). Smoking relapse rates can often be high (up to 90% in the first 3 months), and only 3-5% of quitters who are unsupported maintain this for 6 months or longer (2).

The benefits of quitting smoking, for both society and the smoker themselves, are clear. Smoking kills over half of its users as well as causing significant long-term damage and distress due to poor quality of life. 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 (3). Treating smoking-related illness is estimated to cost the National Health Service (NHS) at least £2 billion per year (4).

A wide range of interventions that can help smokers make a successful quit attempt are available through local stop smoking services (LSSS). Intervention typically involves teaching people to anticipate and cope and usually requires behavioural, cognitive and pharmacological components (5).Several interventions including behavioural support, nicotine replacement therapy (NRT), bupropion and varenicline have been identified as cost-effective and are recommended to be made available for all adults who smoke in NICE guidelines (6).

Relapse prevention strategies typically focus on teaching people skills to cope with temptations or urges to smoke. Therefore, as with smoking cessation, effective relapse prevention is likely to require behavioural, cognitive and pharmacological components. Behavioural techniques teach patients to identify high risk scenarios that may increase the chance of a smoking relapse, and what to do in these situations including coping techniques such as writing tasks, cue exposure and aversion tactics (7). Extending the typical duration of pharmacotherapy may continue to reduce smoking urges in people who have quit, therefore decreasing the risk of smoking relapse. Interventions like NRT, bupropion and varenicline may continue to be cost-effective for several weeks beyond their suggested dosage which is usually discontinued after 12-weeks (8).

This is the first NICE guideline to include a full review of the effectiveness and cost-effectiveness of interventions for smoking relapse prevention.

Objectives

The key research questions from the NICE scope that were prioritised for economic modelling are listed below.

- What interventions are effective and cost-effective for preventing a relapse in people who have recently quit smoking?

Methods

Overview

The following section summarises methods applied during the analysis of review questions related to smoking relapse prevention. As outlined in the NICE scope, the new tobacco guidelines update and bring together NICE's existing guidelines on tobacco, which included a new review area on smoking relapse prevention. The PHAC prioritised relapse prevention for further economic analysis as: there was no relevant economic modelling conducted in previous guidelines; and new effectiveness evidence had been generated from the NICE evidence reviews which had not been incorporated into any of the identified cost-effectiveness literature (9).

Review question:

- Which interventions are effective and cost-effective for preventing a relapse in people who have recently quit smoking?

For the base case analysis, all relapse prevention interventions were applied in populations of ex-smokers who had achieved aided cessation i.e. through interventions offered by LSSS or available privately over the counter (OTC). It was assumed that any relapse prevention intervention would be delivered to populations at 3-months after their initial quit date. This assumption was applied to avoid any overlap with smoking cessation interventions offered by LSSS whose cost-effectiveness was analysed in the cessation report (10).

The interventions included in this analysis are listed below. These interventions were selected if relevant evidence was available on their effectiveness in NICE evidence review N (9).

- Low intensity behavioural support
- High intensity behavioural support
- NRT short acting
- Bupropion
- Varenicline
- Bupropion + NRT short acting

Low intensity behavioural support included materials such as booklets and online material on the benefits, triggers and methods to prevent smoking relapse in addition to minimal contact support from healthcare professionals e.g. through text messages and online services. High intensity behavioural support comprised of more comprehensive interventions delivered by healthcare professionals for example in person individual or group support sessions and telephone support sessions. The cost-effectiveness of both behavioural support interventions was compared versus usual care which comprised of no formal intervention aside from a brief leaflet on relapse prevention. We did not include a formal intervention as part of usual care as pharmacological interventions are typically administered for smoking cessation and advice is to discontinue treatment or reducing dosage after 12 weeks (8). Similarly, behavioural support for smoking cessation is not typically delivered for a duration of more than 12 weeks, so was not included as part of the comparator (11).

The pharmacological products for relapse prevention included short acting NRT products in the form of NRT gum and NRT inhalators; bupropion; varenicline; and combination therapy with NRT gum + bupropion. All pharmacological products were compared versus placebo. Following the same reasoning as for the behavioural support analyses, the comparator for

the pharmacological products (placebo) did not include any formal intervention for relapse prevention.

Modelling Approach

This analysis used an economic model to establish the cost-effectiveness of the relapse prevention interventions. The economic model was an adapted version of the model previously used to inform NICE guidelines on smoking cessation [NG92] (6). The NG92 economic model has since been updated to inform separate questions in the current NICE scope for the new tobacco guideline, specifically on smoking cessation in the general population (10). The updated NG92 model was further adapted for this relapse prevention analysis: the model was restructured such that the population entering the model was defined as “former-smokers” rather than “current smokers”; and the effectiveness of interventions was measured in terms of preventing smoking relapses, rather than promoting successful quit attempts.

Model Structure

The adapted relapse prevention economic model includes the same health states and structure as the cessation model (10), these being “former smoker”, “current smoker” and “dead” and is depicted in Figure 1. The relapse prevention model differed from the cessation model as the population enter the model in the “former smoker” rather than the “current smoker” health state. The economic analysis was conducted for two specific populations: (i) assisted abstainers, who had achieved abstinence through a formal smoking cessation intervention, and (ii) unaided abstainers who had achieved abstinence without a formal smoking cessation intervention. The effectiveness of relapse prevention interventions is included in the model as the probability of the population transitioning from the “former smoker” to “current smoker” health state after the first 12-month cycle. This probability was informed by effectiveness evidence on relapse prevention obtained from NICE evidence review N (9).

After the first 12-months, populations transition between each health state in annual cycles across a lifetime (100-year) time horizon. The transitions between health states are determined by the natural rate of cessation and relapse in the population each year. The model structure and epidemiological inputs after the initial 12-months are identical to the updated NG92 cessation model, with is described in full elsewhere (10).

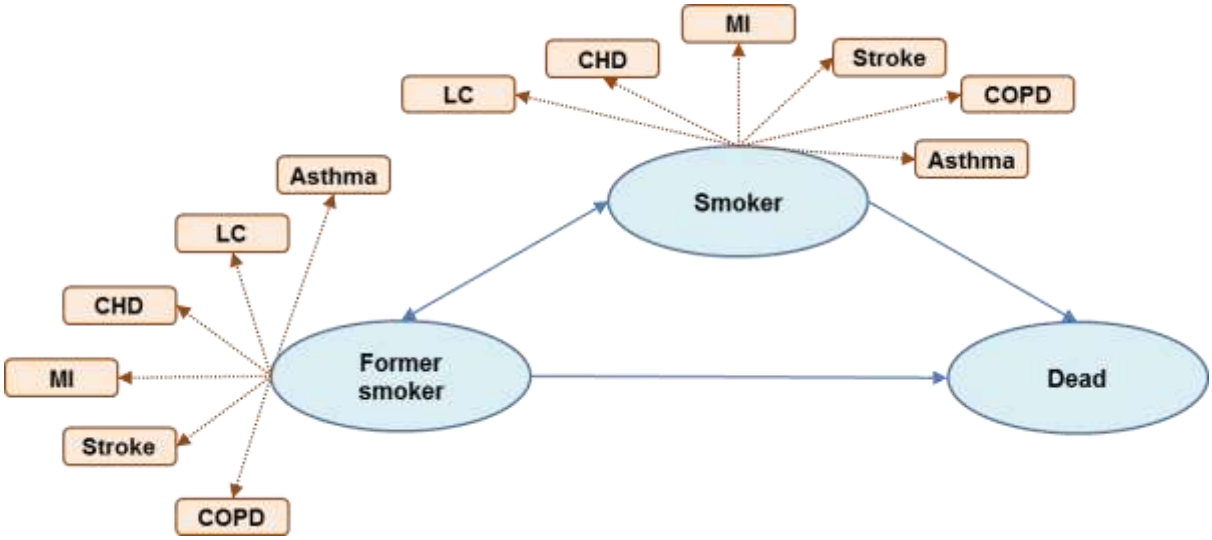
In summary the model includes the following six smoking related comorbidities: lung cancer (LC), coronary heart disease (CHD), myocardial infarction (MI), stroke, chronic obstructive pulmonary disease (COPD), and asthma. The model uses published literature sources to establish the prevalence of LC, CHD, MI, stroke and COPD, and incidence of asthma, for smokers and non-smokers by age and gender. Each comorbidity has an associated NHS treatment cost and disutility. These costs and disutilities are applied based on prevalence and incidence rates for each cycle and summed to estimate lifetime costs and QALYs across all cycles. The model also calculates the lost productivity due to work absenteeism for each comorbidity using a human capital approach. This multiplies the percentage of days absent from work due to smoking related morbidities by mean ONS (2019) wage estimates per age and gender (12). A similar model structure has been used in past cost-effectiveness models for smoking interventions (PHG10, PHG45, Taylor *et al.* 2011 (13)).

The model calculates the average lifetime costs, lifetime QALYs, and subsequent cost-effectiveness across all adult populations. Average outcomes are calculated across all

populations between the ages of 12 and 100. This age range was selected as it represented the youngest and oldest ages where we could identify smoking related prevalence rates. For people aged 12 to 15 smoking was defined as smoking at least one cigarette per week based on the Action on Smoking and Health (ASH) fact sheet on young people and smoking (14). For people aged 16 to 100 smoking was defined by self-reported status as a current, ex or non-smoker in the Health Survey for England (2019) report (15).

Average outcomes across the population are calculated by obtaining results for each specific age and applying a weighted average based on the number of people of that age in the UK population as reported by the ONS (2019) (16). For example, the model obtains results for populations specifically aged 12, then aged 13, then aged 14, 15, 16 and so on until the final age of 100. Results for people aged 12, 13, 14, …, 100 are then multiplied by the percentage of people aged 12, 13, 14 , …, 100 and summed across all ages.

Figure 1: Model structure



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

Model Parameters

All model parameter values are as reported in the economic modelling report for smoking cessation in the general population (10). This excluded intervention effectiveness i.e. the probability of smoking abstinence, and intervention costs which were applied specifically for the relapse prevention interventions.

Assisted Abstainers

Effectiveness

Effectiveness estimates for a population of assisted abstainers were obtained using results from the meta-analyses reported in NICE evidence review N (9). The meta-analyses reported

the relative risks for several interventions versus a relevant comparator as described below. Full details of the meta-analyses are provided in NICE evidence review N (9):

The meta-analysis for *low intensity behavioural support* included six studies. The interventions included self-help booklets on relapse prevention (n=2), an anti-smoking self-help parenting program (n=1), and telephone support (n=2). The comparators included a brief leaflet on smoking harm, standard treatment and no intervention. The pooled estimate for low intensity behavioural support was less effective than the comparator with a RR=0.93, (see NICE evidence review N Figure 10 (9)).

The meta-analysis for *high intensity behavioural support* included four studies. The studies included in the meta-analysis involved the following interventions and comparators: group meetings plus telephone support versus no intervention; group support sessions plus NRT versus NRT only; cognitive behavioural skills training, group counselling, NRT and a booklet versus NRT plus a booklet; and group support sessions including coping strategies plus weekly meetings versus weekly meetings only. The total number of support sessions varied across the four studies, ranging from 4 to 10. The pooled estimate for high intensity behavioural support was more effective than the comparator with a RR=1.06, however this effect was not statistically significant (p=0.67), (see NICE evidence review N Figure 10 (9)).

All of the pharmacotherapy interventions were compared to placebo. The meta-analysis for *NRT short acting* was informed by two studies (Covey 2007 (17), Croghan 2007 (18)) which applied different NRT interventions, these being NRT gum and an NRT inhaler. Covey (2007) (17) compared 2mg Nicotine gum with placebo; Croghan compared a nicotine inhaler administered for 3-months versus placebo. The two studies recruited people who were abstainers following a formal cessation programme lasting either eight weeks or three months. These studies showed a non-significant increase in not smoking after provision of NRT gum for an extended period after quitting, RR=1.04 (NICE evidence review N, GRADE profile 6 (9)).

The meta-analysis for *bupropion* included six studies with a total of nine intervention arms versus placebo. The studies administered bupropion at a dose between 150mg and 300mg, meanwhile the duration of bupropion varied ranging from 45 days months to 1 year. The pooled estimate for bupropion was non significantly more effective than placebo, RR=1.15, p=0.08 (NICE evidence review N, GRADE profile 6 (9)). There was uncertainty in the effectiveness estimate for bupropion as the duration of prior abstinence (i.e. how long people had quit smoking for) was not specified in seven of the nine intervention arms. Therefore, a scenario analysis was conducted using a pooled estimate across two studies where the duration of previous abstinence was specified as being less than four weeks. The scenario analysis included a RR=1.11 (p=0.46).

The meta-analysis for *NRT plus bupropion* included two studies: the first study by Covey (2007) (17) compared 2mg Nicotine gum + 300mg bupropion versus double placebo. The second study by Croghan (2007) (18) compared 3 months of NRT inhaler + 300mg bupropion versus placebo. The pooled estimate for NRT + bupropion was non-significantly more effective than placebo, RR=1.11, p=0.09 (NICE evidence review N, GRADE profile 6 (9)).

