National Institute for Health and Care Excellence

Draft for consultation

Tobacco: preventing uptake, promoting quitting and treating dependence

[Q] Economic Modelling Report: Smoking Cessation

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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ISBN:

Table of Contents

List of abbreviations

BNF	British National Formulary
CHD	Coronary heart disease
COPD	Chronic obstructive pulmonary disease
HSCIC	The Health and Social Care Information Centre
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
LC	Lung cancer
LSSS	Local stop smoking services
MI	Myocardial infarction
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net-monetary benefit
NRT	Nicotine replacement therapies
OTC	Over the counter
PHAC	Public Health Advisory Committee
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Risk ratio
UC	Usual care

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, also known as 'heart attack'), stroke, chronic obstructive pulmonary disease (COPD) and asthma. Interventions that promote quitting are usually beneficial to the National Health Service (NHS) because they can decrease the chance of smoking-related diseases, thereby improving health and reducing the associated NHS treatment costs.

We conducted cost-effectiveness modelling to help the Public Health Advisory Committee (PHAC) develop recommendations on smoking cessation guidance. The analysis updated an economic model used in previous NICE guidelines on stop smoking interventions and services. The updated model uses the best available information in order to understand how different smoking cessation interventions might affect the general health of people who would otherwise continue smoking, as well as the impact interventions might have on the costs to the NHS, local authorities and society as a whole.

The analysis evaluated the cost-effectiveness of ten pharmaceutical smoking cessation interventions:

- Nicotine replacement therapy (NRT), either long *or* short acting forms ('NRT l/s')
- NRT, using a combination of long *and* short acting forms ('NRT l&s')
- Bupropion
- Varenicline
- E-cigarettes
- Bupropion *and* NRT l/s
- Bupropion and NRT l&s
- Varenicline *and* NRT l/s
- Varenicline *and* bupropion
- E-cigarettes *and* NRT l/s.

We established whether each intervention was cost-effective compared against 'no intervention' (represented by 'placebo' in the trials). We also established which intervention was cost-effective when compared with each of the other interventions.

We used evidence from NICE reviews to calculate how effective each intervention was in promoting smoking cessation. Specifically, we used evidence from a 'network meta-analysis' (a way of combining results from lots of different trials), which was informed by best available evidence from randomised controlled trials. The evidence was used to determine how many current smokers would quit smoking at 12-months when treated with each of the smoking cessation interventions or placebo.

Once we had calculated the number of smokers and non-smokers at 12-months, the economic model estimated the likelihood that people who did / did not smoke would die or develop a range of health complications, including: lung cancer, coronary heart disease, COPD, heart attack, 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 quit 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 quit smoking.

For each intervention, the overall health benefits in terms of QALYs and NHS treatment costs avoided, were calculated. The lifetime QALYs gained and NHS treatment costs saved were compared with the costs to deliver each intervention. Interventions were considered to be cost-effective if the 'extra cost' per 'extra QALY' was less than £20,000 (this is the predefined value used by NICE).

The results indicated that all of the smoking cessation interventions were cost-effective. The cost-effectiveness analysis found that, when compared with placebo, each intervention increased lifetime QALYs *and* led to NHS savings of a greater value than the upfront intervention costs. When compared with one another, 'bupropion + NRT l&s' was the most cost-effective intervention. Bupropion + NRT l&s had the highest smoking quit rate at 12-months, leading to increased QALYs and reduced NHS costs when compared with all other interventions.

We changed some of the models' key inputs and checked whether the results remained the same. The most important input in the economic model was the intervention's effectiveness. We changed the effectiveness parameters from the average values identified in the NICE evidence, to the value of the highest and lowest plausible values. Even when we used the lowest effectiveness value, all of the interventions remained cost-effective compared with placebo. However, when compared with one-another using the lowest plausible values, 'NRT l&s' was the most cost-effective strategy, not 'bupropion + NRT l&s'.

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 for the model. We found that the probability of each intervention being cost-effective compared with placebo was very high, always being in excess of 99%. In contrast, we found high uncertainty in the cost-effectiveness results comparing each intervention to one another, as 'bupropion + NRT l&s' was only the most cost-effective around 54% of the time, meaning it was not the most cost-effective option in 46% of cases.

Finally, we conducted an analysis to establish the cost-effectiveness specifically for people with mental health problems. We adapted the economic model to include inputs that are most relevant to people with mental health conditions. This analysis was also informed by a separate evidence base, which only included effectiveness estimates from RCTs in populations with mental health problems. In total, the evidence included effectiveness estimates for six interventions:

- Nicotine replacement therapy (NRT) long *or* short form ('NRT l/s')
- Nicotine replacement therapy (NRT) long *and* short form ('NRT l&s')
- Bupropion
- Varenicline
- Bupropion + NRT l/s
- Bupropion + NRT l&s

The subgroup analysis results found that all interventions were cost-effective versus placebo. For the mental health subgroup bupropion + NRT l/s was found to be the cost-effective strategy when comparing each intervention to one another (which differed from the base case where bupropion + NRT l&s was most cost-effective).

As with any cost-effectiveness analysis, there were some factors that could be challenged, or alternative approaches that could have been taken. We were not able to account for patient choice within the effectiveness estimates, so it is not clear whether the effectiveness

estimates from the trials used for the evidence base would be applicable to the real-world setting.

We also left several factors out of our analysis (for example due to being unable to find suitable evidence). 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. If we had included additional factors such as the additional smoking-related conditions, the effects of passive smoking, or the impact of smoking on social care needs, the benefits attached to quitting smoking would have been greater still and reinforced the original findings from the economic model. That is, that effective interventions are almost always also cost-effective.

Introduction

Background

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

An estimated 16% (77,800) of all deaths in 2017 were attributed to smoking (2). Treating smoking-related illness is estimated to cost the National Health Service (NHS) at least £2 billion per year (3). In order to reduce the number of smokers and smoking- related illness, the NHS and Local Authorities provides services to assist smokers who wish to quit outright and smokers who wish to reduce their level of tobacco use. A wide range of interventions are available through local stop smoking services (LSSS) including individual and group behavioural support, pharmacological products and a variety of nicotine replacement therapies (NRT).

In addition, many interventions to help people quit smoking or reduce tobacco harm can be privately purchased over the counter (OTC) including NRT and electronic cigarettes (e-cigarettes). There are some concerns regarding the population impact of some OTC products, particularly e-cigarettes about which the long-term health impacts are unknown, and some argue that they may act as a gateway to tobacco uptake in non-smokers. There is also concern that the increased popularity of e-cigarettes may have been responsible for the decline in the use smoking treatments and services available through LSSS (4). Smokers who use OTC e-cigarettes instead of prescribed smoking cessation aids may have less frequent contact with healthcare professionals which could reduce their engagement with other important non-pharmaceutical interventions offered by LSSS.

Effective and cost-effective interventions are offered by LSSS. Previous work commissioned by NICE has shown that many interventions can be considered cost-effective (Public Health Guidance (NG92)). Previous tobacco committees have taken care to distinguish between smoking cessation interventions and the LSSS who provide them. For instance, the analyses take account of the costs of treatment plus adviser time only and do not include the full cost of providing a LSSS for example costs associated with managers and premises.

The current tobacco guideline will update and amalgamate the following existing NICE guidelines:

- smoking: workplace interventions (PH5)
- smoking: preventing uptake in children and young people (PH14)
- smoking prevention in schools (PH23)
- smoking: stopping in pregnancy and after childbirth (PH26)
- smokeless tobacco: South Asian communities (PH39)
- smoking: harm reduction (PH45)
- smoking: acute, maternity and mental health services (PH48)

- stop smoking interventions and services (NG92)

In addition, the NICE scope includes the development of new guidelines on smoking relapse prevention.

The aim of NICE's work is to bring together all the above guidelines, and review new questions for example on relapse prevention and the efficacy of e-cigarettes, to form a single coherent set of guidance. For the purposes of the NICE scope, the information is presented under the headings 'preventing uptake' and 'treating tobacco dependence'. These distinctions are not intended to reflect the structure of the final published guidance, but to organise and provide an overview of what evidence will be updated. NICE's existing recommendations on promoting quitting will also appear in the final guidance. But because the evidence on these recommendations will not be reviewed, promoting quitting is not covered in this scope.

Whilst the current project conducts economic modelling to inform NICE's new tobacco guidelines on preventing update, promoting quitting and treating dependence, this report will focus only on smoking cessation. The PHAC prioritised items in the NICE scope for further economic analysis by determining whether more recent evidence was available since the last guidance or if economic modelling had previously not been conducted. The outcomes from the economic modelling will help to inform the Committee's guidance decisions.

Objectives

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

Smoking cessation and harm reduction:

- What are the most effective and cost-effective means of smoking[a] cessation (including e-cigarettes[b])?
- Are e-cigarettes effective and cost-effective for smoking harm reduction?

Modelling Approach

This analysis updated an existing economic model which was previously used to inform NICE NG92 guidelines on smoking cessation. Updates to the NG92 were limited to parameter values including intervention costs, resource usage, and effectiveness in terms of smoking abstinence. The cessation interventions included in the economic model were informed by effectiveness evidence in NICE evidence review K (5). Specifically this was a network meta-analysis originally conducted by Thomas et al. (2020) (6), amended according to committee requirements and updated by NICE. Formal economic modelling was not possible for research questions related to smoking harm reduction as no relevant evidence was identified in NICE effectiveness reviews regarding the impact of e-cigarettes on smoking harm reduction.

[a] Throughout, smoking refers to the use of all smoked tobacco products.
[b] E-cigarettes refer here to any type of e-cigarette which contains nicotine

Methods

Overview

This section summarises the economic modelling that was conducted to inform research questions related to smoking cessation and harm reduction.

Review question 1:

- What are the most effective and cost-effective means of smoking cessation (including e-cigarettes)?

The smoking cessation interventions included in the economic modelling were obtained from NICE evidence review K (5). Specifically, these were the interventions informing the updated network meta-analysis (NMA) (Thomas et al. (2020) (6)). The version of Thomas (2020) that was considered by the NICE guideline committee was based on a draft version of the manuscript dated July 2019. That version is yet to undergo a full peer and editorial review process in line with the NIHR Journals Library Policy. The interventions included in the NMA by Thomas et al. (2020) (6), were grouped into following classes based on committee discussion:

- Long-acting or short-acting NRT: use of either long- or short-acting NRT. Long-acting NRT is made up of patches. Short-acting NRT is made up of gum, nasal spray, mouth spray, lozenge, sublingual tablet or inhalator
- Long-acting and short-acting NRT: contemporaneous use of long- and short-acting modes of NRT in one treatment period
- Varenicline: a single intervention class, as NICE guideline recommendations do not differentiate by dosage and instead cross refer readers to the BNF for this information (7)
- Bupropion: a single intervention class, as NICE guideline recommendations do not differentiate by dosage and instead cross refer readers to the BNF on this information (7)
- E-cigarettes: any e-cigarette device which includes nicotine
- Combination treatments:
- Combinations of two or more included interventions were also eligible (for example, e-cigarettes + NRT long/short). Not every possible combination appears in the results, as some were not investigated by any studies.
- Placebo: placebo version of the active intervention
- No drug treatment: arms where no intervention was given, or arms with counselling or behavioural intervention only
- Waitlist: participants waiting for treatment
- Usual care: as described by the paper. This could be various treatments dependent on what the usual care in the context involves and so will encompass a range of care.

The interventions included in the economic modelling are listed below. These included all pharmaceutical smoking cessation aids within the intervention classes identified by the PHAC (i.e. all non-control categories) and for which effectiveness evidence was available.

1. NRT[c] monotherapy long *or* short acting (NRT l/s)
2. NRT combination of long *and* short acting (NRT l&s)
3. Bupropion
4. Varenicline
5. E-cigarettes
6. Bupropion + NRT l/s
7. Bupropion + NRT l&s
8. Varenicline + NRT l/s
9. Varenicline + Bupropion
10. E-cigarettes + NRT l/s

As informed by the NICE scope, this analysis aimed to identify the most cost-effective cessation intervention across ten intervention classes selected by the committee, including e-cigarettes. The PHAC were mindful of the need to take account of smoker's previous preferences and experience with products. For instance, one of the aims of the initial interaction with patients is to determine what is the most appropriate treatment at that time for each individual.

Whilst the objective of the NICE scope was to establish the most cost-effective intervention, the PHAC also wished to consider the cost-effectiveness of each intervention class versus a relevant comparator. Consequently, placebo was added as an eleventh intervention to the base case incremental cost-effectiveness analysis. The inclusion of placebo as an intervention was not expected to impact on the cost-effectiveness results between each of the other interventions: intervention effectiveness was obtained from a network meta-analysis (NMA) conducted by NICE (5), which included placebo as a comparator. Consequently, relative effectiveness for any intervention versus any other intervention would remain consistent whether placebo was included as part of the comparison or not [d]. A scenario analysis was conducted which excluded placebo to demonstrate the validity of this logical assumption.

It was assumed that both the intervention arms and placebo would be eligible to receive behavioural support. This assumption was based on the RCTs which informed the effectiveness estimates, where the majority of studies included some form of behavioural support as part of both the intervention and comparator. There was, however, some heterogeneity between the studies informing the effectiveness estimates: The type of behavioural support was consistent within studies (i.e. for the intervention and comparator), but differed between different studies. There were also a minority of studies that did not include behavioural support in either the intervention arm or the comparator.

The economic analysis was conducted in a UK setting, where individual and/or group behavioural support behavioural support may be offered through LSSS.

The economic analysis established the cost-effective means of smoking cessation across the ten intervention classes and placebo by updating an economic model that was previously developed to inform NICE NG92 guidelines (8). The original NG92 model is a cohort model

[c] Any NRT product available in the UK through LSSS or OTC. Long acting NRT includes patches; short acting NRT includes gum, lozenge, inhalators and spray.

[d] For example: The relative risk (RR) for varenicline vs NRT l/s = 1.24. The RR for NRT l/s vs placebo = 1.83 and the RR for varenicline vs placebo = 2.27. (NICE evidence review K, see Table 20).
These results are internally consistent where:
(RR for varenicline vs. placebo)/ (RR for NRT l/s vs. placebo) = RR for NRT l/s vs varenicline
2.27/1.83 = 1.24
The introduction of placebo does not have an impact on the comparison of varenicline versus NRT l/s as the effectiveness estimates remain consistent for scenarios which include or exclude placebo.

that was developed in line with the NICE methods manual (9). The model was developed from a public sector perspective which allows intervention costs to be categorised as falling on the NHS, the Local Authority or a combination of the two. The model also includes productivity costs and private costs which fall outside of the public sector and can be reported within the model or as separate outcomes. The model allows for various time horizons to be reported and incorporates a lifetime time horizon in order to capture all relevant costs and benefits. Discount rates of 3.5% for both costs and benefits are applied as stipulated in the NICE methods manual (9).