Finally, the effectiveness estimate for *varenicline* was obtained from a single RCT by Tonstad (2006) (19). The study compared 2mg of varenicline for 12 weeks versus placebo. The study found that varenicline was significantly (p<0.05) more effective than placebo, with an RR=1.18 (NICE evidence review N, GRADE profile 6 (9)).

The probability of abstinence for each intervention and comparator are reported in Table 1~~Table 1~~. Abstinence rates for each comparator were calculated as the pooled number of events divided by the pooled number of participants in the relevant meta-analysis control

arms. Abstinence rates for interventions were calculated by multiplying the relative risk (RR) of abstinence vs. control by the (previously calculated) probability of abstinence for the relevant comparator.

The economic model required probabilities of smoking abstinence at 12-months post intervention. The meta-analyses in NICE evidence review N obtained outcomes for continued abstinence across a variety of time points. For high intensity behavioural support NRT, bupropion, varenicline and NRT + bupropion all studies measured outcomes at least 12 months post initial quit. For low intensity behavioural support four out of the six studies measured outcomes at least 12-months post initial quit. Therefore, ~~As some studies measured outcomes at up to 12-months post intervention,~~ no further adaptions were made to the absolute probabilities of abstinence for the base case, i.e. effectiveness rates were assumed to be measured at 12-months and be directly applicable to the model cycle lengths.

The validity of this assumption was investigated within a sensitivity analysis, where probabilities of abstinence were reduced by 25% to account ~~for the possibility of relapse~~for potential differences between trial endpoints and the assumed 12-month endpoint applied in the economic model. The value of 25% ~~is likely to be an overestimate of relapse~~represents a reduction in smoking abstinence, for example due to increased relapse and therefore provides a conservative estimate of cost-effectiveness. For example, in a Health Technology Assessment by Coleman (2010) (20) the relapse rate between 6 and 12-months following cessation with bupropion, NRT or varenicline is estimated to be less than 15%.

Table 1: Intervention effectiveness: relapse prevention, assisted abstainers

	RR of abstinence vs. control *Mean (95% CI)*	**P(abstinence) at 12-months** *Mean (95% CI)*
Base case analyses:		
Low intensity behavioural support	0.93 (0.81, 1.06)	31.15% (27.13% to 35.51%)
Usual care	N/A	33.50% [a]
High intensity behavioural support	1.06 (0.82 to 1.36)	32.81% (25.38% to 42.09%)
Usual care	N/A	30.95% [b]
NRT short acting	1.04 (0.77 to 1.40)	24.32% (18.00% to 32.73%)
Placebo	N/A	23.38% [c]
Bupropion (any prior abstinence duration)	1.15 (0.98 to 1.35)	27.90% (23.78% to 32.75%)
Placebo	N/A	24.26% [d]
Varenicline	1.18 (1.03 to 1.36)	43.55% (38.01% to 50.19%)
Placebo	N/A	36.90% [e]
NRT + Bupropion	1.11 (0.49 to 2.54)	23.85% (10.53% to 54.58%)
Placebo	N/A	21.49% [f]
Scenario analysis		
Bupropion (prior abstinence duration <4 weeks)	1.11 (0.84 to 1.48)	30.22% (22.88% to 40.31%)
Placebo	N/A	27.23% [g]

a: 612/1827 participants in the control arms achieved continued abstinence. Usual care differed across control arms and included a brief leaflet on smoking harm, standard treatment and no intervention.
b: 173/559 participants in the control arms achieved continued abstinence. Usual care differed across control arms and included no intervention, NRT only, NRT + a booklet, and weekly meetings only.
c: 65/278 participants in the control arms achieved continued abstinence.
d: 205/845 participants in the control arms achieved continued abstinence.
e: 224/607 participants in the control arms achieved continued abstinence.
f: 26/121 participants in the control arms achieved continued abstinence.
g: 64/235 participants in the control arms achieved continued abstinence.

Costs

Comparators (usual care/ placebo)

The behavioural support interventions were compared to usual care. For the base case analysis, no costs were assigned to usual care. Pharmacological interventions are not typically provided by LSSS for people who have quit smoking for over 3-months (8) and were therefore not included as a cost. Whilst NRT was included as part of the comparator in two studies informing the effectiveness estimate for the behavioural interventions (9), it was also included as part of the intervention arm. Therefore, the incremental intervention costs (intervention – comparator) for NRT in these studies were assumed to net equal to £0. Usual

care for long term abstainers may include minimal support, for example a UK-based study by Blyth et al. (2015) included costs for a leaflet on smoking relapse prevention with an uprated of £0.71 per person (21). Minimal support costs were not included in the base case analysis for usual care as these were assumed to be insubstantial. To address any uncertainty in this assumption, we included a deterministic scenario for the high intensity behavioural support analysis, which assigned costs for minimal support costs in the usual care arm set equal to the cost of the low-intensity behavioural support intervention i.e. £21.96.

The pharmacological interventions were compared to placebo. No costs were assigned to placebo in the economic analysis. Structured behavioural support and pharmacological interventions were not included as costs as these are not typically provided by LSSS for people who have quit smoking for over 3-months (8, 22). Whilst NRT/behavioural support was included as part of the comparator in a minority of studies informing the effectiveness estimate for the pharmacological interventions (9), in each instance they were also included as part of the intervention arm. Therefore, the incremental intervention costs (intervention – comparator) in these studies were assumed to net equal to £0. Usual care for long term abstainers may include minimal support, for example a UK-based study by Blyth et al. (2015) included costs for a leaflet on smoking relapse prevention with an uprated of £0.71 per person (21). Minimal support costs were not included in the analysis as these were likely to be insubstantial and also expected to occur equally for the interventions and the comparator meaning the incremental costs would be equal to zero.

Low intensity behavioural support

The cost of low intensity behavioural support was informed through a UK-based study by Blyth et al. (2015) which was included in NICE evidence review N (9). The intervention arm in Blyth et al. (2015) contained a behavioural support intervention which comprised a series of eight “Forever Free” booklets containing information on smoking relapse prevention. The booklets covered content such as smoking urges, smoking and weight, smoking stress, and adjustment to life without cigarettes. The total cost of the booklets was £20.78 per person, including £2.22 per person for copyright (as booklets were previously used in the USA), £3.56 for revisions to the booklets, £12.32 in printing costs and £2.68 for postage. The intervention costs from Blyth et al. (2015) were uprated from 2012/2013 prices (£20.78) to 2019/2020 prices using the NHSCII pay and prices indexes reported by PSSRU 2019 (23).

After uprating, the total cost of low intensity behavioural support was equal to £21.96.

High intensity behavioural support

The total number of high intensity behavioural support sessions ranged between 4 and 10 across the studies pooled in the NICE meta-analysis. The total number of sessions for the base case analysis was set equal to 6, this was informed by the study by Smith et al. (2001) (24). This was the most recent study of this intervention type included in the meta-analysis within NICE evidence review N (9), and represented a reasonable mid-point for the total session numbers across all studies. The intervention by Smith et al. (2001) included six 90-minute group sessions of behavioural support (24). Due to the heterogeneity across the included studies, the total session number was reduced to the minimum value of 4 and increased to the maximum value of 10 in deterministic sensitivity analyses.

The unit cost per group behavioural support session was not available from the study by Smith et al. (2001) (24), and all other studies informing the effectiveness estimate were conducted prior to 2000. Therefore, the cost per each high intensity support session was

derived from a UK study by Bauld et al. (2009) (25). The study established the cost of the "smoking concerns" community based intensive behavioural support intervention. The total cost of 7 group therapy behavioural support sessions reported by Bauld et al. (2009) was equal to £314.54 per person, including costs for healthcare professionals' time (£27.02), overheads (£282.96), materials (£4.43), and annual training (£0.13). We did not include an additional cost for NRT (£53.84) reported by Bauld et al. (2009) as this was not part of the high intensity behavioural support intervention in our analysis. Costs were uprated from 2008/09 prices to 2018/19 prices using the NHSCII pay and prices index reported in the PSSRU 2019 (23). This resulted in an overall cost equal to £366.15. The total cost per individual session was therefore equal to £52.31.

To establish the total cost for the high intensity behavioural support intervention we multiplied the total number of sessions (six) from Smith et al. (2001) (24) by the estimated cost per session (£52.13) from Bauld et al. (2009) (25). The intervention costs, for 6 high intensity group behavioural support sessions, was equal to £313.84.

NRT short acting

The NRT short acting interventions were NRT gum and NRT inhalators, these being the NRT interventions included in the studies by Covey et al. (2007) (17) and Croghan et al. (2007) (18) which informed the meta-analysis in NICE evidence review N (9). Healthcare resource usage was informed by these studies: Covey et al. (2007) reported that the mean number of NRT 2mg gums consumed by study participants was equal to 97.5 (17). In the RCT by Croghan et al. (2007) NRT inhalators were used for a duration 3-months, however, the authors did not specify the dosage per day. Therefore, we assumed a dosage for NRT inhalators equal to 2x15mg cartridges per day, equal to a total of 30mg total nicotine intake, which is similar to maximum recommended doses per 24-hours for other NRT products (e.g. 24mg NRT patch) (8).

Unit costs for the NRT products were sourced from published costs reported by the British National Formulary (BNF): The cost of per pack of 96 Nicotinell 2mg medicated chewing gum was equal to £8.26, meaning the cost per individual gum was £0.09. Therefore, the total cost of 97.5 gums was equal to £8.39. The cost per pack of 36 Nicorette 15mg inhalator cartridges was equal to £28.28, meaning the cost per inhalator was £0.79. Therefore, the total cost of NRT inhalators taken twice daily for 12 weeks was equal to £131.97.

The cost of the NRT short acting category was obtained by weighting the costs per NRT product based on the weightings applied in the NICE meta-analysis. These weightings were equal to 52.8% for NRT gum based on (n=145) study participants in Covey et al. (2007) (17) and 47.2% for NRT inhalator based on (n=130) study participants in Croghan et al. (2007) (18). Consequently, the cost for NRT short acting (including both prescribed and over the counter (OTC) purchases) was equal to £66.72.

The final NHS costs for NRT short acting were adjusted to only include prescribed products (i.e. excluding OTC costs that are classified as private purchases). The percentage of prescribed versus OTC costs was obtained from an RCT by Hajek et al. (2019), who reported that 48% of participants allocated to a broad category NRT intervention arm obtained products through prescription, whereas 52% obtained NRT products OTC over the 12-month trial period (26).

The final NHS cost of NRT short acting was equal to £32.03 per person (i.e. 48% of £66.72).

Bupropion

The dosage of the bupropion intervention varied across the studies that informed the meta-analysis in NICE evidence review N (9): this included treatments with either 150mg and 300mg bupropion daily for durations of between 45 days and 1 year. Therefore, we assigned costs based on the assumption that the average dosage regime for relapse prevention was equivalent to the dose previously applied for cessation. The population included assisted abstainers who were thought likely to have used bupropion during their cessation attempt. Therefore, the costs excluded titration that is typically required for bupropion when people begin therapy for smoking cessation. The dosage for bupropion was sourced from the BNF and was equal to 150mg taken twice daily for 9 weeks (8).The unit costs of bupropion was also obtained from the BNF and was equal to £41.76 per pack of 60 Zyban (bupropion) 150mg modified release tablets, or £0.70 per individual tablet. The total cost of the bupropion intervention across 9-weeks was equal to £87.70 per person.

We conducted a scenario analysis which doubled the costs of bupropion to £175.40. The higher costing scenario was added to capture uncertainty around the duration of bupropion treatment which varied from 45 days to 1 year across the studies informing the effectiveness estimate.

Varenicline

Varenicline was assumed to be administered for 1mg twice per day for 12 weeks in line with the dosage applied in the RCTs by Tonstad et al. (2006) (19), the RCT which informed the effectiveness estimate in NICE evidence review N (9). The unit costs for varenicline were obtained from the BNF, and were equal to £54.60 for a pack of 56 Champix 1mg tablets, or £0.98 per tablet.

The total cost of varenicline was £163.80 per person.

NRT + bupropion

The same studies were used to calculate the pooled effectiveness estimate for NRT + bupropion versus placebo as were used for NRT versus placebo as (i.e. Covey et al. (2007) (17) and Croghan et al. (2007) (18)). Both studies administered bupropion at 300mg for between 3 and 4-months which is similar to the duration of dosage assumed for the bupropion intervention. Therefore, the cost of NRT + bupropion was assumed to be the summed total of intervention costs for Bupropion and NRT short acting interventions. The impact of increasing this cost to reflect increased treatment duration was investigated in a scenario analysis.

The total cost of NRT + bupropion was £119.73 per person.

The costs of each relapse prevention intervention are reported in Table 2~~Table 2~~.

Table 2: Intervention effectiveness: Relapse prevention

Intervention	NHS cost	Components	Unit Costs (per session/ dose)	Source
All comparators	£0.00	None. No pharmacotherapy or behavioural intervention is currently recommended by LSSS to prevent smoking	N/A	N/A

Intervention	NHS cost	Components	Unit Costs (per session/ dose)	Source
		relapse after 3-months of smoking abstinence.		
Low intensity behavioural support	£21.96	8 "Forever Free" booklets containing information on smoking relapse prevention.	N/A	Blyth (2015) (21)
High intensity behavioural support	£313.84	6 group behavioural support sessions each 90 minutes in length.	£52.31	Session no. (Smith, 2001) (24) Cost per session (Bauld 2011) (25)
NRT short acting [prescribed only]	£32.03	Weighted based on the number of prescribed (48%) vs. OTC (52%) NRT purchases across 12-months in RCT study participants. Weightings based on any NRT product including long acting patches and short acting gum, inhalator, spray.	N/A	Hajek (2019) (26)
NRT short acting [prescribed + OTC]	£66.72	Weighted average NRT gum (52.8%) and NRT inhalator (47.2%). Includes prescribed and over the counter costs	NA	NICE evidence review N (9)
NRT components				
NRT gum	£8.39	Mean total of 97.5 2mg gums consumed by study members.	2mg=£0.09	Drug costs (BNF (8)) Drug dosage Covey (2007) (17)
NRT inhalator	£131.97	Ad lib administration when cravings occur assumed equal to 2 cartridges per day (i.e. 30mg nicotine), for 12 weeks.	15mg = £0.79	Drug costs and dosage (BNF (8))
Bupropion	£87.70	150mg twice daily for 9 weeks	£0.70	BNF (8)
Varenicline	£163.80	1mg twice daily for 12 weeks.	£0.98	Drug costs and dosage BNF (8)
NRT + bupropion	£119.73	Sum of Bupropion and NRT short acting (includes only prescribed NRT costs).		

Unaided abstainers

Effectiveness

The economic analysis also established the cost-effectiveness of relapse prevention interventions for a population of ex-smokers who had achieved abstinence through unaided abstinence e.g. people who had *not* achieved cessation through a formal intervention offered by LSSS. The analysis was limited to two interventions for which effectiveness evidence was available in this population. NICE evidence review N (9) obtained effectiveness estimates for

low intensity behavioral support vs. usual care and NRT gum vs. placebo for smoking relapse prevention in populations who achieved unaided abstinence from tobacco smoking.

The effectiveness estimates for low intensity support was a pooled estimate across 5 studies. These compared: tailored advice letters and a quit pack versus a quit pack only; self-help booklets versus minimal contact (n=2); self-help materials versus plus an incentive versus an incentive only; self-help booklets + NRT versus NRT only. Low intensity behavioural support was associated with a non-significant increase in smoking abstinence at longest follow up (maximum 12-months) versus usual care, RR=1.08, p=0.13 (see Figure 7 NICE evidence review N (9)).

The effectiveness estimate for NRT gum was obtained from a pooled estimate across two studies. These compared: NRT gum versus placebo; and NRT gum + low intensity support versus low intensity support only. NRT gum was associated with a significant increase in smoking abstinence at 12-months after quit date RR=1.24 p=0.01 (see Figure 9, NICE evidence review N (9)).

Effectiveness rates were calculated as described as previously for assisted abstainers, i.e. by multiplying the RR of smoking abstinence by the probability of abstinence in the control arm. All effectiveness parameters are reported in **Error! Reference source not found.**.

Table 3: Intervention effectiveness: Unaided abstainers

	RR of abstinence vs. control *Mean (95% CI)*	**P(abstinence) at 12-months** *Mean (95% CI)*
Low intensity behavioural support	1.08 (0.98, 1.19)	29.08% (26.39%, 32.05%)
Usual care	N/A	26.93% [a]
NRT gum	1.24 (1.04 to 1.47)	21.34% (17.90%, 25.30%)
Placebo	N/A	17.21% [b]

a: 355/1318 participants in the control arms achieved continued abstinence.
b: 196/1139 participants in the control arms achieved continued abstinence.

Costs

Comparators

As previously described for the population of assisted abstainers, the cost of the comparators (usual care and placebo) was set equal to zero. This was because pharmacological and structured behavioural interventions are not typically provided for relapse prevention by LSSS. Furthermore, had usual care included any costs, these would have been incurred equally for the intervention and the comparator arm, meaning the net cost would be equal to £0.

Low intensity behavioural support

Intervention costs for low-intensity behavioural support were assumed to be consistent with the base case analysis and equal to £21.96 per person (Table 2~~Table 2~~). The cost was based on a series of 8 self-help booklets. This suitably matched the description of intervention in four of the five studies that informed the effectiveness estimate for low-intensity behavioural support in unaided abstainers.

NRT gum

The cost of NRT gum was £4.03. This was equal to the total cost of £8.39 per person assuming average gum consumption equal to 97.5 (Table 2~~Table 2~~) multiplied the assumed percentage of NRT products that are prescribed (i.e. 48% prescribed, 52% purchased OTC (26)).

Economic Evaluation

Decision Rule

Cost-effectiveness models are used to assess the relative benefits of a given treatment using patient outcomes and the costs incurred in achieving those outcomes. Economic evaluations use decision rules to identify the cost-effective intervention. This was an incremental analysis involving pairwise comparisons for each intervention vs. a relevant comparator (e.g. usual care/no intervention/ placebo). The key outcome for this analysis was the incremental cost-effectiveness ratio (ICER) which is calculated by dividing incremental costs by incremental effects as shown in the formula below.

$$ICER = \frac{Cost_{\text{int ervention}} - Cost_{Comparator}}{Effect_{\text{int ervention}} - Effect_{Comparator}}$$

All health benefits in the economic modelling were measured as QALYs. In line with the NICE methods manual (27), a cost-effectiveness threshold equal to £20,000 per QALY was adopted. This meant that any intervention with an ICER less than £20,000 was considered cost-effective vs the comparator.

Discounting

Future costs and outcomes were discounted in the model at a rate of 3.5% per year, in line with the values suggested in the NICE methods manual (27).

Time horizon

In the base case, the time horizon was equal to 100 years, covering the remaining lifetime of the hypothetical study population.

Perspective

The economic modelling was conducted from a healthcare perspective, including health outcomes measured as QALYs and healthcare costs incurred by the NHS and PSS. At the time of publication, relapse prevention interventions are provided by LSSS and funded by local authorities.

In addition, results are reported on two secondary outcomes that do not fall within the healthcare perspective. The additional outcomes are: private intervention costs i.e. over the counter costs for pharmacological interventions such as NRT; and productivity costs measured in terms of work absenteeism.

Sensitivity and Scenario Analyses

Deterministic Sensitivity Analysis

Deterministic sensitivity analysis (DSA) was performed by manually changing the value of individual input parameters and re-estimating the model results. The DSA was performed for key input parameters which included: effectiveness estimates where the RR was varied to equal the value of the 95% upper and lower confidence intervals; intervention costs which were increased and decreased by 25% of the value used in the base case analysis; and the natural rate of smoking relapse per year which was changed from 0% in the base case to 10%. DSA were also conducted for the time horizon which was reduced to 5-years, for increased (5% costs, 5% QALYs) and decreased (1.5% costs, 1.5% QALYs) discount rates; utility values which were set equal for smokers and non-smoker; and disutility and cost per smoking related comorbidities which were increased and decreased by 25%.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis is a technique used in economic modelling that allows the modeler to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs. There is usually uncertainty associated with input parameter values of an economic model, which may have been derived from clinical trials, observational studies or in some cases expert opinion. In the base case analysis, the point estimate of each input parameter value is used. In the probabilistic analysis, these parameters are represented as distributions around the point estimate, which can be summarised using a few parameters (such as mean and standard deviation for a normal distribution).

In a PSA, a set of input parameter values is drawn by random sampling from each distribution, and the model is 'run' to generate outputs (cost and health outcome), which are stored and repeated many times. The key output of PSA is the proportion of times an intervention is identified as cost-effective vs. the comparator across all random samples. It is important to note that PSA does not, usually, quantify uncertainty associated with the model's structure or design – only its quantitative inputs.

The PSA for the relapse prevention model required an added layer of complexity as the base case ICERs were not a single model output but were calculated using weighted averages of incremental costs and QALYs for populations aged between 12 and 100. That is, the base case model was run and obtained incremental costs and QALYs for a population aged 12, then run again to obtain incremental costs and QALYs for populations aged 13, and so on for ages 14, 15, 16, … , 100. Incremental costs and QALYs across all population ages were calculated as a weighting mean across all individual ages with weighting based on the proportion of the UK population at each age.

For each PSA iteration, results were obtained similarly as for the base case model, i.e. by obtaining a weighted average of incremental costs and QALYs across different age ranges. However, to reduce the computational burden, the PSA age categories were condensed from yearly increments i.e. age 12, 13, 14, 15, … , 100, to two-yearly increments. This meant the PSA calculated outcomes for populations aged 13, 15, 17, 19, 21, …, 99. The PSA then calculated a weighted average across the results for populations aged 13, 15, 17, 19, 21, …, 99 to obtain the final model result. The weightings were based on the total number of people aged 13, 15, 17, 19, 21, …, 99 in the population based on ONS UK population estimates (16). In total the PSA was run for 3,000 iterations, with weighted averages calculated within each iteration.

Input parameter distributions for the PSA followed recommendations in Briggs et al. (2006) (28): beta distributions were applied to probabilities, prevalence rates and utilities; inverse normal distributions were applied to RR parameters; and gamma distributions were applied to costs. In addition, a (beta) dirichlet distribution was applied to the age-related probabilities of being a current smoker, former smoker, and non-smoker to ensure the PSA values across these three parameters summed to one. The PSA distributions were fit using standard errors and 95% confidence intervals, or alpha (event rates) and beta (non-event rates) values, if these were available in the published literature i.e. reported alongside the mean estimates used to populate the base case model. If these were not available, then we applied an assumption that the value of the standard error was equal to 15% of the mean (base case) parameter value. The parameters and distributions used in the PSA are summarised in

Table 4

~~Table 4~~.

The PSA analysis was conducted using 3,000 iterations to reduce the computational burden. The iteration number was selected by conducting a PSA with 10,000 iterations. We then plotted a graph with the number of PSA iterations against the associated probabilistic ICER, for iterations 1, 1& 2, 1 & 2 & 3, …, 1 & 2 & 3 … & 10,000. The probabilistic ICER had stabilized at 3,000 iterations, being largely equivalent to the probabilistic ICER obtained at 10,000 iterations.

Table 4: Summary of PSA distributions

Parameter	PSA Distribution	Source
Intervention effectiveness (RR)	Log-normal	(9)
Probability of abstinence (control arms)	Beta [0,1]	(9)
Smoking status (by age & gender) Former smoker Current smoker Non-smoker	 Beta [0,1] (Dirichlet) Beta [0,1] (Dirichlet) Beta [0,1] (Dirichlet)	 (15)
Mortality per 1000 (by age & smoking status)	Beta [0,1000]	(29)
Comorbidities RR parameters Stroke Lung cancer MI CHD COPD	 Log-normal Log-normal Log-normal Log-normal Log-normal	 (30) (31) (32) (33) (34)
Comorbidities prevalence & incidence rates	Beta [0,1]	Assumption
Utilities Smoker/ former smoker/ non-smoker CHD All other comorbidities (excluding CHD)	 Beta [0,1] Beta [0,1] Beta [0,1]	 (35) (36) Assumption
Intervention costs	Gamma	Assumption
Comorbidity costs	Gamma	Assumption

Beta [a, b] = beta distribution with lower and upper bounds equal to a and b.

All assumptions applied a standard error equal to 15% of the mean.

Results

Assisted Abstainers

Low intensity behavioural support

The NICE meta-analysis found that low intensity behavioural support was less effective than usual care[a], RR=0.93 (95% CI = 0.81, 1.06) (see NICE evidence review N, Figure 10 (9)). Consequently, in a population of 1,000 assisted abstainers, the relapse prevention model estimated that low intensity behavioural support would produce 23 fewer continued abstainers at 12-months than usual care. Consequently, low intensity behavioural support was dominated by usual care in the base case analysis. The incremental lifetime healthcare costs of the intervention were equal to £105, meanwhile incremental QALYs were equal to -0.02. Cost-effectiveness results were driven by effectiveness rates: low intensity behavioural support was not effective with more of the population returning to smoking after 12-months. This led to an increase in the prevalence of smoking related comorbidities across the lifetime which detrimentally affected health and incurred additional treatment costs. The incremental treatment costs for stroke (£31 per person) made up around 30% of the difference in total costs.

Low intensity behavioural support also had a net negative impact on societal outcomes, resulting in an additional cost of £26. The societal outcomes were also driven by the increased number of smokers and smoking related comorbidities which were associated with increased work absenteeism. A full breakdown of the base case results is provided in Table 5~~Table 5~~.

Table 5: Cost-effectiveness results (per person): Low intensity behavioural support, assisted abstainers

	Low intensity behavioural support	**Usual care**	**Incremental**
Healthcare perspective			
Intervention costs	£22	£0	£22
Comorbidity costs			
Stroke	£4,907	£4,876	£31
Lung cancer	£985	£971	£15
MI	£1,094	£1,083	£11
CHD	£2,239	£2,232	£7
COPD	£1,217	£1,198	£19
Asthma	£15	£15	£0
Total costs	**£10,480**	**£10,375**	**£105**
QALYs	**15.37**	**15.39**	**-0.02**
ICER			**Dominated**
Societal outcomes			
Intervention costs (OTC)	£0	£0	£0
Productivity costs (absenteeism)	£775	£748	£26

[a] Usual care differed across the studies informing the pooled effectiveness estimate. The different definitions of usual care included a brief leaflet on smoking harm, standard treatment and no intervention.