Consequently, the model facilitates the comparison of multiple interventions, where data allow. To establish the most cost-effective intervention we conducted a fully incremental analysis. Each strategy was ranked from least costly to most costly. We then excluded dominated (costlier and less effective) and extendedly dominated interventions (higher incremental cost-effectiveness ratio (ICER) than that of a more effective intervention). The cost-effective intervention was that with the largest ICER below the £20,000 threshold amongst the remaining non-dominated or extendedly dominated interventions.

For illustrative purposes we also calculated the incremental net-monetary benefit (NMB), which allowed us to rank the cost-effectiveness of each intervention.

Net monetary benefit is a summary statistic that represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit, for example a quality adjusted life year (QALY), is known. The use of NMB scales both health outcomes and use of resources to costs, meaning comparisons without the use of ratios (such as in ICERs) can be made. This analysis monetised QALYs within the model by applying a threshold equal to £20,000 per QALY, in line with recommendations by NICE (9). An incremental NMB greater than zero indicates that the intervention is cost-effective, and larger incremental NMBs indicate interventions are cost-effective vs. other interventions.

The updated economic model calculated the cost-effective cessation intervention by ranking each intervention by its incremental NMB vs. placebo. Placebo was selected as the reference comparator based on the PHAC's discussion who wished to consider the cost-effectiveness of each intervention versus each other and versus placebo.

The incremental NMB formula is as follows:

Incremental NMB = (incremental benefit x threshold) – incremental cost

Review question 2:

- Are e-cigarettes effective and cost-effective for smoking harm reduction?

NICE evidence review K (5) did not identify evidence which established effectiveness of e-cigarettes on reducing smoking harm reduction. Consequently, the PHAC agreed formal economic modelling was not appropriate for this research question.

Model Structure

The updated economic model used the same structure as was developed in the original NG92 model (8), considering long-term epidemiological data in order to capture the lifetime complications associated with six long-term smoking-related illnesses (Figure 1~~Figure 1~~). A similar model structure has been used in past cost-effectiveness models for smoking interventions (PHG10, PHG45, Taylor *et al.* 2011 (10)).

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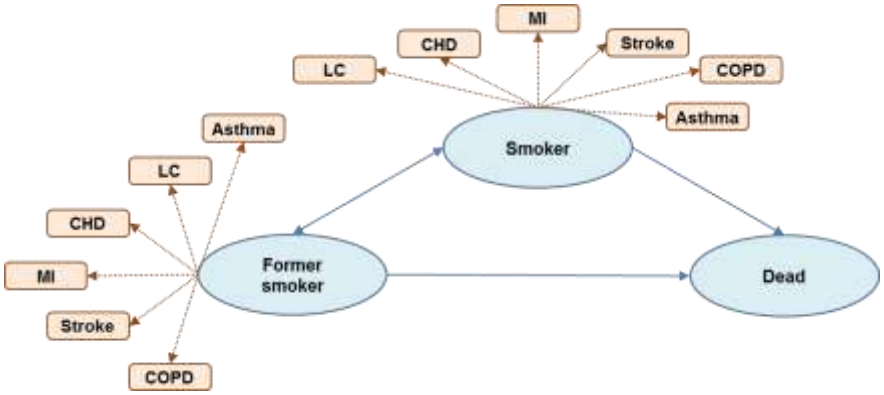
Figure 1: Model structure



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

The Markov model includes annual cycles where smokers have a probability of quitting (and becoming 'former smokers') and former smokers have a probability of relapsing. People from either the 'smoker' or 'former smoker' health state can move to the 'dead' health state. The model doesn't include benefits for tobacco harm reduction. Additional health states would need to be required to model harm reduction, for example previous NICE guidelines on harm reduction (PH45) were informed by an economic analysis which included a health state for "low level" smokers (11). Effectiveness estimates were provided for this analysis by NICE, in terms of the total number of people who quit, not in terms of the number of people who reduced smoking. Therefore, we considered the addition of a specific "low level" smoking health state unnecessary as it would not likely have influenced the cost-effectiveness results for the smoking cessation interventions in this analysis.

The major public health benefit of smoking cessation is a reduction in the health burden and costs of treating long-term comorbidities. Whilst smoking is related to a multitude of health problems, the model is limited to including the following five long-term comorbidities:

- Lung cancer (LC)
- Coronary heart disease (CHD)
- COPD
- Myocardial infarction (MI)
- Stroke

In addition, smokers and former smokers have a probability of experiencing an acute asthma exacerbation. The economic model wasn't updated to include any additional smoking related comorbidities. The inclusion of extra comorbidities would introduce additional healthcare costs and health detriments for smokers. This would likely have a minimal impact on the overall results as interventions that were already cost-effective appear would appear even more favourable.

The prevalence of the five long-term comorbidities by age and smoking status is used to calculate the number of people in each health state and in each annual cycle, who develop one of these diseases.

The model estimates the costs and utilities for each comorbidity using a prevalence based rather than incidence-based approach. An incidence-based model would only be able to model mortality impacts for the comorbidities in the model. A prevalence-based approach allows *all* mortality for smokers vs. non-smokers to be modelled, which includes all comorbidities, even if these are not modelled separately. The incidence of asthma exacerbations is used to calculate the number of people by age and smoking status that develop this acute condition. Based on the available evidence, incidence was used for asthma rather than prevalence. This meant that the model did not include the effects of smoking on asthma related mortality. We did not consider this to be a major limitation due to the relatively low number of asthma related deaths (estimated at around 1,200 per year in the UK population (12)), many of which occur during childhood before people take up smoking.

Throughout the model each health state has a utility value associated with it. Each comorbidity has an associated cost and disutility associated with the disease occurring. These costs and utilities are applied during each annual cycle and summed to estimate lifetime costs and QALYs across all cycles.

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. Age 12 was selected as this was assumed to be the earliest age that someone would take up smoking. 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 population, obtained from 2019 ONS UK population estimates (13). 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.

Model Inputs

This section outlines the model inputs that have been used to populate the economic model and also highlights any area in which there are data gaps. Where required targeted searches were carried out to identify new data to update parameter values in the existing NG92 model. Numerous parameters remained the same as in the original model, since either the same source was found, or no better or more recent source was found.

Effectiveness

Intervention effectiveness was sourced from NICE evidence review K (5) which updated an NMA by Thomas et al. (2020) (6). The NMA established the relative effectiveness of the smoking cessation interventions at up to 6-months post intervention delivery. NICE updated the NMA by conducting a review to establish the relative effectiveness of e-cigarettes at up to 6-months post intervention. The NMA by Thomas et al. (2020) (6) was then updated by NICE to establish the relative effectiveness for intervention classes selected by the committee, including new evidence for e-cigarettes.

The effectiveness estimates from the updated NMA used in the economic model were the relative risks (RR) of smoking abstinence at 6-months. As previously mentioned, the PHAC were interested in comparing the cost-effectiveness of each intervention versus one another

and versus a comparator, and therefore the incremental economic analysis included placebo as an intervention option. We selected placebo as the comparator rather than usual care, waitlist and no drug treatment which were included as additional comparators in the NMA.

Placebo was selected as the comparator for the analysis as firstly, it was one of the most numerous treatment options (i.e. there was a very large number of people given placebo across all RCTs relative to the other comparator options). For instance, placebo control was used in 142 study arms included in the NMA, compared with 12 studies for usual care, 38 studies for no drug treatment, and 3 studies for waitlist control (see Table 19, NICE evidence review K (5)). Secondly, the comparison with placebo was considered most consistent across studies included in the NMA. For example, the definition of usual care varied across studies and could be various treatments and encompass a range of care dependent on what the usual care context involves.

The majority of RCTs informing the NMA (180 out of 189) included behavioural support in both intervention and control arms. The type of behavioural support offered was consistent within trials (i.e. equivalent for placebo and intervention arms), but was not consistent across RCTs.

The economic model included the effectiveness estimates from the NMA by converting the risk ratio (RR) to absolute probabilities of smoking cessation at 6-months. This was done by multiplying the RR for each intervention vs. placebo by the absolute probability of smoking cessation at 6-months for the placebo arm. We estimated the absolute probability of smoking cessation for placebo by summing the total number of events (quitters) across all placebo arms of the RCTs included in the updated NMA and dividing by the total number of participants in the placebo arms. We obtained the number of events and trial participants in the placebo arms from forest plots in NICE evidence review K (Figure 1, 6, 9, 13, 18 and 21) (5). This resulted in an overall probability equal to 11.49% (3,232/ 28,139).

Due to the inconsistency in the type of behavioural support offered as part of the placebo arm across trials, we conducted a deterministic sensitivity analysis where the probability of smoking abstinence for placebo at 6-months was changed by an absolute value of 1.73% (equal to 15% of the mean value). This resulted in a lower estimate for the probability of abstinence in placebo equal to 9.77% and an upper estimate equal to 13.22%. This is considerably more variation around the point estimate than indicated by statistical tests where the value of the lower and upper 95% confidence interval is 11.12% and 11.86% respectively.

To be consistent with the annual cycle lengths included in the economic model, probabilities of smoking cessation at 6-months were converted to probabilities of smoking cessation at 12-months, accounting for smoking relapse between these two time points. Long term relapse curves were used to adjust probabilities providing quit rate at one year. The relapse curve that was used in this model was reported by Coleman *et al.* (2010) (14) in a Health Technology Assessment report (Figure 2~~Figure 2~~). The Health Technology Assessment (HTA) report is used to calculate the percentage of remaining quitters from various time points to one year (e.g. the HTA reported showed that at six months 30.6% had quit, at one year 26.2% had quit). The percentage of remaining quitters was calculated (26.2/30.6=85.6%) and applied to the study data. The relapse curve was based on pooling 16 trials of NRT, bupropion and varenicline. It is noted here that the relapse curve may take a different shape when alternative interventions are used, or within certain subgroups. The potential impact of intervention specific relapse rates was explored within a deterministic sensitivity analysis by varying quit rate probabilities at 12-months.

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Relapse after 12-months was included as part of the natural rate of smoking cessation that was applied in the model. The rate was set equal to 2%, and incorporates both the expected number of people who quit smoking and relapse from smoking annually.

All RRs were obtained from the NMA results in Table 20 of NICE evidence review K (5). The RRs and absolute probabilities of quitting at 6-months and 12-months are outlined in Table 1~~Table 1~~.

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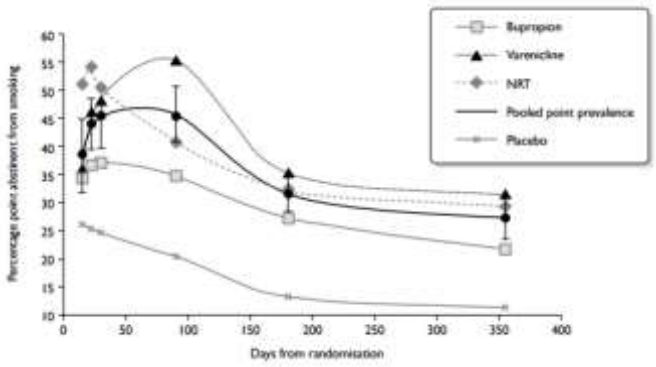
Table 1: Intervention effectiveness

Intervention	RR of abstinence vs. placebo @ 6-months mean (95% CI)	P (quit) 6-months	P (quit) 12-months
Placebo	N/A	11.49%	9.84%
NRT l/s	1.83 (1.67, 2.01)	21.03%	18.00%
NRT l&s	2.71 (2.10, 3.40)	31.14%	26.66%
Bupropion	1.73 (1.52, 1.95)	19.88%	17.02%
Varenicline	2.27 (2.01, 2.55)	26.08%	22.33%
E-cigarettes	2.25 (1.33, 3.58)	25.85%	22.14%
Bupropion & NRT l/s	1.93 (1.50, 2.46)	22.18%	18.99%
Bupropion & NRT l&s	3.51 (1.77, 5.59)	40.33%	34.53%
Varenicline & NRT l/s	2.58 (1.68, 3.70)	29.64%	25.38%
Varenicline & Bupropion	2.75 (1.73, 4.05)	31.60%	27.05%
E-cigarettes & NRT l/s	2.93 (1.52, 4.80)	33.67%	28.82%

Figure 2: Relapse rate from Coleman *et al.* (2010) (14)



Intervention Costs

Behavioural support

The cost of behavioural support was applied equally to both the placebo arms and each intervention arm. This was because the majority of studies informing the NICE NMA included some form of behavioural support in both the intervention and placebo arms. The cost of behavioural support was obtained from a cost-effectiveness study by Li et al. (2020) (15) who estimated mean costs for UK LSSS behavioural support used by participants in addition to their randomly assigned pharmacotherapy (e-cigarettes or NRT). The study by Li et al. (2020) was used as an approximate cost for behavioural support. Due to the number of studies and the variety of behavioural support it was not possible to obtain a precise cost for amongst all participants in the RCTs informing the NICE NMA. The study by Lie et al. (2020) was selected as it was the most recent UK based study with costing information available.

Li et al. (2020) reported that all participants were offered six weekly behavioural support sessions at their LSSS as is standard practice. Across both trial arms participants received a mean of 5.35 behavioural support sessions with mean durations for sessions 1-2 equal to 30 minutes, and all subsequent sessions lasting 20 minutes. The unit costs were equal to £17 per 30-minute session. We calculated the mean cost per person of behavioural support over the 6-month intervention period as equal to £78.49, this being a weighted average based on the reported costs of £80 per person in the e-cigarette arm, and £77 per person in the NRT arm. The cost was uprated to 2019/20 prices using the NHSCII pay and prices index (PSSRU 2019), equalling £82.96. It is noted that Li et al. (2020) did not report costs of NHS helpline telephone helpline support, it is assumed the cost of telephone support is negligible.

The cost of behavioural support (£82.96) was applied to placebo and also added to the cost of each of the pharmaceutical intervention classes listed below.

NRT l/s

The PHAC were interested in establishing the effectiveness and cost-effectiveness for a broad classification of NRT products which were grouped to include long acting patches and short acting: gums, lozenges, sprays and inhalators. Each NRT product was also assumed to be available across a range of strengths and types. For example, both 24-hour and 16-hour NRT patches are available at high (21mg), medium (14mg) and low (7mg) strengths, meanwhile short acting gums and lozenges could include 4mg, 2mg, 1.5m doses (7).

The mean cost per NRT product (e.g. patch, gum lozenge) was calculated as a weighted average of costs across each type and strength available. The weighting reflected the percentage of people who were expected to use each type (and strength) of NRT product. These percentages were calculated using data in the NHS Prescription Cost Analysis (2018) (16) which reports the total number of NRT products and quantity of active ingredient (nicotine) prescribed in England during 2018.

In addition, we assumed NRT products could be obtained either via prescription of privately OTC. Therefore, mean intervention public sector costs for NRT were calculated by applying a percentage purchased via prescription and percentage purchased OTC. Percentages were obtained from an RCT by Hajek et al. (2019) (17) who reported that 48% of participants allocated to a broad category NRT intervention arm obtained products through prescription, whereas 52% obtained NRT products OTC (17). Only prescription costs were included as intervention costs, with private costs (the 52% of OTC purchases) included separately in the

economic model results (see Table 4 for full description). The unit costs and assumed resource use for each NRT product was calculated as reported in Table 2~~Table 2~~.

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Table 2: NRT costs (NHS)

Intervention	Total cost	Components	Unit Costs (per dose)	Source
NRT Patch	£54.84	High strength patch (21mg) daily for 7 weeks, followed by medium strength patch (14mg) for 2 weeks and low strength patch (7mg) for the final 2 weeks. Prescription cost analysis data indicates 24hr patch used by 50.60% of, with the remaining 49.4% using a 16hr patch.	21 mg/24hr =£1.42 14mg/24hr=£1.34 7mg/24hr=£1.30 25 mg/16hr =£1.59 15mg/16hr=£1.59 10mg/16hr=£1.57	Drug costs and dosage (BNF online 2020) (7) % patch use (Prescription Cost Analysis 2018) (16)
NRT Lozenge	£26.93	Ad lib** administration when cravings occur assumed equal to 9 lozenges per day for first six weeks, 5 lozenges per day during weeks 7-9 and 3 lozenges per day during weeks 10-12. Prescription cost analysis data indicates 4mg lozenge used in 36.81% 2mg in 45.07% and 1.5mg in 18.11%.	1.5mg=£0.18 2mg=£0.10 4mg=£0.10	Dosage (Schnoll, 2010) (18) Drug costs (BNF online 2020) (7) Strength (Prescription Cost Analysis 2018) (16)
NRT Gum	£47.89	Ad lib** administration when cravings occur assumed equal to 12 gums per day (1.5 per hour for 16 waking hours) Prescription cost analysis data indicates 4mg gum used in 45.00% and 2mg in 55.00%.	2mg=£0.09 4mg=£0.11	Drug costs and dosage (BNF online 2020) (7) % patch use (Prescription Cost Analysis 2018) (16)
NRT Spray	£50.63	Ad lib** administration when cravings occur assumed equal to 11.1 doses per day (1mg per dose). Prescription cost analysis data indicates nasal spray used in 22.41%, oral spray in 77.59%.	Nasal spray 10mg/ml=£0.16 Oral spray =£0.10	Drug costs (BNF online 2020) (7) Dosage (Rey, 2009)(19) Type (Prescription Cost Analysis 2018) (16)

NRT Inhalator	£63.71	Ad lib** administration when cravings occur assumed equal to 2 cartridges per day (i.e. 30mg nicotine)	15mg = £0.79	Drug costs and dosage (BNF online 2020) (7)

*48% of NRT was assumed to be purchased by prescription with 52% private OTC (Hajek et al. (2019) (17). The costs in the table reflect expected mean NHS costs per person receiving NRT. Mean NHS costs were calculated as total NRT costs for full dose multiplied by 48%.

**Ad lib administration assumed to occur for 12-week period unless otherwise stated.

The mean cost of the NRT I/s classification was calculated by estimating the percentage of people who were expected to use each NRT product (e.g. patch, gum lozenge). These percentages were calculated using data in the NHS Prescription Cost Analysis (2018) (16) which reports the total number of NRT products and quantity of active ingredient (nicotine) prescribed in England during 2018. The following weightings were applied per product to calculate total costs for the NRT I/s classification: NRT patch (23.5%), NRT Lozenge (17.74%), NRT gum (31.48%), NRT Spray (10.15%), NRT Inhalator (17.27%). The unit costs per each NRT product were applied as reported in Table 2~~Table 2~~: NRT patch (£54.84), NRT Lozenge (£26.93), NRT gum (£47.89), NRT Spray (£50.63), NRT Inhalator (£63.71).

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The total cost of NRT I/s when limited to the 48% expected to purchase NRT via prescription was £48.88. The total cost of NRT I/s plus behavioural support was £131.84.

NRT I&s

The cost of NRT I&s was calculated using unit costs per NRT product as previously reported in Table 2~~Table 2~~. Similar to the NRT I/s classification, costs for the NRT I&s classification were calculated as a weighted average across NRT products. It was not possible to identify the proportion of combination therapy from the NHS Prescription Cost Analysis (2018) (16) as this only reports the quantities per individual prescription. Therefore, weightings were calculated by summing the total number of study participants who received each NRT I&s combination therapy across the RCTs informing the updated NICE NMA. All strategies included long acting patches, in combination with short acting sprays (25.45%), gums (50.72%) or inhalators (5.74%). The remaining 18.09% received patches with "any" short acting NRT product. Unit costs for "any" short acting NRT were established as previously described for the NRT I/s category (Table 2~~Table 2~~), but did not include long acting patches within the weighting.

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The costs of NRT I&s limited to the 48% who were expected to purchase NRT products via prescription were £104.17. The total cost of NRT I&s plus behavioural support was £187.13.

Varenicline

The cost of varenicline was calculated using NHS drug tariffs and doses recommended by the British National Formulary (BNF, 2020) (7). This included a total of 12 weeks' treatment comprising of 500 microgram tablets taken once daily for 3 days, increased to 500 microgram tablets twice daily for 4 days, and 1mg tablets taken twice daily for 11 weeks.

The total cost of varenicline was £160.88. The cost of varenicline plus behavioural support was £243.84.

Bupropion

The cost of bupropion was calculated using NHS drug tariffs and doses recommended by the British National Formulary (BNF, 2020) (7). This included a total of 8 weeks' treatment

comprising of 150mg once daily for 1 week, increased to 150mg twice daily for 7 weeks. The dose and duration of bupropion varied across the studies included in the NICE NMA. Due to the number of studies in the NMA, it was not possible to estimate costs based on specific dosages applied in each study. Therefore, the doses and durations recommended by the BNF were used to inform the base case costs and reflect the typical dosage for bupropion across studies in the NMA. The impact of applying different dosages for bupropion was investigated in a scenario analysis which doubled the intervention costs.

The total cost of bupropion was £44.10. The total cost of bupropion plus behavioural support was £127.06.

E-cigarettes

E-cigarettes are not currently licenced by the NHS and, therefore, all costs in the base case analysis were assumed to be private (i.e. NHS or local authority costs = £0.00). A scenario analysis was conducted to establish cost-effectiveness of e-cigarettes if they were licenced and funded by the NHS. The cost of e-cigarettes was equal to £35.81 per person and was obtained from a cost-effectiveness of an RCT by Li et al. (2020) (15), who established the cost-effectiveness of e-cigarettes assuming starter pack products received NHS licence. The study by Li et al. (2020) (15) included costs for one e-cigarette starter pack per person, an additional starter pack provided to 10.6% of people due to breakages, and extra refill bottles for 7.57% of people [10ml bottle= £1.42]. Costs also included further e-cigarette supplies (e.g. e-liquid refills), based on the number of OTC purchases reported by study participants.

The total costs per e-cigarette user are higher in this analysis than reported by Li et al. (2020) as participants in the RCT received old e-cigarette starter packs which are no longer available. Li et al. (2020) report the costs of a more up to date e-cigarette starter pack (One Kit, 2016), which after uprating was equal to £35.81. After uprating, the total cost of the e-cigarette refills was equal to £80.33.

The total NHS cost of e-cigarettes was therefore £116.14 in private purchases OTC. The cost of the intervention to LSSS was £82.96, which only included the cost of behavioural support.

The total NHS cost of e-cigarettes plus behavioural support for a scenario where e-cigarettes receive an NHS licence was £138.71, assuming that 52% of e-cigarette purchases would be OTC, in line with estimates for NRT products.

Combination therapies

All combination therapies were assumed to incur the sum of costs for each of the included pharmacotherapies. A single cost of behavioural support was then added to the summed cost of the combination therapy.

The total costs of each combination therapy in addition to behavioural support were as follows: bupropion + NRT l/s £175.94; bupropion + NRT l&s £231.23; varenicline + NRT l/s £292.74; varenicline + bupropion £287.94; E-cigarettes + NRT l/s £131.84.

The total cost of each of the included interventions, the components used to calculate the costs and the sources are summarised in Table 3~~Table 3~~.

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Table 3: Intervention costs (NHS)

Intervention	Total cost	Components	Unit Costs (per dose)	Source
Behavioural support (applies to placebo *and* all other interventions)	£82.96	Total of 5.35 behavioural support sessions through LSSS. Sessions 1-2 assumed to last 30 minutes, with all subsequent sessions lasting 20 minutes. Total session number derived as a weighted mean trial arm.	N/A	Li et al (2020) (15)
NRT l/s*	£48.88	Weighted average: NRT patch (23.5%), NRT Lozenge (17.74%), NRT gum (31.48%), NRT Spray (10.15%), NRT Inhalator (17.27%)	NRT patch=£54.84 NRT lozenge=£26.93 NRT gum=£47.89 NRT spray=£50.63 NRT inhalator=£63.71	Weightings: Prescription Cost Analysis (2018) (16) Unit costs: Table 2
NRT l&s*	£104.17	100% receive long acting NRT patch plus a weighted average cost across short acting NRT. Weightings for short acting NRT= gum (25.45%), spray (50.72%), any (18.09%), inhalator (5.74%).	NRT patch=£54.84 NRT gum=£47.89 NRT spray=£50.63 NRT inhalator=£63.71 NRT any short acting=£43.56	Weightings: Updated NICE NMA (5) Unit costs: Table 2
Varenicline	£160.88	500 micrograms take once daily for 3 days, 500 micrograms twice daily for 4 days, and 1mg twice daily for 11 weeks.	£0.98 [for both 500 microgram & 1mg]	Drug costs and dosage (BNF online 2020) (7)
Bupropion	£44.10	150mg daily for 1 week, then 150mg twice daily for 8 weeks	£0.70	(BNF online 2020) (7)
E-cigarettes	£0.00	E-cigarettes are not currently licenced by the NHS and therefore all costs are assumed to be incurred OTC for the base case analysis.		
Bupropion & NRT l/s*	£92.98	Cost of bupropion plus cost of NRT l/s.		
Bupropion & NRT l&s*	£148.27	Cost of bupropion plus cost of NRT l&s.		
Varenicline & NRT l/s*	£209.76	Cost of varenicline plus cost of NRT l/s.		
Varenicline & Bupropion	£204.98	Cost of varenicline plus cost of bupropion.		
E-cigarettes & NRT l/s*	£48.88	Cost of e-cigarettes plus cost of NRT l/s.		

Private costs

Intervention costs were also assigned for private purchases of e-cigarettes which are not currently provided by NHS, and for NRT products available OTC.

For the base case analysis, the private cost of e-cigarettes included all costs previously reported for e-cigarettes obtained from Li et al. (2020) (15), that is a cost per person equal to £35.81 including starter packs and extra refill bottles. For the scenario analysis 48% of costs were assumed to incurred via prescription, whilst 52% were purchased OTC.

The private costs of NRT included costs for the 52% of NRT products purchased OTC, the % being informed by the study by Hajek et al. (2019) (17). As there was no information on dose and type of NRT purchased OTC, it was assumed prescribed and private unit costs would be equivalent. Therefore, all costing was as described previously for each NRT intervention classification in Table 3~~Table 3~~.

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The private costs for each intervention are reported in Table 4

Table 4: Private costs (OTC)

Intervention	Private costs (per person)
NRT l/s	£52.96
NRT l&s	£112.85
Bupropion	£0.00
Varenicline	£0.00
E-cigarettes	£116.14
Bupropion & NRT l/s	£52.96
Bupropion & NRT l&s	£112.85
Varenicline & NRT l/s	£52.96
Varenicline & Bupropion	£0.00
E-cigarettes & NRT l/s	£169.10

Comorbidity costs

The economic model includes costs associated with each co-morbidity. The costs reflect on-going annual costs and are multiplied by the number of people with each co-morbidity each cycle. As the model estimates costs using a prevalence-based approach i.e. establishing the total proportion of smokers/ex-smokers in the population with a comorbidity at a certain time, the comorbidity costs represent an “average” cost per year for people with the comorbidity.

The comorbidity costs were sourced from the same publications as were used in the original NG92 model. We conducted a pragmatic literature search in online databases included OVID Medline, Google Scholar and the CEA Registry. The searches combined key terms and synonyms relating to each comorbidity combined with common search terms for healthcare costs and/or economic studies (for example, costs, healthcare costs, NHS costs, burden of illness, economic evaluation). The searches did not identify any relevant evidence from more recent publications. Each annual cost was inflated to 2019 prices from the original source using the PSSRU H&CHS inflation indices (20).

The comorbidity cost sources were reviewed to identify if social care costs were included, and if so whether these costs could be disaggregated. It was not clear if the cost sources for stroke included social care costs. Lung cancer costs, MI costs, COPD costs and asthma costs included hospital and primary care costs. The source for CHD costs separated the costs by ‘community care’ and ‘care provided in other settings’ which may encompass social care. However, given that not all cost sources reported the disaggregated costs it was not

possible to report overall costs for social care separately and, therefore, results are reported for NHS and personal social services as a whole.