The results of the deterministic sensitivity analysis for the low intensity behavioural support analysis are provided in Table 6~~Table 6~~. There was considerable uncertainty in the cost-effectiveness results when modifying the effectiveness estimates: The DSA that applied the upper 95% CI changed low intensity behavioural support from being a dominated to being dominant (i.e. less costly and more effective) versus usual care. Results for all of the other DSAs were robust with low intensity behavioural support remaining dominated by usual care. The consistency in the results is likely to be due to the effectiveness of low intensity behavioural support being less than that of usual care for the base case analysis. Given that low intensity behavioural support incurred additional intervention costs versus usual care, any deterministic scenario that didn't modify the base case analysis was only likely to alter the magnitude of dominance rather than cost-effectiveness result itself.

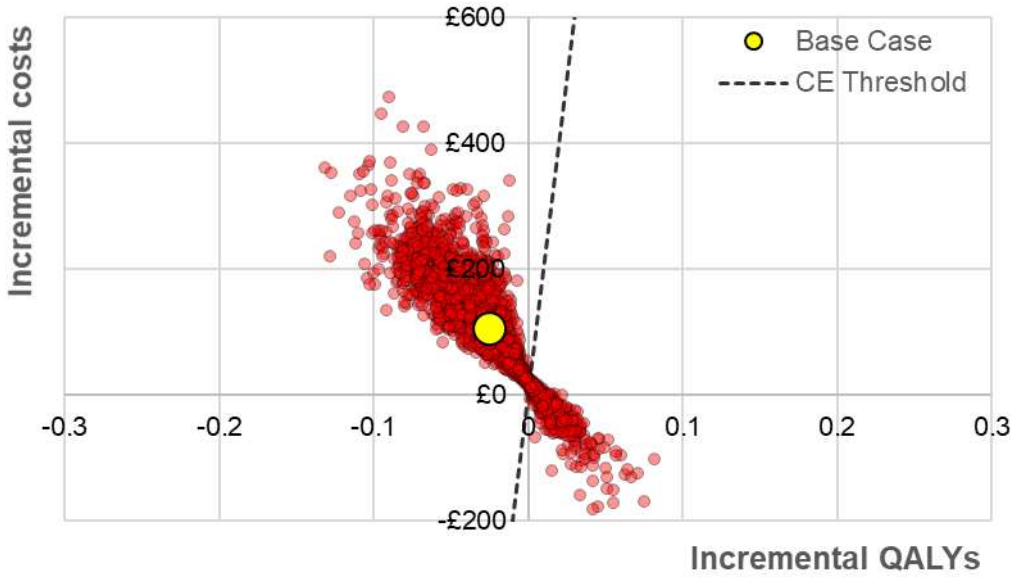
Table 6: Deterministic sensitivity analysis: Low intensity behavioural support, assisted abstainers

DSA Scenario	DSA Parameter Value	Absolute (LIBS)		Incremental (LIBS vs. usual care)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,480	15.37	£105	-0.02	Dominated
Effectiveness	Lower 95% CI RR (0.81)	£10,621	15.33	£246	-0.07	Dominated
	Upper 95% CI RR (1.06)	£10,326	15.41	-£49	0.02	*Dominant*
Intervention costs	Increase by 25%	£10,486	15.37	£111	-0.02	Dominated
	Decrease by 25%	£10,475	15.37	£100	-0.02	Dominated
Time horizon	5 years	£1,824	3.75	£41	-0.00	Dominated
Relapse rate	Increase to 5% per year	£11,645	15.06	£65	-0.01	Dominated
Discount rate	Costs 5%, QALYs 5%	£8,072	12.56	£90	-0.02	Dominated
	Costs 1.5%, QALYs 1.5%	£16,278	21.51	£136	-0.04	Dominated
Utility	Same QoL for smokers and non-smokers	£10,480	15.47	£105	-0.02	Dominated
Disease costs	Decrease by 25%	£7,865	15.37	£84	-0.02	Dominated
	Increase by 25%	£13,094	15.37	£125	-0.02	Dominated
Disease disutility	Decrease by 25%	£10,480	16.39	£105	-0.02	Dominated
	Increase by 25%	£10,480	14.35	£105	-0.03	Dominated
Age of population	Age = 20	£4,743	21.38	£50	-0.02	Dominated
	Age = 60	£15,702	11.84	£155	-0.03	Dominated

LIBS= Low intensity behavioural support

The PSA identified low intensity behavioural support as being the cost-effective strategy in 14.2% of the 3,000 iterations, with usual care being cost-effective in the remaining 85.8%. The results of the PSA are illustrated in Figure 2. The figure plots PSA results on a cost-effectiveness plane, each point (in red) represents one PSA iteration. Interventions are cost-effective if their incremental costs and QALYs fall to the south-east of the cost-effectiveness threshold, equal to £20,000 per QALY.

Figure 2: PSA results, low intensity behavioural support vs. usual care



High intensity behavioural support

The NICE meta-analysis found that high intensity behavioural support was more effective than usual care[b], RR=1.06 (95% CI = 0.82, 1.36) (see Figure 10, NICE Evidence Review N (9)). In a population of 1,000 assisted abstainers, the relapse prevention model estimated that high intensity behavioural support would produce 19 additional continued abstainers at 12-months than usual care. The ICER for high intensity behavioural support vs. usual care was equal to £12,690 meaning the intervention was cost-effective at the threshold of £20,000 per QALY. The incremental lifetime healthcare costs were equal to £248, which included £314 for intervention costs, and £65 of savings due to reduced costs for treating smoking related comorbidities. As the intervention reduced the number of smokers and smoking related comorbidities, it achieved lifetime health benefits, with incremental QALYs equal to 0.02 per person.

High intensity behavioural support also had a net positive impact on societal outcomes, resulting in an additional savings of £21. The societal outcomes were also driven by the decreased number of smokers and smoking related comorbidities which resulted in reduced costs due to work absenteeism. A full breakdown of the base case results is provided in Table 7~~Table 7~~.

Table 7: Cost-effectiveness results (per person): High intensity behavioural support, assisted abstainers.

	High intensity behavioural support	Usual care	Incremental
Healthcare perspective			
Intervention costs	£314	£0	£314

[b] Usual care differed across the studies informing the pooled effectiveness estimate. The different definitions of usual care included no intervention, NRT only, NRT + a booklet, and weekly meetings only. Where interventions were provided as part of usual care they were also included as part of the intervention arm.

Comorbidity costs			
Stroke	£4,885	£4,910	-£25
Lung cancer	£975	£987	-£12
MI	£1,086	£1,095	-£9
CHD	£2,234	£2,239	-£5
COPD	£1,204	£1,219	-£15
Asthma	£15	£15	£0
Total costs	**£10,713**	**£10,465**	**£248**
QALYs	**15.39**	**15.37**	**0.02**
ICER			**£12,690**
Societal outcomes			
Intervention costs (OTC)	£0	£0	£0
Productivity costs (absenteeism)	£756	£777	-£21

The results of the deterministic sensitivity analysis for the high intensity behavioural support analysis are provided in Table 8~~Table 8~~. In general, there was considerable uncertainty in the cost-effectiveness results. In particular the DSA for intervention effectiveness established that high intensity behavioural support was not cost-effective and dominated by usual care when intervention effectiveness was equal to the lower 95% CI RR, whereas the intervention was dominant versus usual care when applying the upper 95% CI RR. The results were also sensitive to relapse rates, which resulted in an ICER above the £20,000 threshold when the relapse was increased to 5% annually. High intensity behavioural support was not cost-effective for a younger population aged 20 due to reductions in incremental QALYs. However, results were consistent when varying intervention and comorbidity costs by 25%, with the ICER remaining below £20,000 for these DSAs. The ICER for high intensity behavioural support decreased slightly to £11,618 when including additional costs in the comparator equal to the costs of low intensity behavioural support (£21), the ICER decreased further to £7,582 when increasing the comparator costs to £100 per person.

Table 8: Deterministic sensitivity analysis: High intensity behavioural support, assisted abstainers

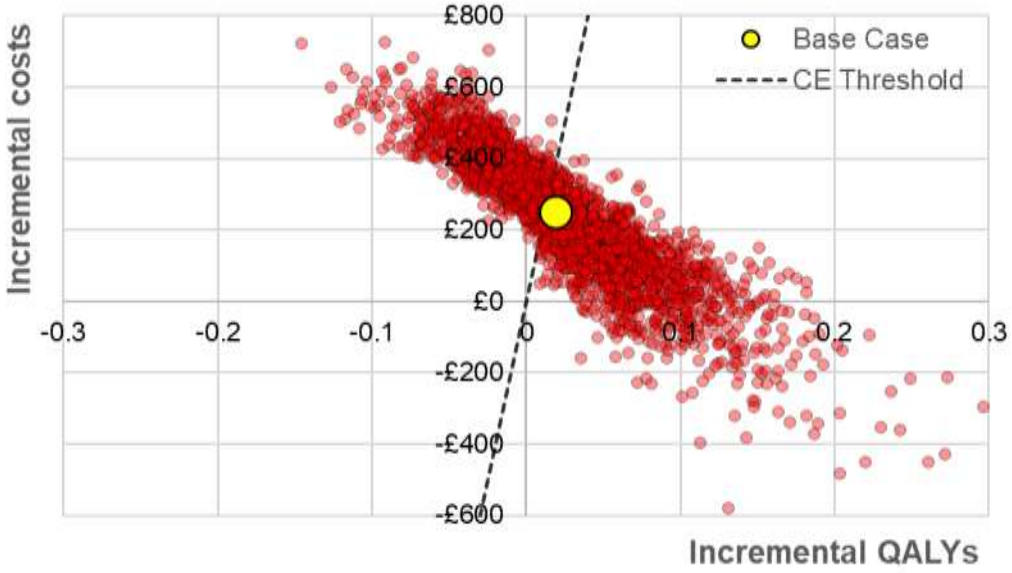
DSA Scenario	DSA Parameter Value	Absolute (HIBS)		Incremental (HIBS vs. usual care)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,713	15.39	£248	0.02	£12,690
Effectiveness	Lower 95% CI RR (0.82)	£10,975	15.31	£510	-0.06	Dominated
	Upper 95% CI RR (1.36)	£10,386	15.48	-£79	0.12	Dominant
Comparator costs	Increase from £0 to £21	£10,713	15.39	£227	0.02	£11,618
	Increase from £0 to £100	£10,713	15.39	£148	0.02	£7,582
Intervention costs	Increase by 25%	£10,792	15.39	£327	0.02	£16,698
	Decrease by 25%	£10,635	15.39	£170	0.02	£8,682
Time horizon	5 years	£2,103	3.76	£299	0.00	£115,971
Relapse rate	Increase to 5% per year	£11,906	15.07	£280	0.01	£25,938
Discount rate	Costs 5%, QALYs 5%	£8,316	12.57	£260	0.02	£17,275
	Costs 1.5%, QALYs 1.5%	£16,490	21.54	£224	0.03	£7,442
Utility	Same QoL for smokers and non-smokers	£10,713	15.49	£248	0.02	£14,807
Disease costs	Decrease by 25%	£8,113	15.39	£265	0.02	£13,526
	Increase by 25%	£13,313	15.39	£159	0.02	£11,885
Disease disutility	Decrease by 25%	£10,713	16.40	£248	0.01	£20,426
	Increase by 25%	£10,713	14.37	£248	0.03	£9,204

Age of population	Age = 20	£5,015	21.39	£291	0.01	£23,299
	Age = 60	£15,900	11.83	£209	0.03	£7,783

HIBS= High intensity behavioural support

The PSA identified high intensity behavioural support as being the cost-effective strategy in 55.9% of the 3,000 iterations, with usual care being cost-effective in the remaining 44.1%. The results of the PSA are illustrated in Figure 3. The PSA results reflected results from the NICE effectiveness reviews where the RR of smoking cessation for the intervention versus usual care was not statistically significant meaning the lower 95% confidence interval was below the line of no effect. Consequently, there was considerable uncertainty in incremental costs and QALYs in the PSA, which ranged from -£600 to £800 and -0.15 to 0.3 respectively, across all 3,000 iterations.

Figure 3: PSA results, high intensity behavioural support vs. usual care



NRT short acting

The NICE meta-analysis identified NRT short acting as more effective than placebo, RR=1.04 (95% CI = 0.77, 1.40) (see Grade Profile 6, NICE Evidence Review N (9)). In a population of 1,000 assisted abstainers, the relapse prevention model estimated that NRT short acting would produce 9 additional continued abstainers at 12-months when compared with placebo. The ICER for NRT short acting vs. placebo was dominant being less costly and more effective. However, incremental costs were almost equivalent being equal to -£1 as the intervention costs of NRT l/s (£32) were only marginally exceeded by the cost savings from reduced treatment for the smoking related comorbidities (-£33). The NRT short acting intervention also resulted in incremental health benefits of 0.01 QALYs due to reductions in smoking related comorbidities which followed on from the increase in smoking abstinence.

In addition, reductions in the number of smoking related comorbidities had a net positive impact on productivity, where NRT was associated with £11 of savings per person due to reductions in work absenteeism. However, NRT did have a private cost. The model estimated that each person receiving the NRT intervention would privately purchase £35 of NRT short acting products OTC. A full breakdown of the base case results is provided in Table 9~~Table 9~~.

Table 9: Cost-effectiveness results (per person): NRT short acting, assisted abstainers.

	NRT short acting	Placebo	Incremental
Healthcare perspective			
Intervention costs	£32	£0	£32
Comorbidity costs			
Stroke	£4,998	£5,010	-£12
Lung cancer	£1,028	£1,034	-£6
MI	£1,126	£1,130	-£4
CHD	£2,258	£2,260	-£3
COPD	£1,274	£1,281	-£8
Asthma	£15	£15	£0
Total costs	**£10,731**	**£10,732**	**-£1**
QALYs	**15.30**	**15.29**	**0.01**
ICER			**Dominant**
Societal outcomes			
Intervention costs (OTC)	£35	£0	£35
Productivity costs (absenteeism)	£852	£862	-£11

The results of the deterministic sensitivity analysis for the NRT short acting analysis are provided in Table 10~~Table 10~~. There was considerable uncertainty in the cost-effectiveness results when modifying the effectiveness estimates: The DSA that applied the lower 95% CI RR changed the results with NRT being dominated (costlier, less effective) by placebo; in contrast the upper 95% RR resulted in NRT being dominant versus placebo. Results for all of the other DSAs were robust with NRT remaining dominant or resulting in ICERs below the £20,000 threshold. NRT was cost-effective: when restricting populations to people aged 20 and 60; after increasing the annual smoking relapse rate to 5%; when increasing intervention costs by 25%, and even for a reduced time horizon of 5-years.

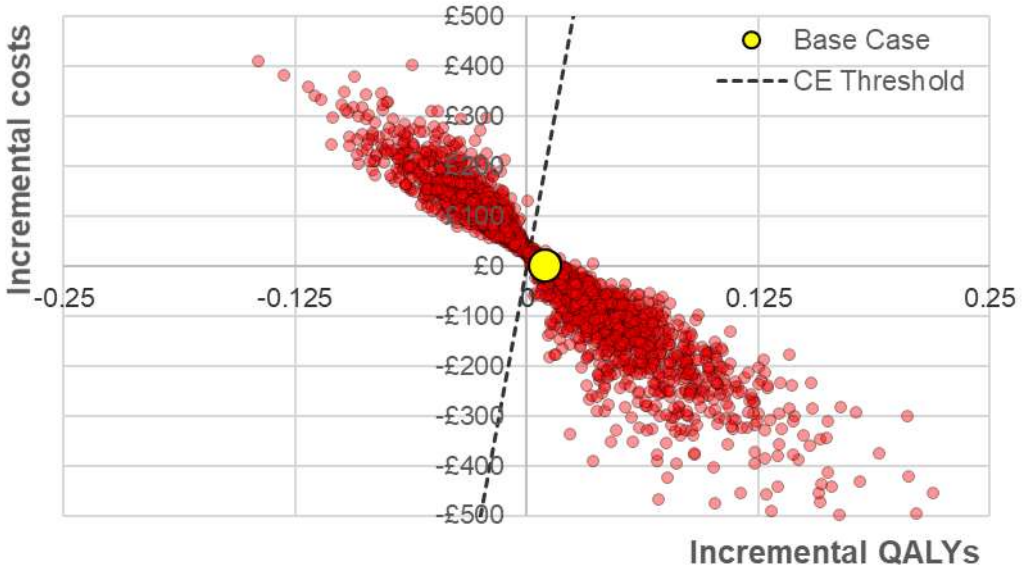
Table 10: Deterministic sensitivity analysis: NRT short acting, assisted abstainers

DSA Scenario	DSA Parameter Value	Absolute (NRT)		Incremental (NRT vs. placebo)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,731	15.30	-£1	0.01	Dominant
Effectiveness	Lower 95% CI RR (0.77)	£10,953	15.23	£221	-0.06	Dominated
	Upper 95% CI RR (1.36)	£10,434	15.29	-£297	0.10	Dominant
Intervention costs	Increase by 25%	£10,739	15.30	£7	0.01	£719
	Decrease by 25%	£10,723	15.30	-£9	0.01	Dominant
Time horizon	5 years	£1,890	3.74	£24	0.00	£18,853
Relapse rate	Increase to 5% per year	£11,780	15.02	£15	0.01	£2,730
Discount rate	Costs 5%, QALYs 5%	£8,280	12.51	£5	0.01	£665
	Costs 1.5%, QALYs 1.5%	£16,620	21.40	-£13	0.02	Dominant
Utility	Same QoL for smokers and non-smokers	£10,731	15.41	-£1	0.01	Dominant
Disease costs	Decrease by 25%	£8,056	15.30	£7	0.01	£742
	Increase by 25%	£13,405	15.30	-£9	0.01	Dominant
Disease disutility	Decrease by 25%	£10,731	16.34	-£1	0.01	Dominant
	Increase by 25%	£10,731	14.25	-£1	0.01	Dominant
	Age = 20	£4,836	21.33	£21	0.01	£3,285

Age of population	Age = 60	£16,099	11.71	-£21	0.01	Dominant

The PSA identified NRT short acting as being the cost-effective strategy in 57.7% of the 3,000 iterations, with placebo being cost-effective in the remaining 42.3%. The results of the PSA are illustrated in Figure 4. The PSA results reflected results from the NICE effectiveness reviews where the lower 95% confidence interval for the RR of smoking cessation for NRT short acting versus placebo was below the line of no effect. PSA iterations with a RR parameter value <1 resulted in NRT being less effective than placebo and, consequently, fewer non-smokers and fewer lifetime QALYs. There was considerable uncertainty regarding whether NRT short acting resulted in costs or savings vs. placebo with incremental NHS costs ranging between -£500 and £400.

Figure 4: PSA results, NRT short acting vs. placebo



Bupropion

Base case analysis

The NICE meta-analysis identified bupropion was more effective than placebo, RR=1.15 (95% CI = 0.98, 1.35) (see Grade Profile 6, NICE Evidence Review N (9)).[c]

In a population of 1,000 assisted abstainers, bupropion resulted in 36 additional continued abstainers at 12-months when compared with placebo. The base case analysis found that bupropion had an overall health benefit of 0.04 QALYs per person, and healthcare cost savings of £40 per person. Consequently, the ICER for bupropion was dominant versus placebo. A full breakdown of the base case results for bupropion versus placebo are provided in Table 11~~Table 11~~. The total NHS savings across all smoking related comorbidities was equal to £128 per person. In addition, bupropion was associated with £41

[c] The effectiveness rate for the base case analysis was from the pooled estimate across 9 intervention arms in six studies. For seven of the nine intervention arms, the duration of prior abstinence was unclear or not reported.

of productivity savings through reduced work absenteeism which occurred due to reductions in the number of smokers and smoking related comorbidities throughout the model.

Table 11: Cost-effectiveness results (per person): bupropion, assisted abstainers.

	Bupropion	Placebo	Incremental
Healthcare perspective			
Intervention costs	£88	£0	£88
Comorbidity costs			
Stroke	£4,950	£4,999	-£48
Lung cancer	£1,006	£1,029	-£23
MI	£1,109	£1,126	-£17
CHD	£2,248	£2,258	-£10
COPD	£1,244	£1,274	-£30
Asthma	£15	£15	-£0
Total costs	**£10,660**	**£10,701**	**-£40**
QALYs	**15.33**	**15.30**	**0.04**
ICER			**Dominant**
Societal outcomes			
Intervention costs (OTC)	£0	£0	£0
Productivity costs (absenteeism)	£811	£852	-£41

The results of the deterministic sensitivity analysis for the bupropion analysis are provided in Table 12~~Table 12~~. The cost-effectiveness results were not robust when modifying the effectiveness estimates, where the DSA that applied the lower 95% CI RR resulted in bupropion being dominated by placebo. In contrast, when applying the upper 95% CI RR, the ICER was dominant, with bupropion resulting in substantial cost savings of -£211 and health benefits of 0.09 per person. Results for all of the other DSAs were robust with bupropion remaining dominant or resulting in ICERs below the £20,000 threshold, this included the scenario where intervention costs were doubled to account for uncertainty in the length of treatment duration. The ICERs were also below £20,000 for scenarios which limited the time horizon to 5-years and substantially increased the natural relapse rate to 5% per year.

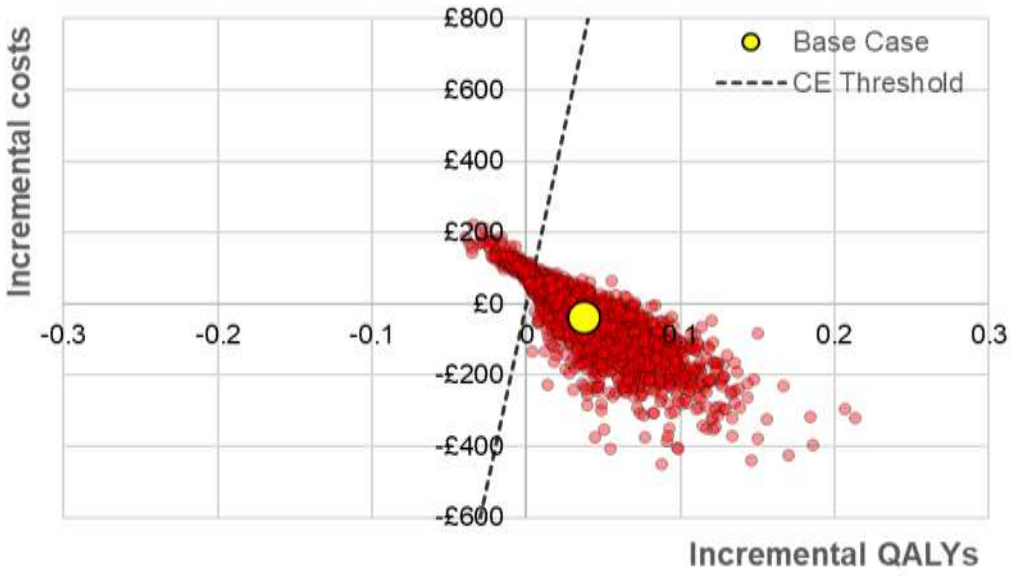
Table 12: Deterministic sensitivity analysis: bupropion, assisted abstainers

DSA Scenario	DSA Parameter Value	Absolute (bupropion)		Incremental (bupropion vs. placebo)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,660	15.33	-£40	0.04	Dominant
Effectiveness	Lower 95% CI RR (0.98)	£10,805	15.29	£105	-0.01	Dominated
	Upper 95% CI RR (1.35)	£10,489	15.39	-£211	0.09	Dominant
Intervention costs	Double (increase to £175)	£10,748	15.33	£47	0.04	£1,231
	Decrease by 25%	£10,638	15.33	-£62	0.04	Dominant
Time horizon	5 years	£1,916	3.75	£58	0.01	£11,544
Relapse rate	Increase to 5% per year	£11,770	15.04	£21	0.02	£984
Discount rate	Costs 5%, QALYs 5%	£8,232	12.53	-£18	0.03	Dominant
	Costs 1.5%, QALYs 1.5%	£16,502	21.46	-£89	0.06	Dominant
Utility	Same QoL for smokers and non-smokers	£10,660	15.44	-£40	0.03	Dominant

Disease costs	Decrease by 25%	£8,017	15.33	-£8	0.04	Dominant
	Increase by 25%	£13,303	15.33	-£73	0.04	Dominant
Disease disutility	Decrease by 25%	£10,660	16.37	-£40	0.02	Dominant
	Increase by 25%	£10,660	14.30	-£40	0.05	Dominant
Age of population	Age = 20	£4,848	21.36	£44	0.02	£1,778
	Age = 60	£15,952	11.76	-£118	0.05	Dominant

The PSA identified bupropion as being the cost-effective strategy in 93.5% of the 3,000 iterations, with placebo being cost-effective in the remaining 6.5% The results of the PSA are illustrated in Figure 5. The PSA results were driven by results from the NICE effectiveness reviews where the 95% confidence interval for the RR of smoking cessation for bupropion versus placebo was largely above the line of no effect. Incremental NHS costs ranged from roughly -£450 to £225, with bupropion being cost saving versus placebo in the majority of PSA iterations.