Table 5: On-going annual comorbidity costs (NHS)

Parameter	Cost	Source
Stroke	£5,618	NICE CG92 Full guideline (21) Inflated from 2007/08 to 2018/19 prices using PSSRU (2019) H&CHS indices (20)
Lung cancer	£10,772	Cancer Research UK (22) Inflated from 2012/13 to 2018/19 prices using PSSRU (2019) H&CHS indices (20)
MI	£1,135	Godfrey *et al.* (23) Inflated from 2011/12 to 2018/19 prices using PSSRU (2019) H&CHS indices (20)
CHD	£1,178	British Heart Foundation. Cardiovascular Disease Statistics (24) Inflated from 2012/13 to 2018/19 prices using PSSRU (2019) H&CHS indices (20)
COPD	£636	NICE ~~CG101~~ NG115 Full guideline (previously CG101) Inflated from 2007/08 to 2018/19 prices using PSSRU (2019) H&CHS indices (20)
Asthma exacerbation	£1,433	Leaviss *et al.* (2014) (25) Inflated from 2010/11 to 2018/19 prices using PSSRU (2019) H&CHS indices (20)

PSSRU Personal Social Services Research Unit

Productivity costs

The base case model was for a health and social care perspective. ~~P~~Productivity costs for smokers and non-smokers were included in the model as part of a scenario analysis which expanded the perspective to include wider societal costs. The excess number of days absent from work per year due to smoking was taken from a 2019 ONS report on sickness and absence in the labour market (26). This being equal to 1.9 days and applied to the proportion of smokers in employment (assumed to be 58% as per the General Household Survey, 2006). It was assumed that people aged over the average retirement age (63 years, ONS 2013 (26)) did not incur any productivity losses. In order to calculate the cost of absenteeism from work, the number of lost days was multiplied by the average wage by age and gender (ONS 2019, (27)) (Table 6). The productivity costs associated with smoking were calculated and applied to the number of smokers at each time point within the model, in each arm of the model.

Table 6: Mean weekly wage

	Men	Women
16 to 24	£324.87	£259.83
25 to 34	£614.35	£470.30

35 to 44	£762.20	£516.70
45 to 54	£801.95	£499.00
55 to 64	£690.45	£412.10
65 to 74	£593.10	£348.90
75+	£593.10	£348.90

Note: Figures include mean wages including both full and part-time workers. Values are obtained as a standard mean estimate, and without weighting applied by full or part time employment status. Obtained from ONS 2019.

Utilities

Utilities are applied in the model by multiplying the relevant value by the proportion of people who are in each health state across each annual cycle (i.e. the number of smokers and former smokers). Utility values for smokers and former smokers were applied across each 1-year cycle to derive QALYs for populations in the smoker/former smoker health states. In addition, the utility values associated with each of the five comorbidities are used to calculate disutilities. The disutilities are applied to the utilities of smokers and former smokers in the model when they experience a comorbidity. Therefore, each disutility represented the average annual disutility experienced per person per comorbidity.

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

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

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

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

The utility inputs included in the model are shown in Table 7. Pragmatic literature searches were carried out to update the utility inputs, however no relevant evidence was identified. Therefore, the same sources were retained as were used in the original model.

Table 7: Utility values

Parameter	Utility value	Source
Stroke	0.48	Tengs and Wallace (28)
Lung cancer	0.61	Bolin *et al.* (2009) (29)

MI	0.80	Tengs and Wallace (28)
CHD	0.76	Stevanovic (30)
COPD	0.73	Rutten-van Molken *et al.* 2006 (31)
Asthma exacerbation*	0.729	For one week. Briggs et al.(2006) (32)
Smoker	0.8486	Vogl *et al.* (2012) (33)
Former smoker	0.8669	Vogl *et al.* (2012) (33)

* Assumed that disutility is incurred for 1 week.

Evidence from the published literature (see Table 7) indicates that:

- Populations of current smokers are associated with lower health utilities than populations of former smokers;
- Populations with comorbidities have lower health utilities than populations without health utilities.

It is likely that some of the reduction in utility for smokers versus former smokers is directly due to reductions in smoking related comorbidities i.e. former smokers feeling better as they experience fewer comorbidities. The level of this dependency was not reported in the published literature.

As our base case analysis applied disutility to both smoking and comorbidities double-counting will potentially be occurring in the model. We selected this approach for the base case analysis as it has been used in previous models and we felt that the disutility associated with smoking would be significant in isolation. To establish the impact of this assumption, we included a sensitivity analysis which only applied disutilities to the comorbidities and removed the disutility based on smoking status.

Comorbidity Epidemiology

The model generates average (or 'expected') outcomes for specific baseline characteristics (i.e. the outcomes are calculated for a person of a pre-specified age, gender and smoking status). However, results are calculated for every possible baseline characteristic, and the model then produces a 'weighted average' output, based on the known demographics of the assessed group. The specific parameters that varied by age group were smoking status, comorbidity prevalence and mortality risk. We were not able to identify age specific variables within the published sources so all other factors within the model were assumed to stay constant by age.

The inputs required to inform the calculations of the prevalence of comorbidities by age, gender and smoking status are summarised in this section. Table 8 summarises the sources used for the prevalence of each comorbidity.

Table 8: Sources for prevalence of comorbidities

Prevalence	Source/notes
Stroke	Bhatnagar *et al.* (2015) (34)*
Lung cancer	Maddams *et al.* (2009) (35)*
MI	Health Survey for England (2017), Table 1: Prevalence of ever having any doctor-diagnosed MI by age and sex. (34)*
CHD	Townsend et al. (2012) (36). Assumed that 12 to 15-year olds had 0% prevalence. This assumption was made based on (i) the prevalence for the 16 to

	24 age group was 0.1% (females) and 0.1% (males) and (ii) the younger age group (12 to 15) would have a lower risk for CHD than those aged 16 to 25. The youngest age group that data was available for was in people aged 16 to 24 years (0.1%)
COPD	Public Health England data set (not reported by gender). Assumed 12 to 15-year olds had 0.1% prevalence (given that the prevalence for the 16 to 24 age group 1.28% and the risk reduces with age). Data were only reported for ages as low as 16 to 24 years (1.28%)

The prevalence of smoking by age and gender was extracted from the Health Survey for England (2018) (37). Inputs for ages 12 to 15 are not reported in the survey. At this age bracket data are only reported for the question 'have you ever smoked?' However, Action on Smoking and Health (ASH) reports the prevalence of regular smoking in 2014 for children aged 11 to 15 and this input is used in the model (38). To calculate the prevalence of never-smokers and former smokers in the 12 to 15 age bracket, the same percentage difference from current smokers was applied as in the 16 to 24 age bracket.

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

Table 9 summarises the sources used for the relative risks by smoker, never-smoker and former smoker by gender. The pragmatic searches identified a new relevant source for the MI RR's, therefore Millet et al. (2018) (39)~~(39)~~ was used as the source for this parameter in the updated model. All other RR values were retained from the original NG92 model. The between group differences in the intervention and comparator arms for the comorbidities are determined by smoking status based on the RR values.

Each RR was obtained from a source in the published literature which applied an appropriate statistical technique to adjust for confounding factors which could also explain differences in comorbidity prevalence rates including age, sex, and disease risk factors.

Table 9: Sources for relative risks (RR) of comorbidities

Relative risks	Source/notes
Stroke	Myint *et al.* (2008) (40)
Lung cancer	Pesch *et al.* (2012) (41)
MI	Millet *et al.* (2018) (39)~~(42)~~
CHD	Shields *et al.* (2013) (42)
COPD	Lokke *et al.* (2006) (43)

The data summarised above show the sources for the prevalence, by age, of each comorbidity in the general population (regardless of smoking status) (A), the relative risk of each co-morbidity by smoking status (smokers versus formers smokers (B) and smokers versus non-smokers (C)) and the prevalence of smoking (D). This can be used to calculate

the prevalence of each co-morbidity for a current smoker (E), former smokers (F) and non-smokers (G), by ensuring that the following equation was satisfied:

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

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

This can be illustrated using the example of a 60-year-old male with lung cancer. The prevalence of lung cancer is provided in Table 10 (35), the relative risk of lung cancer is shown in Table 11~~Table 11~~ (41) and the prevalence of smoking is shown in Table 12 (37).

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Table 10: Prevalence of lung cancer (males)

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

Table 11: Relative risk of lung cancer (males)

RR of lung cancer (men)		
Smoker	**Former**	**Never smoker**
23.6	7.5	1

Table 12: Prevalence of smoking (males)

Age	Never smoker	Former	Smoker
12 to 15*	96.34%	0.66%	3.00%
16 to 24	74.63%	3.09%	22.28%
25 to 34	53.24%	19.71%	27.05%
35 to 44	53.86%	25.33%	20.81%
45 to 54	52.17%	27.10%	20.73%
55 to 64	52.22%	31.79%	15.99%
65 to 74	41.67%	48.49%	9.84%
75+	44.51%	52.13%	3.36%

* From ASH report (38)

Substitute the prevalence of smoking and the actual prevalence rate:

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

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

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

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

(E) = 0.29%

(F)= 0.09%

(G) = 0.01%

This process was repeated for each age and gender for all co-morbidities.

Asthma Exacerbation Inputs

We followed methods in an HTA report by Leaviss et al. (2014) (25), where mortality associated with asthma exacerbation was assumed to equal all-cause mortality (i.e. asthma exacerbations did not result in death). In addition, it was assumed that asthma exacerbations were transient in nature and resolved within one year.

In the Leaviss et al. (2014) HTA report, asthma exacerbation incidence rates were reported for short-term and long-term quitters, Table 13~~Table 13~~. The incidence data for short-term quitters was applied for 4 years after quitting in the economic model by Leaviss et al. (2014). The current model structure in this analysis does not allow the incidence rates to be applied in this way as there is no way to establish the duration populations have been in the ex-smoker health state. Consequently, the incidence rate for long-term quitters (long term status achieved after 4-years of non-smoking) from Leaviss et al. (2014) is applied in the base case (which is not a conservative estimate but may be more accurate given the lifetime time horizon of the model). As indicated in Table 13~~Table 13~~, the Leaviss et al. (2014) report the incidence rates of asthma exacerbations for smokers and long-term quitters (applied to former smokers) by age and gender. The number of people in these health states is multiplied by the relevant incidence rate to determine the number of people that experience an asthma exacerbation each year.

Table 13: Incidence of asthma exacerbations

	Males		
Age	**Smokers**	**Long-term quitters [a] (>4 years)**	**Short-term quitters [a] (<=4 years)**
12 to 15	0.08%	0.05%	0.05%
16 to 24	0.08%	0.05%	0.05%
25 to 34	0.08%	0.05%	0.05%
35 to 44	0.05%	0.05%	0.05%
45 to 54	0.05%	0.05%	0.05%
55 to 64	0.05%	0.05%	0.05%

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

a: Long term (more than 4-years) and short-term (between 0 and 4 years) quitters for asthma incidence follow the same definitions as adopted in the economic model by Leaviss et al. (2014) (25). This definition is not necessarily consistent with other smoking cessation literature which may classify long term quit as smoking abstinence of 12-months or more.

Mortality Epidemiology

The inputs required to inform the calculations of the mortality rates by age, gender and smoking status are summarised in this section. The mortality rates were obtained from Doll et al. (1994) which is an observation study with 40-year follow up using data the British doctors survey (44). The authors of the study have published a more recent paper which provides 50-year follow-up (45). However, the 40-year follow up data was used because it provided annual mortality by smoking habits at age of death, which was not available in the 50-year follow up. The 50-year follow up study did not provide figures for those over 85 or for former smokers under 45 years. The mortality rates from Doll et al. (1994) (44) were adjusted to reflect the general population mortality rates. To adjust the mortality to reflect that found in the general population the mortality per 1,000 men, by age band, was taken from the Doll study.

The Doll et al. (1994) (44) study reports mortality beginning at the age of 35. In order to populate the age bands below this, an exponential distribution was applied and the mortality for the lower age groups was calculated (Table 14~~Table 14~~). The Doll paper (1994) was used to calculate the odds ratio of mortality for smokers versus formers smokers and smokers versus non-smokers in men, which we also applied to women. There are available data in the British Doctors Survey for women however the sample size is much reduced (equal to roughly 6,000 females versus 35,000 males) and we could only find published literature which reported follow up for a maximum of 22-years (46). Therefore, we considered it more appropriate to apply odds ratios from men to women rather than apply separate odds ratios from less robust data sources. ~~.~~

The ONS Life Tables (47) provide the 'real' mortality for each age. The prevalence of smoking for each age and gender was taken from the Health Survey for England (37) (Table 12), for ages 12-15 this was taken from ASH (38). Mortality calculations are shown in Appendix B.

Table 14: Mortality by smoking status

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

* Extrapolated data (exponential).

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

Deterministic Sensitivity Analysis

Deterministic sensitivity analysis (DSA) is a method that can be used to investigate the sensitivity of the results from economic models following variations in a specific input parameter or set of parameters. One or more parameters are manually changed (usually across a pre-specified range) and the results are analysed to determine to what extent the change has an impact on the output values.

We conducted univariate DSA in this analysis, by varying one parameter at a time. Each parameter was varied from the mean values (in the base case analysis) to the 95% lower and upper confidence interval, or +/- 15% of the mean if confidence intervals were not available. We conducted univariate DSA for several key parameters in the economic model, which included: intervention effectiveness (RR), the probability of cessation at 12-months for placebo; the time horizon; intervention costs; the annual rate of cessation and relapse; the discount rate for costs and QALYs; comorbidity costs; comorbidity disutilities, applying the same utility for smokers and former smokers, and applying NHS intervention costs for e-cigarettes. Due to resource constraints we could not conduct DSA for every parameter in the economic model. We prioritised the aforementioned parameters as they were considered most likely to have an influence on the findings from the base case analysis.

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 this economic 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 every ten years. To ensure the results of the PSA were in alignment with the base case analysis, the youngest population age was set equal to 12 (youngest age for the base case model) plus the midpoint of the age increment. This meant the PSA calculated weighted averages for populations aged 17, 27, 37, ., 97. The final results for the PSA were then calculated as a weighted average across results for people aged 17, 27, 37, …, 97 using a corresponding age weighting based on ONS population estimates (13).

PSA results (i.e. the probabilistic ICER and NMB) began to stabilise between 2,000 and 3,000 iterations. Therefore, the PSA was run for 3,000 iterations, with weighted averages calculated within each iteration.

The relative risk (intervention effectiveness) PSA parameter values were provided directly by NICE. This was in the form of Coda data, which contains correlated outputs for each iteration of the NMA. The other input parameter distributions for the PSA followed recommendations in Briggs et al. (2006) (48): 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 15~~Table 15~~.

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Table 15: Summary of PSA distributions

Parameter	PSA Distribution	Source
Intervention effectiveness (RR)	NMA Coda	NICE[a]
Probability of abstinence (placebo)	Beta [0,1] [b]	(5)
Smoking status (by age & gender) Former smoker Current smoker Never-smoker	 Beta [0,1] (Dirichlet) Beta [0,1] (Dirichlet) Beta [0,1] (Dirichlet)	(49)
Mortality per 1000 (by age & smoking status)	Beta [0,1000]	(50)
Comorbidities RR parameters Stroke Lung cancer MI CHD COPD Asthma	 Log-normal Log-normal Log-normal Log-normal Log-normal Log-normal	 (40) (41) (37) (42) (43) Assumption
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]	 (33) (30) Assumption
Intervention costs	Gamma	Assumption
Comorbidity costs	Gamma	Assumption

a: Results from the NMA Coda were provided directly by NICE.

b: Values in square brackets indicate the limit of the beta distribution. For example, beta [0,1] indicates that a beta distribution is applied bounded between 0 and 1.

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Scenario Analyses

We further investigated uncertainty in the model by establishing cost-effectiveness results in four scenario analyses. The scenario analyses involved relatively large changes to the model when compared with the DSA which only changed individual parameter values. The four-scenario analysis included: (i) changing the decision problem to estimate cost-effectiveness without placebo; (ii) conducting the analysis using a different set of effectiveness estimates obtained from a scenario analysis in the NICE NMA; (iii) estimating cost-effectiveness specifically for a mental health subgroup; and (iv) including additional health harms associated with e-cigarettes.

Base case analysis: Incremental cost-effectiveness without placebo

The research question in the NICE scope was to identify the most cost-effective smoking cessation intervention. The PHAC also wished to establish whether each intervention was cost-effectiveness versus a comparator. Consequently, the base case analysis included a fully incremental economic analysis which incorporated placebo as one of the treatment options. The rationale for including placebo was due to effectiveness rates for each intervention being obtained from the NMA in NICE evidence review K (5), where placebo was included as a comparator. As stated in the main report, this meant that we could apply a logical assumption that placebo would not affect the size of the relative effectiveness estimates for any non-placebo intervention treatment versus any other non-placebo intervention.

We conducted a scenario analysis to confirm that the inclusion of placebo did not have an impact on the cost-effectiveness findings. The scenario analysis was conducted by comparing all interventions to NRT l/s rather than placebo. NRT l/s was selected as the reference category as it contained the largest number of study participants across all intervention categories included in the NICE NMA.

We estimated the absolute probability of smoking cessation for placebo by summing the total number of events (quitters) across all NRT l/s arms of the RCTs included in the updated NMA and dividing by the total number of participants in the NRT l/s arms. We obtained the number of events and trial participants in the NRT l/s arms from forest plots in NICE evidence review K (see Figures 1, 3, 4, 5, 8, 12, 16, 22, and 27) (5). This resulted in an overall probability of cessation at 6-months equal to 18.23% (6,340/ 34,785).

The relative risk of smoking abstinence at 6-months was obtained for all other interventions versus NRT l/s, with the RR parameters being obtained directly from NICE Evidence review K (see Table 20). As with the base case analysis, the probabilities of cessation at 6-months in the scenario analysis were adjusted to account for relapse between 6-months and 12-months based on the relapse curves in Figure 2~~Figure 2~~.

All effectiveness rates for the scenario analysis are reported in Table 16~~Table 16~~. We note that the effectiveness rates for all interventions are slightly less for the scenario than the base case analysis due to variation in the probability of cessation for the NRT l/s reference category. There were no differences in the ordering of intervention effectiveness as the RR parameters were equivalent for the analyses which included/excluded placebo. All other model parameters (excluding the effectiveness estimates) in the scenario analysis were consistent with the base case analysis.

Table 16: Intervention effectiveness: Scenario analysis excluding placebo, NRT l/s as the NMA reference category

	Scenario analysis			Base case [a]
Intervention	**RR of abstinence vs. NRT l/s @ 6-months**	**P (quit) 6-months**	**P (quit) 12-months**	**P (quit) 12-months**
NRT l/s	N/A	18.23%	15.61%	18.00%
NRT l&s	1.48	26.99%	23.11%	26.66%
Bupropion	0.94	17.23%	14.75%	17.02%
Varenicline	1.24	22.61%	19.36%	22.33%
E-cigarettes	1.23	22.41%	19.19%	22.14%
Bupropion & NRT l/s	1.05	19.22%	16.46%	18.99%
Bupropion & NRT l&s	1.91	34.96%	29.94%	34.53%
Varenicline & NRT l/s	1.41	25.70%	22.01%	25.38%
Varenicline & Bupropion	1.50	27.39%	23.46%	27.05%
E-cigarettes & NRT l/s	1.60	29.18%	24.99%	28.82%

a: Column displays the probability of quit for the base case analysis which included placebo. The base case probabilities are obtained directly from Table 1~~Table 1~~.

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NMA effectiveness scenario analysis: inclusion of e-cigarette study

At the request of the PHAC, a scenario analysis was conducted which included an additional study in the NMA. The additional study was conducted by Hajek et al. (2019) (17) and compared e-cigarettes with NRT l/s. The study did not meet the full study inclusion criteria for the base case NMA, as it did not collect biochemically validated abstinence rates at 6-months. The committee agreed that the Hajek et al. (2019) (17) study did not meet the inclusion criteria for the NMA. However, the committee highlighted this study as a key piece of evidence that ought to be considered when forming guidelines on e-cigarettes. Consequently, a scenario analysis was conducted where the NICE NMA included cessation rates from the Hajek et al. (2019) (17) study.

All effectiveness rates for the scenario analysis are reported in Table 17~~Table 17~~. We note that the effectiveness rates for the majority intervention remain almost identical to the base case analysis. However, the probability of cessation at 12-months for: e-cigarettes increased from 22% in the base case to 27% in the scenario analysis; and e-cigarettes + NRT l/s increased from 29% in the base case to 34% in the scenario analysis. All other model parameters remained consistent with the base case analysis.

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Table 17: Intervention effectiveness: Scenario analysis including Hajek et al. (2019) (17) study

	Scenario analysis			Base case [a]
Intervention	**RR of abstinence vs. placebo @ 6-months**	**P (quit) 6-months**	**P (quit) 12-months**	**P (quit) 12-months**
Placebo	N/A	11.49%	9.84%	9.84%
NRT l/s	1.83	21.03%	18.00%	18.00%
NRT l&s	2.57	29.53%	25.28%	26.66%
Bupropion	1.73	19.88%	17.02%	17.02%
Varenicline	2.26	25.97%	22.23%	22.33%
E-cigarettes	2.75	31.60%	27.05%	22.14%
Bupropion & NRT l/s	1.91	21.95%	18.79%	18.99%
Bupropion & NRT l&s	3.47	39.87%	34.14%	34.53%
Varenicline & NRT l/s	2.57	29.53%	25.28%	25.38%
Varenicline & Bupropion	2.74	31.48%	26.96%	27.05%
E-cigarettes & NRT l/s	3.47	39.87%	34.14%	28.82%

a: Column displays the probability of quit for the base case analysis which excluded the Hajek (2019) study. The base case probabilities are obtained directly from Table 1~~Table 1~~.

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Mental Health Subgroup

Whilst not specifically included as a research question for economic analysis in the NICE scope, the PHAC was interested in investigating the cost-effectiveness of pharmacotherapies for smoking cessation specifically for a population with mental health problems. Therefore, a subgroup analysis was conducted to establish cost-effectiveness for this population. The characteristics of the mental health subgroup was informed by the populations included in

the updated NMA by Thomas et al. (2020) (6) in NICE evidence review K (5). This included people with depression, psychiatric disorder, bipolar, schizophrenia and post-traumatic stress disorder.

Effectiveness evidence for the mental health subgroup was available for a subset of smoking cessation strategies from the updated NICE NMA, where effectiveness was measured as RR of smoking abstinence vs. placebo at 6-months. The probability of smoking cessation at 6-months was calculated by multiplying the RR for each intervention vs. placebo by the absolute probability of smoking cessation at 6-months in placebo arms. The absolute probability of smoking cessation for usual care was calculated in this analysis using data reported in the NICE updated NMA by Thomas et al. (2020) (6). In total the pooled probability of smoking cessation across all placebo arms of the RCTs included in the mental health subgroup in the NMA was equal to 6.54% (a total of 227 events of smoking cessation in 3,472 total participants obtained from NICE evidence review K, Grade Profile 36, 40 and 42).

As for the base case-analysis, probabilities of cessation at 6 months were adjusted to 12-month probabilities by accounting for smoking relapse. Rather than being a full review question, the cost-effectiveness of pharmacotherapies in mental health populations was specified as sub-group analysis in the NICE protocol. Due to resource constraints, it was not possible to conduct full literature searches to identify specific model parameters for the subgroup analysis. However, pragmatic literature searches were conducted by YHEC for several key parameters which involved searching for key terms across databases including Google Scholar, the CEA Registry and the burden of illness database HEORO. The pragmatic searches did not identify any smoking relapse rates specific for the mental health subgroup, so these were assumed to be equal to the relapse rates applied in the base case (i.e. 14.4% relapse between months 6 and 12, as indicated in Figure 2~~Figure 2~~). All cessation strategies and probabilities for the mental health subgroup are displayed in Table 18~~Table 18~~.

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Table 18: Intervention effectiveness: Mental Health Subgroup

Intervention	RR of abstinence vs. UC @ 6-months mean (95% CI)	P (quit) 6-months	P (quit) 12-months
Placebo	N/A	6.54%	5.60%
NRT l/s	1.89 (1.06, 5.40)	12.36%	10.58%
NRT l&s	3.97 (0.16, 7.92)	25.96%	22.23%
Bupropion	1.79 (0.85, 4.01)	11.71%	10.02%
Varenicline	2.29 (1.33, 4.34)	14.98%	12.82%
Bupropion + NRT l&s	4.24 (0.83, 7.63)	27.73%	23.74%
Bupropion + NRT l/s	7.0 (1.95,7.98)	45.78%	39.20%

All intervention costs were assumed to be consistent with the base case analysis. This assumption was informed through the RCTs included in the NMA which tended to use similar doses as applied for the general population. For example, when assessing effectiveness of pharmacotherapies vs. placebo in populations with depression, Anthenelli et al. (2016) (51) applied standard doses across 12 weeks of 1mg twice daily for varenicline, 150mg twice daily for bupropion and 21 mg for NRT patches. As it is possible that doses may differ for the mental health subgroup, a sensitivity analysis was performed which increased and decreased all intervention costs in the mental health subgroup by 25%.

The pragmatic searches conducted by YHEC attempted to identify relevant inputs to populate the model for the mental health sub-group including for mortality, utilities, risk of comorbidities, and costs per comorbidities. The searches did not identify any studies which reported the relevant parameters for mental health populations separately across health states included in the model (i.e. never, current and former smokers). Therefore, it was assumed that health risks by smoking status in the base case were applicable to the mental health subgroup. For example, mortality rates in the base case for non-, former and current smokers at age 75-84 were 67.4, 77.3 and 106.0 per 1000. To estimate mortality rates in the mental health subgroup, each of these rates was multiplied by the same relative risk of mortality for people with mental health problems, rather than a specific relative risk by each health state.

The overall relative risk of mortality in mental health populations was identified in a meta-analysis by Walker et al. (2016) (52). The meta-analysis identified the relative risk of mortality (equal to 2.22) for populations with any type of mental health conditions vs. the general population. The relative risk was multiplied by existing mortality rates for current, former and non-smokers in the base case model to establish overall mortality for the mental health subgroup, Table 19~~Table 19~~.

Table 19: Mortality by smoking status, mental health subgroup

Age	Mortality per 1000 men		
	Never	Former	Smoker
12 to 15	0.31	0.45	0.77
16 to 24	0.57	0.80	1.35
25 to 34	1.37	1.88	3.06
35 to 44	3.55	4.44	6.22
45 to 54	8.88	10.88	17.98
55 to 64	21.09	29.75	45.07
65 to 74	52.61	70.15	104.34
75 to 84	149.63	171.61	235.32
85+	374.29	398.93	485.51

Value obtained by multiplying mortality rates in the general population (see Table 14~~Table 14~~) by RR=2.22 of mortality in mental health populations from Walker et al (2016) (52).

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The pragmatic searches identified a meta-analysis by Dare et al. (2019) (53) which established the odds of having a chronic physical disease for mental health populations vs. general a general population. Dare et al. (2019) (53) included diabetes, obesity, cancer, COPD and coronary heart disease as physical diseases, and defined mental health populations as anxiety, depression, schizophrenia, and bipolar disorder. The odds ratio from Dare et al. (2019), equal to 3.1, was converted to a relative risk for each morbidity using the formula RR=OR/(1-p+(p*OR)), where p is the underlying probability of each morbidity. Each RR was then multiplied by the existing probabilities per morbidity for current, former and never-smokers in the base case model to establish overall occurrence of morbidities for the mental health subgroup.

This analysis applied equivalent costs per morbidity as with the base case analysis. Whilst it is possible that treatment costs per morbidity may be increased in mental health populations when compared with the general population, this is unlikely to influence the cost-

effectiveness results. Adding extra costs per morbidity to the model would result in cost-effective strategies appearing more favourable.

The overall disutility for mental health populations vs. general populations was identified from a study by Fernandez et al. (2010) (54). This study used regression models to estimate the mean reduction in SF-6D scores over 12-months for people with mood disorders (-0.196), anxiety disorders (-0.043) and substance misuse disorders (-0.278). A mean utility reduction across all mental health populations was calculated using the utility reductions reported by Fernandez, and weighting by the number of people with each condition in the study population (mood disorder = 38.8%, anxiety disorder = 51.6%, substance misuse disorder = 9.6%). The weighted disutility (-0.125) was applied to each baseline utility value in the base case model and applied equally across each smoking related health state.

E-cigarette health harm and uptake

There is some controversy regarding the use of e-cigarettes for smoking cessation due to concerns around the associated health harms and possibilities for e-cigarettes to promote uptake of smoking in non-smoking populations.