Figure 5: PSA results, bupropion vs. placebo



Scenario analysis

We established the cost-effectiveness of bupropion for a scenario analysis where the effectiveness estimate was limited to studies which reported the duration of prior abstinence equal to <4 weeks. The NICE meta-analysis identified bupropion was more effective than placebo, RR=1.11 (95% CI = 0.84, 1.48) (see Figure 15 in NICE Evidence Review N (9)).[d]

In a population of 1,000 assisted abstainers, the scenario analysis found that bupropion resulted in 30 additional continued abstainers at 12-months when compared with placebo. The base case analysis found that bupropion had an overall health benefit of 0.03 QALYs per person, and healthcare cost savings of £18 per person. Consequently, the ICER for bupropion was dominant versus placebo. A full breakdown of the results of the scenario analysis are provided in Table 13~~Table 13~~.

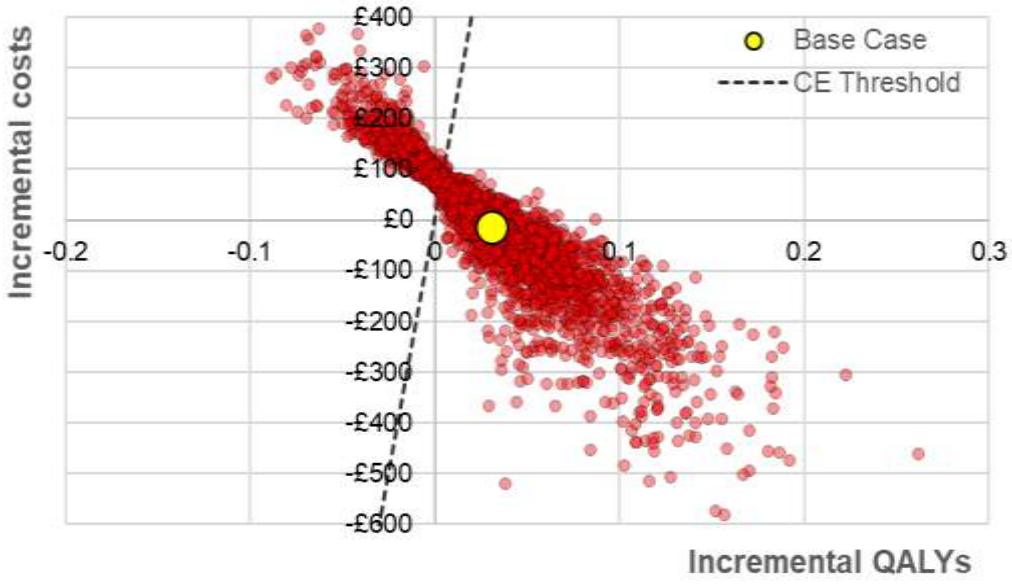
[d] The effectiveness rate for the base case analysis was from the pooled estimate across the two studies where duration of prior abstinence was < 4 weeks.

Table 13: Cost-effectiveness results (per person): bupropion, assisted abstainers.

	Bupropion	Placebo	Incremental
Healthcare perspective			
Intervention costs	£88	£0	£88
Comorbidity costs			
Stroke	£4,919	£4,959	-£40
Lung cancer	£991	£1,010	-£19
MI	£1,098	£1,112	-£14
CHD	£2,241	£2,250	-£8
COPD	£1,225	£1,250	-£25
Asthma	£15	£15	-£0
Total costs	**£10,578**	**£10,596**	**-£18**
QALYs	**15.36**	**15.33**	**0.03**
ICER			**Dominant**
Societal outcomes			
Intervention costs (OTC)	£0	£0	£0
Productivity costs (absenteeism)	£785	£819	-£34

The results of the PSA indicated that bupropion was the cost-effective strategy in 74.0% of the 3,000 iterations in the scenario analysis, with placebo being cost-effective in the remaining 26.0%. The results of the PSA are illustrated in Figure 6. The PSA results were slightly more uncertain than the base case analysis due to the decreased precision of the effectiveness parameter i.e. a wider confidence around the RR for bupropion versus placebo.

Figure 6: PSA results, bupropion vs. placebo (scenario analysis)



Varenicline

Informed by a single study by Tonstad (2006) (19), NICE evidence review N (9) found that varenicline was more effective than placebo, RR=1.18 (95% CI = 1.03, 1.36). In a population of 1,000 assisted abstainers, varenicline resulted in 66 additional continued abstainers at 12-months when compared with placebo. The base case analysis found that varenicline had substantial health benefit of 0.07 QALYs per person coupled with healthcare cost savings of £70 per person. Consequently, the ICER for varenicline was dominant versus placebo. A full breakdown of the base case results for varenicline versus placebo are provided in Table 14~~Table 14~~. The total NHS savings across all smoking related comorbidities for varenicline was equal to £234 per person. In addition, varenicline was associated with £75 of productivity savings through reduced work absenteeism which occurred due to substantial reductions in the number of smokers and subsequent smoking related comorbidities throughout the model.

Table 14: Cost-effectiveness results (per person): varenicline, assisted abstainers.

	Varenicline	**Placebo**	**Incremental**
Healthcare perspective			
Intervention costs	£164	£0	£164
Comorbidity costs			
Stroke	£4,742	£4,831	-£88
Lung cancer	£908	£949	-£42
MI	£1,036	£1,067	-£31
CHD	£2,204	£2,223	-£18
COPD	£1,116	£1,170	-£55
Asthma	£15	£15	-£0
Total costs	**£10,185**	**£10,255**	**-£70**
QALYs	**15.50**	**15.43**	**0.07**
ICER			**Dominant**
Societal outcomes			
Intervention costs (OTC)	£0	£0	£0
Productivity costs (absenteeism)	£635	£710	-£75

The full DSA results for varenicline are reported in Table 15~~Table 15~~. The base case results were robust, with varenicline remaining cost-effective versus placebo in all of the scenarios. This included when reducing the effectiveness of varenicline equal to the 95% lower CI RR which resulted in an ICER of £10,694, this being substantially lower than the cost-effectiveness threshold of £20,000 per QALY. In addition, varenicline remained cost-effective with ICERs less that £20,000 for two pessimistic scenarios which increased relapse rates to 5% per year and reduced the time horizon to 5-years. Varenicline was highly cost-effective for older populations (aged 60) with substantial NHS savings of £212 and health benefits of

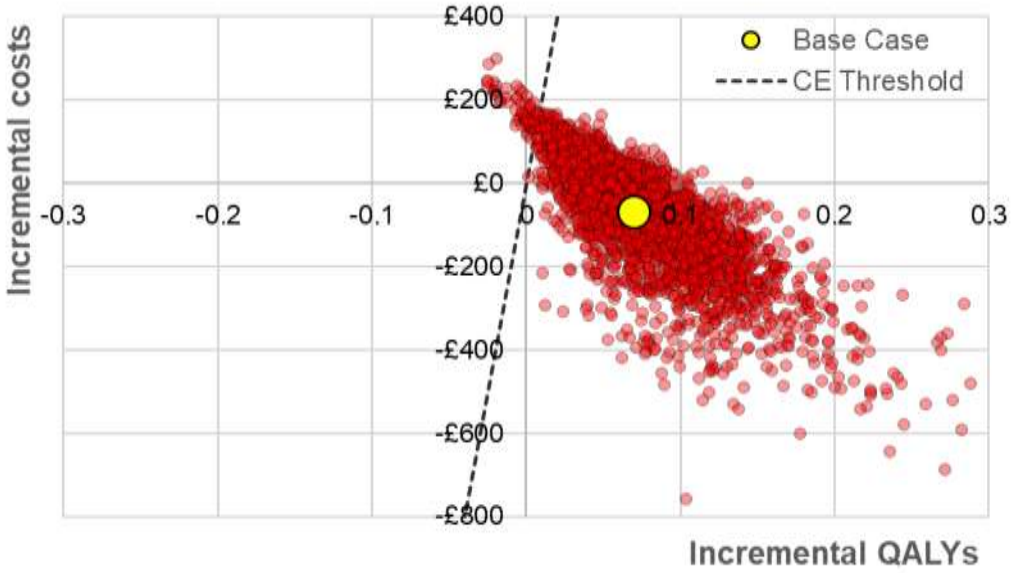
0.10 QALYs per person. Varenicline was also cost-effective for a younger population aged 20 with an ICER equal to £1,862. For all other scenarios varenicline remained dominant versus placebo.

Table 15: Deterministic sensitivity analysis: varenicline, assisted abstainers

DSA Scenario	DSA Parameter Value	Absolute (varenicline)		Incremental (varenicline vs. placebo)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,185	15.50	-£70	0.07	Dominant
Effectiveness	Lower 95% CI RR (1.03)	£10,380	15.44	£125	0.01	£10,694
	Upper 95% CI RR (1.35)	£9,951	15.57	-£304	0.14	Dominant
Intervention costs	Increase by 25%	£10,226	15.50	-£29	0.07	Dominant
	Decrease by 25%	£10,144	15.50	-£111	0.07	Dominant
Time horizon	5 years	£1,866	3.77	£110	0.01	£11,948
Relapse rate	Increase to 5% per year	£11,559	15.13	£42	0.04	£1,080
Discount rate	Costs 5%, QALYs 5%	£7,856	12.66	-£28	0.05	Dominant
	Costs 1.5%, QALYs 1.5%	£15,819	21.71	-£159	0.11	Dominant
Utility	Same QoL for smokers and non-smokers	£10,185	15.58	-£70	0.06	Dominant
Disease costs	Decrease by 25%	£7,680	15.50	-£12	0.07	Dominant
	Increase by 25%	£12,690	15.50	-£129	0.07	Dominant
Disease disutility	Decrease by 25%	£10,185	16.47	-£70	0.04	Dominant
	Increase by 25%	£10,185	14.53	-£70	0.10	Dominant
Age of population	Age = 20	£4,735	21.46	£83	0.04	£1,862
	Age = 60	£15,143	11.99	-£212	0.10	Dominant

The PSA identified varenicline as being the cost-effective strategy in 97.8% of the 3,000 iterations, with placebo being cost-effective in the remaining 2.2% The results of the PSA are illustrated in Figure 7. The PSA results were driven by results from the NICE effectiveness reviews where the 95% confidence interval for the RR of smoking cessation for varenicline versus placebo was above the line of no effect. Incremental NHS costs ranged from -£800 to £250, with varenicline being cost saving versus placebo in the majority of PSA iterations.

Figure 7: PSA results, varenicline vs. placebo



NRT + bupropion

The NICE meta-analysis pooled two studies and found that NRT + bupropion was more effective than placebo with a RR= 1.11 (0.49, 2.54), (see figure 12, NICE Evidence review N (9)) . In a population of 1,000 assisted abstainers, NRT + bupropion resulted in 24 additional continued abstainers at 12-months when compared with placebo. The base case analysis found that NRT + bupropion had a health benefit of 0.02 QALYs per person but had healthcare costs of £36. The intervention was cost-effective versus placebo with an ICER of £1,463, substantially lower than the £20,000 threshold. The total NHS savings across all smoking related comorbidities was equal to £83 per person which is less than the overall intervention costs of £120 per person.

Due to reductions in the number of smoking related comorbidities NRT + bupropion had a net positive impact on productivity and was associated with £27 of savings per person due to reductions in work absenteeism. However, NRT + bupropion had a private cost. The model estimated that each person receiving the NRT intervention would privately purchase £35 of NRT products OTC. A full breakdown of the base case results for NRT + bupropion versus placebo are provided in Table 16~~Table 16~~.

Table 16: Cost-effectiveness results (per person): NRT + bupropion, assisted abstainers.

	NRT + bupropion	Placebo	Incremental
Healthcare perspective			
Intervention costs	£120	£0	£120
Comorbidity costs			
Stroke	£5,004	£5,036	-£31
Lung cancer	£1,031	£1,046	-£15
MI	£1,128	£1,139	-£11

CHD COPD Asthma	£2,259 £1,277 £15	£2,265 £1,297 £15	-£7 -£19 -£0
Total costs	**£10,835**	**£10,798**	**£36**
QALYs	**15.29**	**15.27**	**0.02**
ICER			**£1,463**
Societal outcomes			
Intervention costs (OTC)	£35	£0	£35
Productivity costs (absenteeism)	£857	£884	-£27

The DSA results for the NRT + bupropion versus placebo are provided in Table 17~~Table 17~~. There was considerable uncertainty in the cost-effectiveness results when modifying the effectiveness estimates: The DSA applying the lower 95% CI resulted in NRT + bupropion being dominated by placebo i.e. costlier and less effective, in contrast, the DSA applying the upper 95% CI resulted in NRT + bupropion being dominant versus placebo i.e. less costly and more effective. The variation in results was substantial across the two scenarios, for instance incremental costs ranged from -£506 (i.e. savings) for the higher effectiveness estimate, to £1,046 (i.e. costs) for the lower effectiveness estimate.