The impact of long-term health harms associated with e-cigarettes was investigated in a scenario analysis, where negative QALYs and healthcare costs were approximated per each e-cigarettes user and subtracted from the base case results. The negative QALYs and healthcare costs were applied to represent the potential mean lifetime burden associated with e-cigarette safety issues, per person. As there is limited evidence regarding the type of potential harms and no evidence regarding the size of these effects, a threshold analysis was performed to determine the total amount of QALYs/costs worth of adverse events that would be required per person to make e-cigarettes not cost-effective vs. usual care.

Similarly, the potential gateway effect of e-cigarettes in promoting smoking uptake in non-smokers was investigated in a scenario analysis. The scenario analysis was conducted first by using the economic model to estimate the incremental lifetime costs and QALYs per quitter when compared with a person who continues to smoke. To identify the lifetime costs and QALYs per quitter, the economic model parameters were changed such that the probability of smoking cessation at 12-months was equal to 100%, with 0% chance of relapse to smoking during any subsequent cycles, resulting in 100% of people remaining in either the non-smoking or dead health states throughout the model. To identify the lifetime costs and QALYs per smoker, the economic model parameters were changed such that the probability of smoking cessation at 12-months was equal to 0%, with 0% chance of smoking cessation during any subsequent cycles, resulting in 100% of people remaining in either the smoking or dead health states throughout the model.

The differences between the lifetime costs and QALYs per quitter and smoker were used as an approximation of the lifetime costs and QALYs expected per person who takes up smoking due to e-cigarettes. A threshold analysis was performed using a two-way data table to indicate when e-cigarettes wouldn't be cost-effective vs. usual care. The outcome in the data table was the net budgetary impact based on the total healthcare savings and QALYs gained in populations who quit smoking due to e-cigarettes minus the total healthcare costs and QALYs lost in populations who take up smoking due to e-cigarettes. The two-way data table estimated budgetary impact for a range of populations by simultaneously varying the percentage of non-smokers who take up e-cigarettes, and the percentage of people who uptake smoking due to e-cigarettes.

Results

Cost-effectiveness Results: Base case analysis

Fully incremental analysis

The research question specified in the NICE scope is to establish the *most* effective and cost-effective means of smoking cessation. The following section answers this question directly, reporting results from a fully incremental analysis, which compares the cost-effectiveness of each of the smoking cessation interventions with one-another and to placebo in the general population. All results are obtained as weighted averages of results for populations aged 12 to 100, this representing everybody who could feasibly have been classified as smokers when entering the model.

The base case results for the fully incremental analysis are displayed in Table 20~~Table 20~~. Bupropion + NRT l&s was the most cost-effective strategy and was dominant versus each of the other interventions having the lowest total healthcare costs (£10,802) and highest lifetime QALYs (15.37) per person, and subsequently the highest net monetary benefit vs. placebo, equal to £5,928 per person.

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Table 20: Cost-effectiveness results (per person): Fully incremental analysis

Intervention	RR (mean, rank)	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE Rank
Placebo	1.00 (11)	98	£11,523	15.11	£0	11
Bupropion	1.73 (10)	170	£11,314	15.18	£1,723	10
NRT l/s	1.83 (9)	180	£11,285	15.19	£1,960	9
Bupropion + NRT l/s	1.93 (8)	190	£11,294	15.20	£2,158	8
Varenicline	2.27 (6)	223	£11,244	15.24	£2,913	7
E-cigarettes	2.25 (7)	221	£11,090	15.24	£3,026	6
Varenicline + NRT l/s	2.58 (5)	254	£11,186	15.27	£3,615	5
Varenicline + bupropion	2.75 (3)	271	£11,122	15.29	£4,031	4
NRT l&s	2.71 (4)	267	£11,035	15.29	£4,035	3
E-cigarettes + NRT l/s	2.93 (2)	288	£10,903	15.31	£4,623	2
Bupropion + NRT l&s	3.51 (1)	345	£10,802	15.37	£5,928	1

RR= relative risk versus placebo
CE= cost-effectiveness

The cost-effectiveness results were driven by the effectiveness parameters. Bupropion + NRT l&s resulted in 345 quitters at 12-months per 1,000, this being 58 more than the next most effective intervention (E-cigarettes + NRT l/s). The influence of the effectiveness parameter on cost-effectiveness results is illustrated by comparing the RR rank and CE rank, which generally corresponded (Table 20~~Table 20~~). The RR and CE ranks weren't equivalent for (i) varenicline and e-cigarettes and (ii) varenicline + bupropion and NRT l&s. However, in both cases the effectiveness estimates (RR's) were very similar and resulted in very minimal differences in the number of quitters at 12-months (varenicline n=223, e-cigarettes =221; varenicline + bupropion = 271, NRT l&s = 267).

In contrast, intervention costs had a relatively minor influence on the cost-effectiveness results. Despite applying to the entire population (i.e. both quitters and non-quitters), the total intervention costs across the population were modest when compared with the lifetime net monetary benefit associated with those who quit smoking due to the cessation interventions. For example, intervention costs for bupropion + NRT l&s were £148 per person more than placebo. As indicated in Table 20~~Table 20~~, the net monetary for bupropion + NRT l/s versus placebo was £5,928. This would mean that at the given effectiveness rates the costs for bupropion + NRT l/s could be over 35 times higher and the intervention would still be considered cost-effective versus placebo. That is, £148 x 30 = £4,4400, which is substantially less than the NMB for bupropion + NRT l/s versus placebo.

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Pairwise analyses vs. placebo

As well as establishing the most cost-effective treatment option, the PHAC requested that the economic analysis identified the cost-effectiveness of each intervention versus placebo. A full breakdown of the pairwise comparisons is provided in Table 21~~Table 21~~.

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All of the interventions were highly cost-effective, and dominated placebo as they each resulted in healthcare savings and additional QALYs. All of the interventions resulted in substantially more quitters at 12-months, and consequently reductions in the prevalence of smoking related diseases and smoking related mortality.

Table 21: Incremental cost-effectiveness results (per person): Pairwise results vs. placebo

Intervention	RR vs. placebo	Incremental outcomes vs. placebo			ICER
		Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	
Bupropion	1.73	72	-£209	0.07	Dominant
NRT l/s	1.83	82	-£238	0.08	Dominant
Bupropion + NRT l/s	1.93	92	-£229	0.09	Dominant
Varenicline	2.27	125	-£279	0.13	Dominant
E-cigarettes	2.25	123	-£433	0.13	Dominant
Varenicline + NRT l/s	2.58	156	-£337	0.16	Dominant
Varenicline + bupropion	2.75	173	-£401	0.18	Dominant

NRT l&s	2.71	169	-£488	0.18	Dominant
E-cigarettes + NRT l/s	2.93	190	-£620	0.20	Dominant
Bupropion + NRT l&s	3.51	247	-£721	0.26	Dominant

Deterministic Sensitivity Analysis (DSA)

The following section reports the results of the univariate DSA, which were conducted for: intervention effectiveness (RR), the probability of cessation at 12-months for placebo; the time horizon; intervention costs; the annual rate of cessation and relapse; the discount rate for costs and QALYs; comorbidity costs; comorbidity disutilities, applying the same utility for smokers and former smokers, and applying NHS intervention costs for e-cigarettes.

Effectiveness (RR)

Applying the lower 95% CI RR values did not affect the pairwise results as each intervention remained cost-effective and dominant (decreased lifetime costs, increased QALYs) versus placebo, Table 22~~Table 22~~. However, the DSA affected the fully incremental analysis: NRT l&s became the most cost-effective and dominant strategy with the lowest lifetime healthcare costs and largest lifetime QALYs. There were also substantial changes to the cost-effectiveness ranks, for example varenicline had the seventh highest NMB in the base case analysis but the second highest in the DSA, meanwhile E-cigarettes + NRT l/s were ranked as having the second highest NMB in the base case analysis, but only the eighth highest in the DSA.

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Table 22: Cost-effectiveness results (per person): DSA, lower 95% CI RR

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1.00	98	£11,523	15.11	£0	11	11
E-cigarettes	1.33	131	£11,409	15.14	£799	10	6
Bupropion + NRT l/s	1.50	148	£11,443	15.16	£1,117	9	8
E-cigarettes + NRT l/s	1.52	150	£11,392	15.16	£1,210	8	2
Bupropion	1.52	150	£11,387	15.16	£1,215	7	10
Varenicline + NRT l/s	1.68	165	£11,497	15.18	£1,436	6	5
Varenicline + bupropion	1.73	170	£11,475	15.18	£1,562	5	4
NRT l/s	1.67	164	£11,340	15.18	£1,573	4	9

Bupropion + NRT l&s	1.77	174	£11,405	15.19	£1,716	3	1
Varenicline	2.01	197	£11,334	15.21	£2,284	2	7
NRT l&s	2.10	207	£11,246	15.22	£2,559	1	3

RR= relative risk versus placebo
CE= cost-effectiveness

The results of the DSA when applying RRs equal to the 95% upper confidence interval values are displayed in Table 23~~Table 23~~. The DSA did not result in substantial changes to the base case cost-effectiveness results, as all interventions remained cost-effective versus placebo, meanwhile bupropion + NRT l&s remained the dominant strategy.

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The size of the NMB versus placebo increased substantially when compared with the first DSA and the base case analysis. For example, bupropion + NRT l&s had an NMB equal to £1,716 for the lower 95% CI RR DSA, £5,928 for the base case analysis, and £10,081 when applying the upper 95% CI RR value. The substantial difference in the value of the NMB was driven by high levels of variability in the results of the network meta-analysis: The lower 95% RR and associated number of quitters at 12-months was equal to 1.77 and 174 for the lower 95% CI RR scenario; 3.51 and 345 for the base case; and 5.50 and 642 for the upper 95% CI RR scenario.

Table 23: Cost-effectiveness results (per person): DSA, upper 95% CI RR

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1.00	98	£11,523	15.11	£0	11	11
Bupropion	1.95	192	£11,238	15.21	£2,256	10	10
NRT l/s	2.01	198	£11,222	15.21	£2,396	9	9
Bupropion + NRT l/s	2.46	242	£11,110	15.26	£3,441	8	8
Varenicline	2.55	251	£11,147	15.27	£3,591	7	7
NRT l&s	3.40	335	£10,796	15.36	£5,706	6	3
E-cigarettes	3.58	352	£10,629	15.38	£6,246	5	6
Varenicline + NRT l/s	3.70	364	£10,797	15.39	£6,326	4	5
Varenicline + bupropion	4.05	398	£10,671	15.42	£7,178	3	4
E-cigarettes + NRT l/s	4.80	472	£10,255,	15.50	£9,150	2	2
Bupropion + NRT l&s	5.59	642	£10,081	15.58	£10,963	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

Probability of cessation at 12-months for placebo

The second deterministic scenario varied the probability of smoking cessation at 12-months for placebo. This DSA differed from the effectiveness DSA as placebo is the reference category for the analysis: each intervention's effectiveness was established by multiplying the RR versus placebo by the "reference" probability of cessation in the placebo arm. Therefore, changing the value of placebo gives an indication of the cost-effectiveness results in populations who have a higher/lower rate of cessation than observed in the placebo arm for the general population.

Table 24~~Table 24~~ displays results when applying a lower estimate, where the probability of cessation in placebo was reduced to 9.77% (from the base case value equal to 11.49%). The DSA did not result in any changes to the base case cost-effectiveness results, as all interventions remained cost-effective versus placebo, meanwhile bupropion + NRT l&s remained the dominant strategy. Furthermore, each intervention retained the same CE ranking when ordered by NMB versus placebo. Reducing the probability of abstinence in the placebo arm reduced the overall probability of abstinence in all other intervention arms proportionately. This is because each intervention's effectiveness is calculated by multiplying the associated relative risk versus placebo with the baseline rate of abstinence in the placebo arm. Therefore, reducing abstinence in placebo reduces abstinence across the entire network of treatments in the NMA. Consequently, the number of quitters was reduced across all interventions, which subsequently increased lifetime healthcare costs and reduced lifetime QALYs.

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Table 24: Cost-effectiveness results (per person): DSA, probability of cessation for placebo, lower estimate (9.77%)

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1.00	84	£11,575	15.09	£0	11	11
Bupropion	1.95	145	£11,404	15.16	£1,459	10	10
NRT l/s	2.01	153	£11,380	15.17	£1,660	9	9
Bupropion + NRT l/s	2.46	161	£11,394	15.17	£1,821	8	8
Varenicline	2.55	190	£11,362	15.20	£2,453	7	7
E-cigarettes	3.58	188	£11,207	15.20	£2,573	6	6
Varenicline + NRT l/s	2.58	216	£11,319	15.23	£3,042	5	5
Varenicline + bupropion	2.75	230	£11,265	15.25	£3,397	4	4
NRT l&s	2.71	227	£11,176	15.24	£3,416	3	3
E-cigarettes + NRT l/s	2.93	245	£11,055	15.26	£3,924	2	2

Bupropion + NRT l&s	3.51	293	£10,984	15.31	£5,018	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

Table 25~~Table 25~~ displays results when applying an upper estimate, where the probability of cessation in placebo was increased to 13.22% (from the base case value equal to 11.49%). The DSA did not result in any changes to the base case cost-effectiveness results, as all interventions remained cost-effective versus placebo, meanwhile bupropion + NRT l&s remained the dominant strategy. There was only one change in the CE ranks where NRT l&s had the third highest NMB versus placebo in the base case analysis whereas varenicline + bupropion had the third highest NMB versus placebo in the DSA. The impact of increasing the probability of cessation for placebo was to increase the number of quitters proportionately across all treatment arms. Therefore, due to reductions in the number of smokers, each treatment was associated with reduced lifetime costs and increased lifetime QALYs.

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Table 25: Cost-effectiveness results (per person): DSA, probability of cessation for placebo, upper estimate (13.22%)

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1.00	113	£11,471	15.12	N/A	11	11
Bupropion	1.95	196	£11,224	15.21	£1,989	10	10
NRT l/s	2.01	207	£11,189	15.22	£2,263	9	9
Bupropion + NRT l/s	2.46	219	£11,193	15.23	£2,497	8	8
Varenicline	2.55	257	£11,126	15.27	£3,376	7	7
E-cigarettes	3.58	254	£10,973	15.27	£3,482	6	6
Varenicline + NRT l/s	2.58	292	£11,051	15.31	£4,191	5	5
NRT l&s	2.75	307	£10,893	15.33	£4,659	4	3
Varenicline + bupropion	2.71	311	£10,978	15.33	£4,669	3	4
E-cigarettes + NRT l/s	2.93	331	£10,750	15.35	£5,326	2	2
Bupropion + NRT l&s	3.51	397	£10,619	15.42	£6,843	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

5-year time horizon

Table 26~~Table 26~~ displays the cost-effectiveness results for a scenario where the time horizon was reduced from lifetime to 5-years. At a cost-effectiveness threshold of £20,000 per QALY, all of the interventions were cost-effective versus placebo, having a positive NMB. Furthermore, bupropion, NRT l/s, NRT l&s, bupropion + NRT l&s, E-cigarettes, and E-cigarettes + NRT l/s remained dominant versus placebo being both more effective and saved the NHS money. As only 5 years of costs and QALYs were included, the total costs and QALYs were substantially decreased for all interventions. However, the change to the time horizon did not alter the cost-effectiveness results substantially, with the majority of interventions remaining at the same net monetary benefit ranking as observed in the base case analysis.

Table 26: Cost-effectiveness results (per person): DSA, 5-year time horizon

Intervention	RR	Quitters @ 12 months (per 1,000)	5-year costs	5-year QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1.00	98	£2,289	3.69	£0	11	11
Bupropion	1.73	170	£2,275	3.70	£213	10	10
Bupropion + NRT l/s	1.93	190	£2,308	3.70	£235	9	8
NRT l/s	1.83	180	£2,272	3.70	£244	8	9
Varenicline	2.27	223	£2,349	3.71	£289	7	7
Varenicline + NRT l/s	2.58	254	£2,374	3.71	£347	6	5
Varenicline + bupropion	2.75	271	£2,355	3.71	£412	5	4
E-cigarettes	2.25	221	£2,190	3.71	£441	4	6
NRT l&s	2.71	267	£2,258	3.71	£499	3	3
E-cigarettes + NRT l/s	2.93	288	£2,185	3.72	£632	2	2
Bupropion + NRT l&s	3.51	345	£2,238	3.72	£737	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

Age of population

Table 27~~Table 27~~ and Table 28~~Table 28~~ displays the cost-effectiveness results for two scenarios where the age of the cohort entering the model was (arbitrarily) set equal to 20 and equal to 60. In both DSA scenarios, all of the interventions remained cost-effective and dominant versus placebo, being associated with reduced healthcare costs and increased QALYs. Changing the population age had a very minimal impact on the cost-effectiveness

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results, with both scenarios resulting in largely equivalent cost-effectiveness (NMB) ranks for each intervention as identified in the base case. The age of the cohort impacted on the size of the net monetary benefit, which substantially were decreased in the younger cohort aged 20. In addition, the older cohort, aged 60, had substantially higher baseline healthcare costs and fewer lifetime QALYs across all interventions.

Table 27: Cost-effectiveness results (per person): DSA, cohort age= 20

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£5,087	21.21	£0	11	11
Bupropion	1.73	170	£5,044	21.26	£957	10	10
NRT l/s	1.83	180	£5,037	21.27	£1,150	9	9
Bupropion + NRT l/s	1.93	190	£5,069	21.27	£1,182	8	8
E-cigarettes	2.25	221	£4,938	21.29	£1,451	7	6
Varenicline	2.27	223	£5,096	21.29	£1,609	6	7
Varenicline + NRT l/s	2.58	254	£5,108	21.31	£2,021	5	5
NRT l&s	2.71	267	£4,987	21.32	£2,100	4	3
Varenicline + bupropion	2.75	271	£5,083	21.33	£2,396	3	4
E-cigarettes + NRT l/s	2.93	288	£4,906	21.34	£2,419	2	2
Bupropion + NRT l&s	3.51	345	£4,936	21.38	£3,249	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

Table 28: Cost-effectiveness results (per person): DSA, cohort age= 60

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£17,187	11.46	£0	11	11
Bupropion	1.73	170	£16,825	11.57	£1,838	10	10
NRT l/s	1.83	180	£16,774	11.58	£1,987	9	9
Bupropion + NRT l/s	1.93	190	£16,762	11.6	£2,375	8	8

E-cigarettes	2.25	221	£16,491	11.64	£2,904	7	6
Varenicline	2.27	223	£16,641	11.64	£3,054	6	7
Varenicline + NRT l/s	2.58	254	£16,517	11.69	£3,930	5	5
NRT l&s	2.71	267	£16,339	11.71	£4,152	4	3
Varenicline + bupropion	2.75	271	£16,417	11.71	£4,230	3	4
E-cigarettes + NRT l/s	2.93	288	£16,161	11.74	£4,574	2	2
Bupropion + NRT l&s	3.51	345	£15,937	11.82	£5,950	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

All other DSAs

Supplementary Appendix 1 reports the full results for several additional DSAs. This included scenarios which: increased and decreased intervention costs by 25%; increased the annual natural cessation rate from 2% in the base case to 5%; applied discounting equal to 1.5% for costs & QALYs and 5% for costs & QALYs; increased and decreased the smoking related disease costs by 25%; increased and decreased the utility associated with each smoking related disease by 25%; and set utilities to be equivalent for smokers and former smokers. In each DSA, all cessation interventions remained cost-effective versus placebo. There were also very minimal changes to the cost-effectiveness results, each intervention typically recorded the same NMB rank in the DSA as was observed in the base case analysis.

Probabilistic Sensitivity Analysis (PSA)

The results of the PSA, conducted at a cost-effectiveness threshold of £20,000 per QALY are displayed in Table 29~~Table 29~~. All interventions were highly cost-effective in the pairwise comparison, with each intervention being cost-effective in above 99% of the 3,000 PSA iterations versus placebo.

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The PSA results for the fully incremental analysis indicated that bupropion + NRT l&s was cost-effective in 54.3% of iterations. Meanwhile, E-cigarettes + NRT l/s was cost-effective in 22.87% of iterations; varenicline + bupropion was cost-effective in 10.67% of PSA iterations; varenicline + NRT l/s in 4.53% of PSA iterations; NRT l&s was cost-effective in 4.5% of PSA iterations; and e-cigarettes were cost-effective in 3.13% of PSA iterations. Each of the other interventions had a very low probability of cost-effectiveness close or equal to 0%.

Table 29: PSA results, cost-effectiveness threshold = £20,000

Intervention	Probability cost-effective	
	Pairwise analysis (Vs. placebo)	Fully incremental analysis (Vs. all other interventions)

Placebo	N/A	0%
Bupropion	100%	0%
NRT l/s	100%	0%
Bupropion + NRT l/s	100%	0%
Varenicline	100%	0%
E-cigarettes	99.97%	3.13%
Varenicline + NRT l/s	100%	4.53%
Varenicline + bupropion	100%	10.67%
NRT l&s	100%	4.50%
E-cigarettes + NRT l/s	99.90%	22.87%
Bupropion + NRT l&s	99.93%	54.30%

At the request of the PHAC the results of one of the pairwise comparison (for e-cigarettes versus placebo) is displayed in Figure 3~~Figure 3~~. 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.

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Figure 3: Cost-effectiveness plane e-cigarettes versus placebo

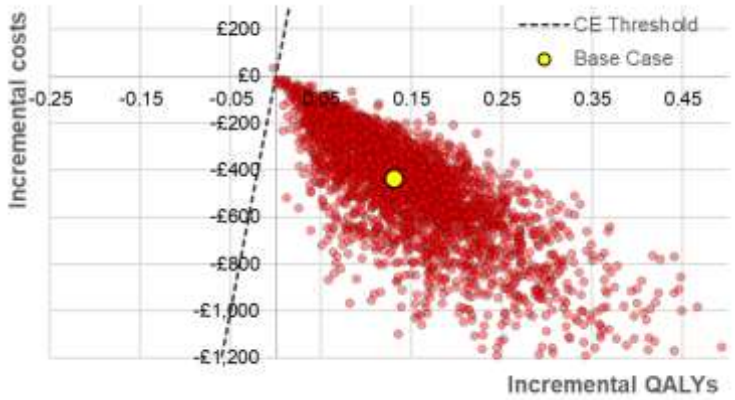

Figure 4~~Figure 4~~ displays the results of the fully incremental PSA in a cost-effectiveness acceptability curve (CEAC) for the four interventions with the largest probability of being cost-effective. The CEAC is a graph summarising the impact of uncertainty on the result of an economic evaluation, frequently expressed as an ICER (incremental cost-effectiveness ratio) in relation to possible values of the cost-effectiveness threshold. The graph plots a range of cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost-effective at that threshold on the vertical axis. The CEAC indicates

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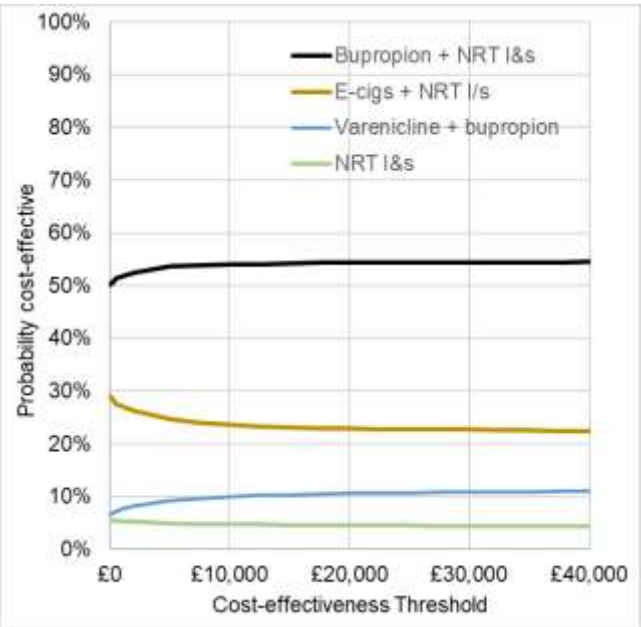
that changes to the cost-effectiveness threshold had a very minimal impact on each intervention's probability of being the most cost-effective treatment option. This is because it is the uncertainty in the *effectiveness* rather than uncertainty in cost-effectiveness which affects the ranking.

Figure 4: Cost-effectiveness acceptability curves, fully incremental analysis [a].



a: Figure plots the CEACs for the four interventions with the highest probability of cost-effectiveness. Bupropion, NRT l/s, bupropion + NRT l/s, varenicline, e-cigarettes and varenicline + NRT l/s were not included in the graph as the associated probability of cost-effectiveness was insubstantial (i.e. below 5%).

Scenario analyses

Fully incremental analysis excluding placebo

A scenario analysis was conducted where placebo was removed from the fully incremental analysis. In the scenario analysis the ten interventions were compared with one-another with NRT l/s acting as the reference category. The results of the scenario analysis were consistent with the results of the base case analysis (which included placebo).

Table 30~~Table 30~~ displays results for the incremental analysis without placebo. The DSA did not result in any changes to the base case cost-effectiveness results, as bupropion + NRT l&s remained the dominant strategy. Furthermore, each intervention retained the same CE ranking when ordered by NMB. The only difference between the analyses which included and excluded placebo was the absolute values of lifetime costs and QALYs within each intervention arm which increased and decreased in the scenario analysis respectively. This

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was due to variation in the effectiveness rate applied for the reference category, i.e. the probability of cessation for NRT l/s. As intervention effectiveness was relatively lower for NRT l/s in the scenario analysis than in the base case, all other interventions had a lower effectiveness rates (as NRT l/s acted as the reference category). The impact was equivalent to reducing the effectiveness rate for placebo in the base case analysis.

Table 30: Cost-effectiveness results (per person): Scenario analysis, fully incremental analysis without placebo

Intervention	RR vs NRT l/s	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs NRT l/s	CE rank DSA	CE rank (base case)
Bupropion	N/A	156	£11,394	15.16	-£205	10	10
NRT l/s	1.48	231	£11,369	15.17	£0	9	9
Bupropion + NRT l/s	0.94	148	£11,383	15.18	£166	8	8
Varenicline	1.24	194	£11,349	15.21	£811	7	7
E-cigarettes	1.23	192	£11,194	15.21	£930	6	6
Varenicline + NRT l/s	1.05	165	£11,305	15.24	£1,4,13	5	5
Varenicline + bupropion	1.91	293	£11,249	15.25	£1,774	4	4
NRT l&s	1.41	220	£11,160	15.25	£1,791	3	3
E-cigarettes + NRT l/s	1.50	235	£11,039	15.27	£2,308	2	2
Bupropion + NRT l&s	1.60	250	£10,964	15.32	£3,426	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

Including additional e-cigarette study

At the request of the PHAC, a scenario analysis was conducted which included an additional study in the NMA. The additional study was conducted by Hajek 2019 (17) and compared e-cigarettes with placebo.

The results of the scenario analysis are displayed in Table 31~~Table 31~~. Results were not consistent with the base case analysis which did not include the study by Hajek 2019 (17). E-cigarettes + NRT l/s became the most cost-effective strategy. E-cigarettes + NRT l/s resulted in the same number of quitters at 12-months when compared with bupropion + NRT l&s but had lower intervention costs and was therefore cost-effective. The individual e-cigarettes strategy also had an increase in the associated NMB rank, moving from ranking sixth in the base case to third in the scenario analysis.

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Table 31: Cost-effectiveness results (per person): Scenario analysis, including Hajek 2019 (17) study

Intervention	RR vs placebo	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs placebo	CE rank DSA	CE rank (base case)
Placebo	N/A	98	£11,523	15.11	N/A	11	11
Bupropion	1.73	170	£11,314	15.18	£1,723	10	10
NRT l/s	1.83	180	£11,284	15.19	£1,960	9	9
Bupropion + NRT l/s	1.91	188	£11,285	15.20	£2,110	8	8
Varenicline	2.26	222	£11,189	15.24	£2,889	7	7
Varenicline + NRT l/s	1.91	252	£11,189	15.27	£3,591	6	5
NRT l&s	2.57	253	£11,083	15.27	£3696	5	3
Varenicline + bupropion	2.74	270	£11,125	15.29	£4,007	4	4
E-cigarettes	2.75	271	£10,917	15.29	£4,236	3	6
Bupropion + NRT l&s	3.47	341	£10,816	15.36	£5,831	2	1
E-cigarettes + NRT l/s	3.47	341	£10,716	15.36	£5,930	1	2

RR= relative risk versus placebo
CE= cost-effectiveness

Applying costs of e-cigarettes to the NHS

A scenario analysis was conducted which applied costs of e-cigarettes to the NHS. This contrasted from the base case analysis where e-cigarettes were assumed to only be available via private purchase. In the scenario analysis the NHS cost of e-cigarettes was equal to £55.75 which assumed for 48% of costs would be incurred via prescriptions and 52% would be purchased privately OTC. When including costs for usual care the total costs of: e-cigarettes increased from £82.96 in the base case to £138.71 in the scenario analysis; and e-cigarettes + NRT l/s increased from £131.84 in the base case to £187.59 in the scenario analysis.