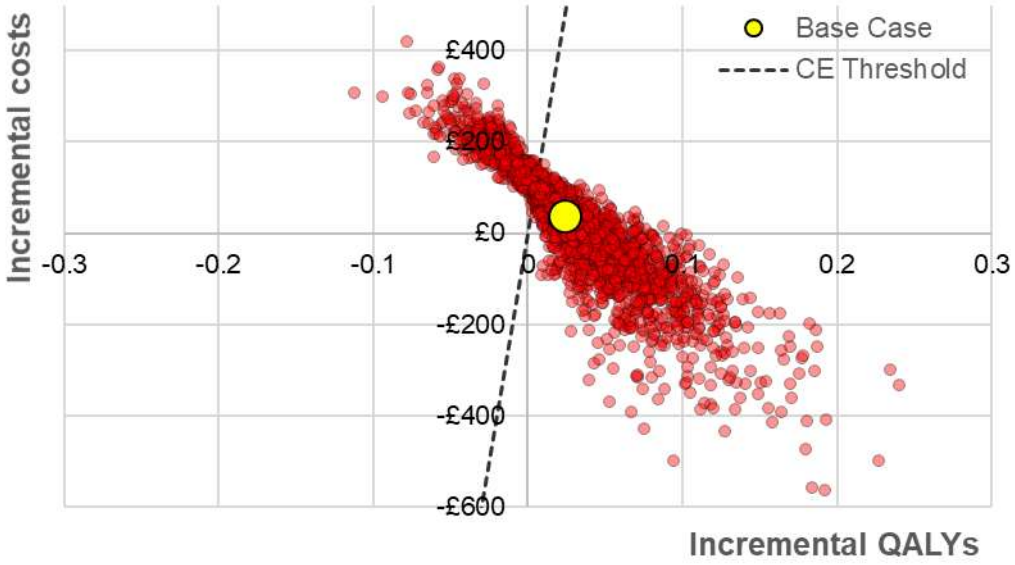
Results were robust for the majority of other DSAs with NRT plus bupropion remaining cost-effective versus placebo. This included scenarios where intervention costs were increased by 25%, the natural relapse rate was increased to 5% per year, comorbidity disease costs were decreased by 25%, comorbidity disutility was decreased by 25% and where the starting age of the population was set equal to 20 and 60. NRT + bupropion was not cost-effective when the time horizon was reduced from lifetime to 5-years as this scenario resulted in an ICER of £30,674, marginally above the cost-effectiveness threshold of £20,000.

Table 17: Deterministic sensitivity analysis: NRT + bupropion, assisted abstainers

DSA Scenario	DSA Parameter Value	Absolute (NRT + bupropion)		Incremental (NRT + bupropion vs. placebo)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,835	15.29	£36	0.02	£1,463
Effectiveness	Lower 95% CI RR (0.49)	£11,304	15.15	£506	-0.12	Dominated
	Upper 95% CI RR (2.54)	£9,752	15.62	-£1046	0.35	Dominant
Intervention costs	Increase by 25%	£10,865	15.29	£66	0.02	Dominant
	Decrease by 25%	£10,805	15.29	£7	0.02	£262
Time horizon	5 years	£1,981	3.74	£101	0.003	£30,674
Relapse rate	Increase to 5% per year	£11,877	15.01	£76	0.01	£5,555
Discount rate	Costs 5%, QALYs 5%	£8,381	12.50	£51	0.02	£2,678
	Costs 1.5%, QALYs 1.5%	£16,730	21.39	£5	0.04	£131
Utility	Same QoL for smokers and non-smokers	£10,835	15.41	£36	0.02	£1,707
Disease costs	Decrease by 25%	£8,156	15.29	£57	0.02	£2,298
	Increase by 25%	£13,513	15.29	£16	0.02	£627
Disease disutility	Decrease by 25%	£10,835	16.34	£36	0.02	£2,354
	Increase by 25%	£10,835	14.24	£36	0.03	£1,061
Age of population	Age = 20	£4,930	21.33	£91	0.02	£5,721
	Age = 60	£16,213	11.70	-£14	0.03	Dominant

The PSA identified NRT+ bupropion as being the cost-effective strategy in 73.6% of the 3,000 iterations, with placebo being cost-effective in the remaining 26.4% The results of the PSA are illustrated in Figure 8. The PSA results were driven by uncertainty in the results from the NICE effectiveness reviews where the lower 95% confidence interval for the RR of smoking cessation for NRT + bupropion versus placebo was considerably lower than the line of no effect. NRT + bupropion typically incurred NHS costs versus placebo which ranged from roughly -£250 to £450 across all PSA iterations.

Figure 8: PSA results, NRT + bupropion vs. placebo



Unaided Abstainers

Low intensity behavioural support

The NICE meta-analysis found that low intensity behavioural support was non significantly more effective than usual care in a pooled estimate that included 5 studies (RR=1.08, p0.13) (See Figure 7 NICE evidence review N (9)). In a population of 1,000 unaided abstainers, the relapse prevention model estimated that low intensity behavioural support would produce 22 additional abstainers at 12-months than usual care. The cost-effectiveness results found that low intensity behavioural support was dominant versus usual care being associated with a health benefit of 0.02 QALYs and healthcare cost savings of £54. The incremental treatment costs for low intensity behavioural support were relatively modest (£22) and were exceeded by total cost savings of £76 associated with a reduction in smoking related morbidities. Low intensity behavioural support was also associated with £24 of productivity savings due to reduced work absenteeism. A full breakdown of the scenario analysis results is provided in Table 18~~Table 18~~.

Table 18: Cost-effectiveness results (per person): Low intensity behavioural support, unaided abstainers.

	Low intensity	Usual care	Incremental

	behavioural support		
Healthcare perspective			
Intervention costs	£22	£0	£22
Comorbidity costs			
Stroke	£4,935	£4,963	-£29
Lung cancer	£998	£1,012	-£14
MI	£1,104	£1,114	-£10
CHD	£2,244	£2,250	-£6
COPD	£1,234	£1,252	-£18
Asthma	£15	£15	£0
Total costs	£10,553	£10,606	-£54
QALYs	15.35	15.32	0.02
ICER			Dominant
Societal outcomes			
Intervention costs (OTC)	£0	£0	£0
Productivity costs (absenteeism)	£798	£822	-£24

The cost-effectiveness results were robust for all but one of the DSAs with low intensity support remaining the cost-effective strategy versus usual care. This included scenarios which increased costs by 25%, reduced the time horizon to 5 years, increased the natural relapse rate to 5% per year, and decreased costs and utilities for disease comorbidities by 25%. The only DSA where low intensity behavioural support was no cost-effective in unaided abstainers was the application of a RR of smoking cessation using the lower 95% confidence interval. In this case the intervention was less effective and therefore dominated by usual care given the costs associated with intervention delivery. The full DSA results are displayed in Table 19~~Table 19~~.

Table 19: Deterministic sensitivity analysis: low intensity behavioural support, unaided abstainers

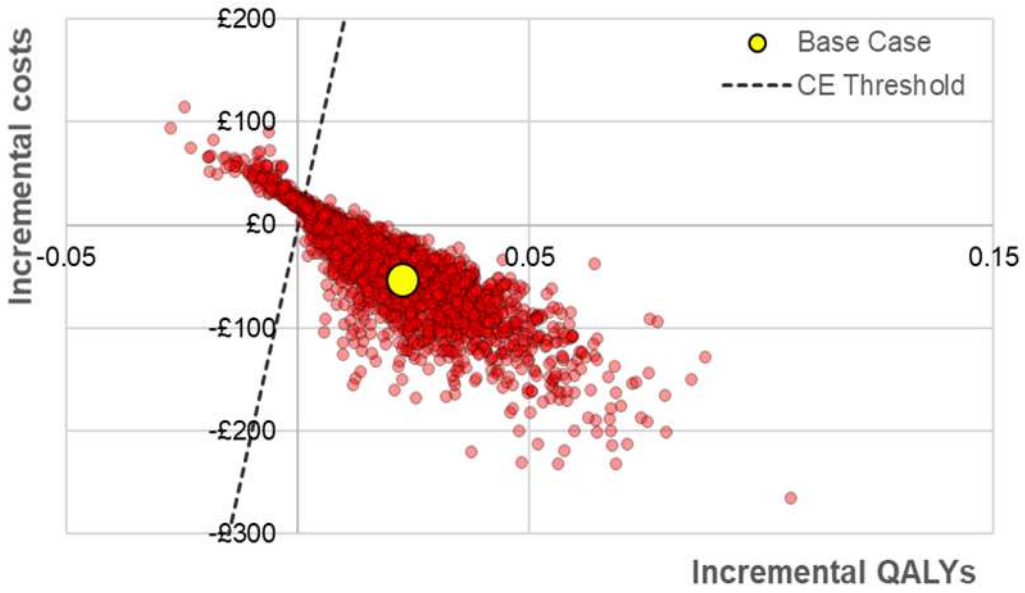
DSA Scenario	DSA Parameter Value	Absolute (LIBS)		Incremental (LIBS vs. usual care)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,553	15.35	-£54	0.02	Dominant
Effectiveness	Lower 95% CI RR (0.98)	£10,647	15.32	£41	-0.01	Dominated
	Upper 95% CI RR (1.19)	£10,448	15.38	-£158	0.05	Dominant
Intervention costs	Increase by 25%	£10,558	15.35	-£48	0.02	Dominant
	Decrease by 25%	£10,547	15.35	-£59	0.02	Dominant
Time horizon	5 years	£1,841	3.75	£5	0.003	£1,522
Relapse rate	Increase to 5% per year	£11,683	15.04	-£18	0.01	Dominant
Discount rate	Costs 5%, QALYs 5%	£8,132	12.54	-£40	0.02	Dominant
	Costs 1.5%, QALYs 1.5%	£16,379	21.48	-£83	0.03	Dominant
Utility	Same QoL for smokers and non-smokers	£10,553	15.45	-£54	0.02	Dominant
Disease costs	Decrease by 25%	£7,920	15.35	-£35	0.02	Dominant
	Increase by 25%	£13,185	15.35	-£73	0.02	Dominant
Disease disutility	Decrease by 25%	£10,553	16.38	-£54	0.01	Dominant
	Increase by 25%	£10,553	14.32	-£54	0.03	Dominant
	Age = 20	£4,768	21.36	-£4	0.01	Dominant

Age of population	Age = 60	£15,819	11.78	-£100	0.03	Dominant

LIBS = Low intensity behavioural support

For the population of unaided abstainers, the PSA identified low intensity behavioural support as being the cost-effective strategy in 92.8% of the 3,000 iterations, with usual care being cost-effective in the remaining 7.2% The results of the PSA are illustrated in Figure 9.

Figure 9: PSA results, low intensity behavioural support vs. usual care (unaided abstainers)



NRT gum

The NICE meta-analysis found that NRT gum was significantly more effective than placebo in a pooled estimate that included 2 studies (RR 1.24, p=0.01) (See Figure 9 NICE evidence review N (9)). In a population of 1,000 unaided abstainers, the relapse prevention model estimated that NRT gum would produce 41 additional continued abstainers at 12-months versus placebo. The cost-effectiveness results found that NRT gum was dominant being associated with a health benefit of 0.04 QALYs and healthcare cost savings of £141. The prescribed treatment costs for NRT gum were very low, being equal to £4, and were exceeded by total cost savings of £146 due to reductions in the number of smoking related morbidities. The intervention had modest incremental personal costs of £4 per person through OTC purchases of NRT gum, but produced £46 of productivity savings due to reduced work absenteeism. A full breakdown of the scenario analysis results for NRT gum is provided in Table 20~~Table 20~~.

Table 20: Cost-effectiveness results (per person): NRT gum, unaided abstainers.

	NRT gum	Placebo	Incremental

Healthcare perspective			
Intervention costs	£4	£0	£4
Comorbidity costs			
Stroke	£5,038	£5,092	-£55
Lung cancer	£1,047	£1,073	-£26
MI	£1,140	£1,159	-£19
CHD	£2,266	£2,277	-£11
COPD	£1,298	£1,322	-£34
Asthma	£15	£15	-£0
Total costs	£10,807	£10,949	-£141
QALYs	15.27	15.22	0.04
ICER			Dominant
Societal outcomes			
Intervention costs (OTC)	£4	£0	£4
Productivity costs (absenteeism)	£885	£932	-£46

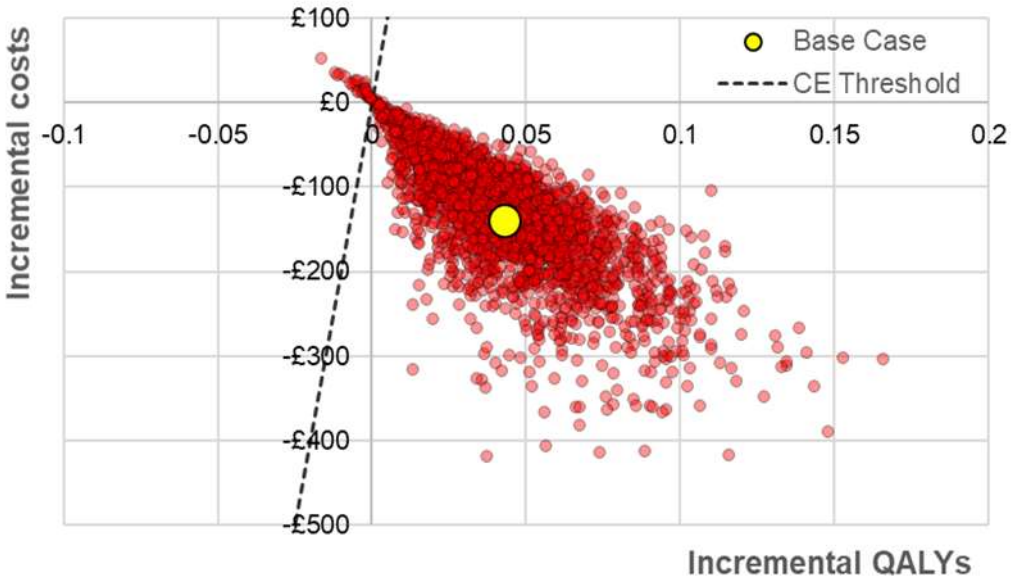
The full DSA results for NRT gum vs. placebo analysis in the scenario analysis for unaided abstainers are provided in Table 21~~Table 21~~. The base case results were robust across all DSAs, with NRT gum remaining dominant versus placebo in each instance. This included the effectiveness scenario applying the 95% lower CI RR, increasing the annual relapse rate to 5%, increasing intervention costs by 25%, and reducing the model time horizon to 5-years.

Table 21: Deterministic sensitivity analysis: NRT gum, unaided abstainers

DSA Scenario	DSA Parameter Value	Absolute (NRT gum)		Incremental (NRT gum vs. placebo)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£10,807	15.27	-£141	0.04	Dominant
Effectiveness	Lower 95% CI RR (1.04)	£10,929	15.23	-£20	0.01	Dominant
	Upper 95% CI RR (1.47)	£10,668	15.31	-£281	0.09	Dominant
Intervention costs	Increase by 25%	£10,808	15.27	-£140	0.04	Dominant
	Decrease by 25%	£10,806	15.27	-£142	0.04	Dominant
Time horizon	5 years	£1,886	3.74	-£29	0.01	Dominant
Relapse rate	Increase to 5% per year	£11,807	15.00	-£72	0.02	Dominant
Discount rate	Costs 5%, QALYs 5%	£8,338	12.48	-£115	0.03	Dominant
	Costs 1.5%, QALYs 1.5%	£16,737	21.35	-£196	0.07	Dominant
Utility	Same QoL for smokers and non-smokers	£10,807	15.38	-£141	0.04	Dominant
Disease costs	Decrease by 25%	£8,107	15.27	-£105	0.04	Dominant
	Increase by 25%	£13,501	15.27	-£178	0.04	Dominant
Disease disutility	Decrease by 25%	£10,807	16.33	-£141	0.03	Dominant
	Increase by 25%	£10,807	14.21	-£141	0.06	Dominant
Age of population	Age = 20	£4,844	21.31	-£46	0.03	Dominant
	Age = 60	£16,240	11.67	-£230	0.06	Dominant

For the population of unaided abstainers, the PSA identified NRT gum as being the cost-effective strategy in 99% of the 3,000 iterations, with placebo being cost-effective in the remaining 1% The results of the PSA are illustrated in Figure 10.

Figure 10: PSA results, NRT gum vs. placebo (unaided abstainers)



Discussion

Key findings

Assisted abstainers

This economic evaluation demonstrated the cost-effectiveness of several smoking relapse prevention interventions. In populations who had achieved assisted smoking abstinence through a smoking cessation intervention, high intensity behavioural support was cost-effective versus usual care. Meanwhile short acting NRT products, bupropion, varenicline, and combination therapy with NRT and bupropion were all cost-effective versus placebo. Low intensity behavioural support was the only intervention that was not cost-effective in this population, as it was no more effective at achieving continued smoking abstinence at 12-months than usual care.

The results of the relapse prevention model were driven by intervention effectiveness which determined the number of smokers and non-smokers in the model and consequently the lifetime health and economic burden of smoking. Across all the base case analyses, if an intervention was effective it was also cost-effective. In the model, populations who relapse to tobacco smoking have an increased risk of stroke, myocardial infarction, lung cancer, coronary heart disease, COPD and asthma throughout the remainder of their lifetime. The total discounted cost and QALYs associated with these smoking related diseases that were avoided by the relapse prevention interventions outweighed the relatively modest upfront intervention costs.

The PSA identified very low levels of uncertainty in the cost-effectiveness results for varenicline and bupropion where, 94% and 98% of PSA iterations were cost-effective versus placebo respectively. In contrast there were high levels of uncertainty in the cost-effectiveness results for NRT short acting, high intensity behavioural support, and combination therapy with NRT and bupropion. The uncertainty was driven directly by uncertainty in intervention effectiveness estimates: The lower 95% CI RR of continued abstinence for NRT short acting, high intensity behavioural support, and combination therapy with NRT and bupropion were all below an RR of 1, i.e. substantially less effective than usual care or placebo.

Two deterministic scenarios were conducted to address key areas of uncertainty in the economic modelling: Firstly, the costs of comparators were set equal to zero in the base case analyses as it was assumed that pharmaceuticals and/or structured behavioural support would not be part of usual care for relapse prevention. This assumption was discussed with the PHAC and NICE team, who generally agreed but raised concerns that comparator costs may not be equal to zero for high intensity behavioural support. When including comparator costs of £21 (equal to the cost of low-intensity support), results for high intensity behavioural support remained consistent with the base case, with the intervention being cost-effective, and with a reduced ICER. Furthermore, the comparator costs had little impact on the PSA results: the probability of cost-effectiveness was 56% in the base case which would have only increased slightly to 60% if £100 costs had been assigned to the comparator[e]. The key driver of the cost-effectiveness results was intervention effectiveness and the comparator costs had substantially less influence.

Secondly, we conducted a deterministic scenario for bupropion due to uncertainty around the effectiveness estimate where in the base case seven out of the nine trial arms informing the intervention effectiveness estimate did not state the length of abstinence since quitting

[e] The impact on the PSA result was estimated by subtracting £100 from the incremental costs for each PSA iteration i.e. the additional cost assigned to the comparator.

smoking. The scenario analysis was conducted for the two studies where abstinence duration had been reported, this being less than 4 weeks. The scenario analysis found that bupropion remained dominant versus placebo. The PSA was associated with slightly more uncertainty than the base case, but the probability of cost-effectiveness for bupropion versus placebo remained high (74%).

Unaided abstainers

In populations who had achieved unaided abstinence, i.e. without formal use of a prescribed smoking cessation intervention, low intensity behavioural support was cost-effective versus usual care, and NRT gum was cost-effective versus placebo. The PSA demonstrated very little uncertainty associated with the cost-effectiveness results for both interventions in this population, both interventions had a probability of cost-effectiveness in excess of 92.5%.

There were no differences in the way the cost-effectiveness analyses were conducted for assisted and unaided abstainers. Consequently, any differences in results between the two populations are directly due to differences in the probabilities of abstinence at 12-months for the interventions and comparators. For both the low intensity behavioural support and NRT analyses, the relative risk of smoking abstinence was less in populations who had initially achieved assisted abstinence than for populations who achieved unaided abstinence. This coincided with a higher probability of continued cessation at 12-months in both control arms (usual care and placebo) for assisted abstainers versus unaided abstainers.

As unaided abstainers are more likely to relapse within 12-months, they have potentially more to gain from the relapse prevention interventions, which might explain why cost-effectiveness outcomes were more favourable in these populations. This may be particularly true for low intensity behavioural support which was not effective or cost-effective for assisted abstainers, but was effective and cost-effective for unaided abstainers.

Length of treatment duration

The evidence from this economic modelling report could be used to directly inform a question of interest raised by the PHAC. That is, is it cost-effective to continue delivering smoking cessation interventions over longer periods than are currently recommended i.e. around 12-weeks. The base case results in this report are directly applicable to this research question as the population included assisted abstainers who by definition had already achieved cessation using a formal cessation intervention. Therefore, each relapse prevention intervention was given in addition to any interventions prescribed for the original quit attempt.

The likely cost-effectiveness of extended treatment durations is clearly demonstrated using the example of varenicline: Effectiveness evidence for varenicline in NICE evidence review N (9) was informed by Tonstad et al. (2006) (19) who report results for an RCT where the population included people who had already been treated with an initial 12-weeks of varenicline for smoking cessation. Consequently, the analysis investigated whether a single course of 12-week varenicline was effective in promoting smoking abstinence versus 12-weeks of varenicline (for cessation) plus an additional 12-weeks of varenicline to prevent smoking relapse. The results from the economic model found that varenicline is cost-effective for relapse prevention. This essentially means that it cost-effective to prescribe 24 weeks of varenicline as opposed to the typical 12-week course for smoking cessation, with the caveat of discontinuing treatment if people don’t achieve cessation after 12-weeks.

Following the same reasoning, our results may suggest that high intensity behavioral support, short acting NRT, bupropion and NRT + bupropion are likely to be cost-effective if

they are delivered over an extended duration in populations who are making a quit attempt. However, these conclusions should be interpreted with some caution, as the populations in the NICE effectiveness review N (9) were grouped as all assisted abstainers. Therefore, populations may have been treated with different interventions for cessation and relapse prevention. Analyses only directly address the research questions related to continued treatment duration for populations who achieved cessation with the same intervention as used for relapse prevention.

Furthermore, the results of the economic modelling do not, establish a maximum cost-effective treatment duration for any of the interventions. To establish the maximum cost-effective treatment duration would require additional evidence on intervention effectiveness versus the next best alternative. For instance, it is possible that varenicline is cost-effective if continued for a third 12-week cycle in people who remain abstinent after 24-weeks (i.e. total 36-weeks). There are reasons why the effectiveness of varenicline may reduce with each treatment cycle. For instance, the absolute probability of relapse decreases the longer a person has successfully quit (2). If varenicline was no more effective at promoting smoking cessation over 36 weeks when compared with 24-weeks, then it could not be considered cost-effective versus the 24-week program as it would incur additional treatment costs whilst achieving the same health outcomes. In addition, in this example it would not be appropriate to compare the 36-week program to the original 12-week program as 12-week varenicline is not the next best alternative.

Comparison with other cost-effectiveness studies

Results from this economic modelling report were comparable to results reported by studies that were included in the NICE cost-effectiveness evidence review (9): Three non-UK based studies in Sweden (Bolin) (37), the USA (38) and Canada (39) found varenicline for relapse prevention to be highly cost-effective versus placebo when using the same effectiveness estimates by Tonstad et al. (2006) (19) as were applied in this analysis; a UK based study Taylor et al. (2011) (40) found bupropion, to dominate usual care, and NRT and varenicline to be highly cost-effective versus usual care both with ICERs less than £2,500; and a USA based study by Ruger et al. (2008) (41) established high intensity behavioural support in the form of motivational interviews were cost-effective versus usual care for preventing relapse in pregnant women.

The results for low-intensity behavioural support differ from the cost-effectiveness results from a UK study by Blyth et al. (2015) (21) who found that a series of eight booklets were cost-effective versus usual care (i.e. a brief leaflet). The reason for the difference in the cost-effectiveness results is due to differences in the underlying effectiveness estimates. Blyth et al. (2015) (21) found the low intensity behavioural support to be slightly more effective than usual care. If this single effectiveness estimate had been used to inform the economic modelling then low intensity behavioural support would have been cost-effective in this analysis. As with the results from our analysis the results from Blyth et al. (2015) (21) were highly uncertain, primary due to uncertainty in the underlying uncertainty and lack of statistical significance in the effectiveness estimate.

A theme across all of the economic modelling results in the smoking relapse prevention literature is that effective interventions are highly cost-effective. As demonstrated in this economic analysis, continued abstinence from smoking reduces the likelihood of smoking related diseases later in life and is subsequently associated with substantial health benefits and cost savings across the lifetime, even after discounting. These benefits typically outweigh the relatively modest costs associated with intervention delivery.

Limitations

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 sub-groups with different risk profiles for example, patients with severe mental illness or with underlying cardiovascular conditions.

The model does not explicitly include additional quit attempts made after the initial relapse prevention intervention. It is possible that people who relapse to smoking would make several quit attempts shortly after a relapse. If a large proportion of the population made successful cessation attempts after relapsing then the model may overstate the health impact of the initial relapse and therefore exaggerate the cost-effectiveness of the relapse prevention interventions.

Similarly, the model does not explicitly model the effects of the interventions on longer term relapse that occurs after the first 12-months, or on repeated relapses that may occur after a person has quit smoking for a second time. If relapse prevention interventions reduce the likelihood of relapse after the initial 12-month intervention period, then the cost-effectiveness of the relapse prevention interventions may have been underestimated.

Whilst neither future quit attempts and future relapses prevented are explicitly modelled, a background 'net' quit rate is incorporated which captures the overall trend of relapse and cessation in the population. The value used in the base case was equal to 2% meaning that on average 2% more of the population would quit smoking than would relapse annually. The cost-effectiveness results were robust when varying this parameter in the deterministic sensitivity analysis. Therefore, it seems unlikely that either future quit attempts or relapse prevented would change the direction of the cost-effectiveness results if they were included in the model, so these limitations are unlikely to impact on the model's conclusions.

Finally, 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 comorbidities 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 preventing a smoking relapse. Given that the conclusion of this report is that effective relapse prevention interventions are highly likely to be cost-effective, or even be more effective and cost-saving, then including these additional benefits would make effective interventions appear more cost effective. This would not alter any of the conclusions presented.

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