The results of the scenario analysis are displayed in Table 32~~Table 32~~. Results were very similar to the base case analysis. Bupropion + NRT l&s remained the cost-effective strategy. There was a minor change in the results for the e-cigarettes intervention, which became the seventh ranking cost-effective strategy as opposed to the sixth ranking strategy in the base case analysis (trading positions with varenicline). All other strategies had an identical NMB rank.

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Table 32: Cost-effectiveness results (per person): Scenario analysis, applying NHS costs for e-cigarettes

Intervention	RR vs placebo	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs placebo	CE rank DSA	CE rank (base case)
Placebo	1.00	98	£11,523	15.11	£0	11	11
Bupropion	1.73	170	£11,314	15.18	£1,723	10	10
NRT l/s	1.83	180	£11,285	15.19	£1,960	9	9
Bupropion + NRT l/s	1.93	190	£11,294	15.20	£2,158	8	8
E-cigarettes	2.25	221	£11,146	15.24	£2,970	7	6
Varenicline	2.27	223	£11,244	15.24	£2,913	6	7
Varenicline + NRT l/s	2.58	254	£11,186	15.27	£3,615	5	5
Varenicline + bupropion	2.75	271	£11,122	15.29	£4,031	4	4
NRT l&s	2.71	267	£11,035	15.29	£4,035	3	3
E-cigarettes + NRT l/s	2.93	288	£10,959	15.31	£4,567	2	2
Bupropion + NRT l&s	3.51	345	£10,802	15.37	£5,928	1	2

Mental health subgroup analysis

Fully incremental analysis

The cost-effectiveness results for the mental health subgroup are displayed in Table 33~~Table 33~~. The fully incremental analysis identified Bupropion + NRT l/s as the most cost-effective and dominant strategy versus each of the other interventions. This differed from results in the general population where bupropion + NRT l&s was the most cost-effective strategy.

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Bupropion + NRT l/s had the lowest total healthcare costs (£18,728) and highest lifetime QALYs (12.06) per person, and subsequently the highest net monetary benefit vs. placebo, equal to £6,797 per person. As with the base case analysis, cost-effectiveness was driven by the effectiveness parameters. The RR rank for each intervention directly corresponded with the net monetary benefit rank is the cost-effectiveness analysis, Table 33~~Table 33~~. The major difference between the mental health subgroup and the base case analysis were related to the values of lifetime total costs, which substantially increased, and lifetime total QALYs, which substantially decreased.

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Table 33: Cost-effectiveness results (per person): Fully incremental analysis, mental health subgroup

Intervention	RR vs. placebo (mean, rank)	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE Rank
Placebo	1.00 (7)	56	£20,541	11.81	£0	7
Bupropion	1.79 (6)	102	£20,327	11.84	£870	6
NRT l/s	1.89 (5)	106	£20,229	11.84	£981	5
Varenicline	2.29 (4)	128	£20,444	11.84	£1,332	4
NRT l&s	3.97 (3)	223	£19,674	11.86	£3,334	3
Bupropion + NRT l&s	4.24 (2)	237	£19,575	11.94	£3,657	2
Bupropion + NRT l/s	7.00 (1)	392	£18,728	12.06	£6,797	1

RR= relative risk versus placebo
CE= cost-effectiveness

Pairwise results vs. placebo

Table 34~~Table 34~~ displays the pairwise cost-effectiveness results for each intervention in the mental health subgroup versus placebo. As with the base case analysis (in the general population), each intervention was highly cost-effective versus placebo. All interventions had a dominant ICER as they each resulted in healthcare savings and additional QALYs. All of the interventions resulted in substantially more quitters at 12-months, and consequently reductions in the prevalence of smoking related diseases and smoking related mortality for the mental health subgroup.

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Table 34: Incremental cost-effectiveness results (per person): Pairwise results vs. placebo, mental health subgroup

Intervention	RR vs. placebo	Incremental outcomes vs. placebo			ICER
		Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	
Bupropion	1.79	46	-£214	0.03	Dominant
NRT l/s	1.89	50	-£312	0.03	Dominant
Varenicline	2.29	72	-£97	0.03	Dominant
NRT l&s	3.97	167	-£867	0.05	Dominant
Bupropion + NRT l&s	4.24	181	-£966	0.13	Dominant
Bupropion + NRT l/s	7.00	336	-£1,813	0.25	Dominant

Deterministic sensitivity analysis (RR values)

A DSA was conducted for the mental health subgroup where the effectiveness rates were set equal to the lower 95% CI RR value. The full results for the lower effectiveness scenario are presented in Table 35~~Table 35~~. When applying the lower 95% RR, bupropion + NRT l&s became the most cost-effective strategy. Bupropion + NRT l/s moved from being most cost-effective to being less effective and cost-effective than placebo. In addition, NRT l&s, and bupropion had lower 95% CI RR values below 1 resulting in fewer quitters at 12-months than placebo, and were consequently dominated by placebo in the DSA. NRT l/s was marginally more effective than placebo (lower 95% CI RR = 1.06) and resulted in 3 extra quitters at 12-months. In the DSA, NRT l/s was associated with increased healthcare costs versus placebo, but generated additional lifetime QALYs, and was cost-effective in the DSA with a positive NMB equal to £21. Finally, varenicline had a lower 95% CI RR value substantially in excess of 1 and therefore dominated placebo in the DSA.

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Table 35: Cost-effectiveness results (per person): Fully incremental analysis, mental health subgroup: DSA lower 95% CI RR

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
NRT l&s	0.16	9	£20,920	11.77	-£1,077	7	3
Bupropion + NRT l/s	0.83	47	£20,690	11.80	-£290	6	1
Bupropion	0.85	48	£20,635	11.80	-£218	5	6
Placebo	1.00	56	£20,541	11.81	£0	4	7
NRT l/s	1.06	59	£20,571	11.81	£21	3	5
Varenicline	1.33	75	£20,594	11.82	£221	2	4
Bupropion + NRT l&s	1.95	109	£20,379	11.85	£951	1	2

RR= relative risk versus placebo
CE= cost-effectiveness

In contrast, the DSA applying upper 95% CI values for the RR parameters resulted in all interventions being highly cost-effective versus placebo. Application of the upper 95% CI RR resulted in substantially increased numbers of quitters for each intervention versus placebo, which substantially increased each intervention's associated NMB. Full results for the higher effectiveness DSA are displayed in Table 36~~Table 36~~. Bupropion + NRT l/s remained the cost-effective strategy, meanwhile similar NMB ranks were observed for the other interventions across the DSA and base case analyses.

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Table 36: Cost-effectiveness results (per person): Fully incremental analysis, mental health subgroup: DSA upper 95% CI RR

Intervention	Upper 95% CI RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1.00	56	£20,541	11.81	£0	7	7
Bupropion	4.01	225	£19,601	11.93	£3.440	6	6
Varenicline	4.34	243	£19,610	11.94	£3,705	5	4
NRT l/s	5.40	302	£19,152	11.99	£5,044	4	5
Bupropion + NRT l&s	7.63	427	£18,467	12.08	£7,582	3	2
NRT l&s	7.92	444	£18,383	12.09	£7,906	2	3
Bupropion + NRT l/s	7.98	447	£18,408	12.10	£7,931	1	1

RR= relative risk versus placebo
CE= cost-effectiveness

Probabilistic Sensitivity Analysis (PSA)

The results of the PSA for the mental health subgroup, conducted at a cost-effectiveness threshold of £20,000 per QALY, are displayed in Table 37~~Table 37~~. All interventions were highly cost-effective in the pairwise comparison versus placebo: bupropion, varenicline, NRT l/s, bupropion + NRT l/s and bupropion + NRT l&s were all cost-effective in over 90% of the 3,000 PSA iterations. There was more uncertainty associated with NRT l&s which was cost-effective in 79% of all PSA iterations versus placebo.

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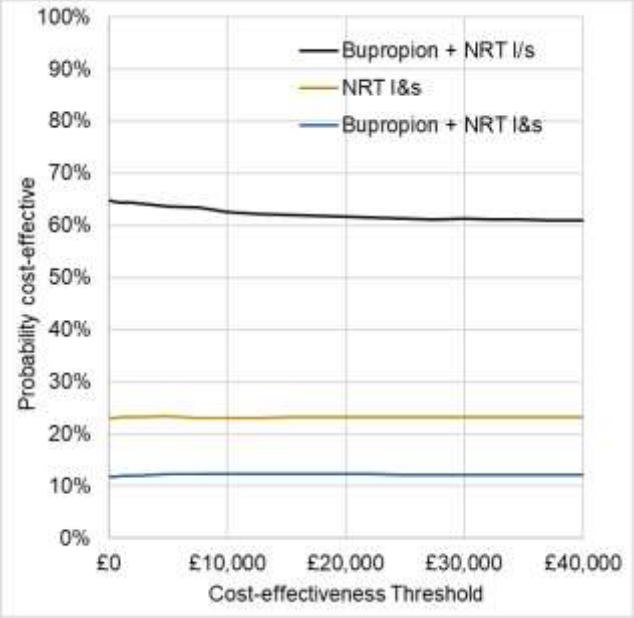
The PSA results for the fully incremental analysis indicated that bupropion + NRT l/s was cost-effective in 62% of iterations. Meanwhile, NRT l&s was cost-effective in 23.2% of PSA iterations and bupropion + NRT l&s was cost-effective in 12.2% of PSA iterations. Each of the other interventions had a very low probability of cost-effectiveness close or equal to 0%.

Table 37: PSA results mental health subgroup, cost-effectiveness threshold = £20,000

Intervention	Probability cost-effective	
	Pairwise analysis (Vs. placebo)	Fully incremental analysis (Vs. all other interventions)
Placebo	N/A	0%
Bupropion	92.83%	1.57%
Varenicline	95.23%	0.60%
NRT l/s	95.13%	0.73%
Bupropion + NRT l&s	93.20%	12.27%
NRT l&s	78.83%	23.17%
Bupropion + NRT l/s	96.33%	61.67%

Figure 5~~Figure 5~~ displays the results of the fully incremental PSA in a cost-effectiveness acceptability curve (CEAC) for the three interventions with the largest probability of being cost-effective in the mental health subgroup. As with the base case analysis, the CEAC indicates that changes to the cost-effectiveness threshold had a very minimal impact on each intervention's probability of being the most cost-effective treatment option.

Figure 5: Cost-effectiveness acceptability curves, mental health subgroup, fully incremental analysis [a]



a: Figure plots the CEACs for the three interventions with the highest probability of cost-effectiveness. Bupropion, NRT l/s, and varenicline were not included in the graph as the associated probability of cost-effectiveness was insubstantial (i.e. below 2.5%).

Exploratory analysis: E-cigarette health harms

A threshold analysis was performed to determine the total amount of QALYs/costs worth of adverse events that would be required per person to make e-cigarettes not cost-effective vs. usual care. The results of the threshold analysis are displayed in Figure 6~~Figure 6~~, which depicts the net monetary benefit for E-cigarettes vs. placebo. In each instance, the NMB has been re-estimated to account for safety impacts per person associated with e-cigarettes, and the number of e-cigarette users who have an adverse event. The Figure includes the cost per adverse event in £, which could include NHS treatment costs, or health benefits as monetized QALYs (for example, by using the NICE CE threshold equal to £20,0000). For example, E-cigarettes would not be cost-effective if 5% of people who used E-cigarettes experienced an AE, and the net cost per AE was equal to £75,000.

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Figure 6: E-cigarettes health harms

	NMB [1]	Cost per AE per person							
		£500	£1,500	£5,000	£10,000	£25,000	£50,000	£75,000	£100,000
Absolute % of e-cig users with AE	1.00%	£3,020	£3,010	£2,975	£2,925	£2,775	£2,525	£2,275	£2,025
	2.50%	£3,013	£2,988	£2,900	£2,775	£2,400	£1,775	£1,150	£525
	5.00%	£3,000	£2,950	£2,775	£2,525	£1,775	£525	-£725	-£1,975
	7.50%	£2,988	£2,913	£2,650	£2,275	£1,150	-£725	-£2,600	-£4,475
	10.00%	£2,975	£2,875	£2,525	£2,025	£525	-£1,975	-£4,475	-£6,975
	12.50%	£2,963	£2,838	£2,400	£1,775	-£100	-£3,225	-£6,350	-£9,475
	15.00%	£2,950	£2,800	£2,275	£1,525	-£725	-£4,475	-£8,225	-£11,975
	17.50%	£2,938	£2,763	£2,150	£1,275	-£1,350	-£5,725	-£10,100	-£14,475
	20.00%	£2,925	£2,725	£2,025	£1,025	-£1,975	-£6,975	-£11,975	-£16,975
	22.50%	£2,913	£2,688	£1,900	£775	-£2,600	-£8,225	-£13,850	-£19,475
	25.00%	£2,900	£2,650	£1,775	£525	-£3,225	-£9,475	-£15,725	-£21,975

1: Results are displayed as incremental net monetary benefit (NMB) vs. placebo. Any NMB greater than zero indicates that the intervention is cost-effective. The cost-effectiveness threshold was set equal to £20,000.

Exploratory analysis: E-cigarette uptake

A scenario analysis was performed to illustrate the potential gateway impact of e-cigarettes. The scenario analysis investigated the level of smoking uptake due to e-cigarettes in non-smokers that would be required before e-cigarettes were considered to do more harm than good in the UK population. This given the population benefits that e-cigarettes generate due to increasing smoking cessation in current smokers who want to quit in the UK.

The analysis involved two calculations, firstly we approximated the total population benefit of e-cigarettes assuming e-cigarettes were available as a smoking cessation treatment in the UK. Secondly, we approximated the total harm from e-cigarettes in the UK population of non-smokers who took up smoking due to e-cigarettes. We then summed these values to identify the net impact of e-cigarettes in the UK population

Population health benefits if e-cigarettes are provided to aid smoking cessation

The total population benefits for e-cigarettes due to smoking cessation were estimated by multiplying the total health care savings and QALYs gained per person for e-cigarettes versus placebo (as identified in the base case analysis), by the number of people in the population who use e-cigarettes to aid with smoking cessation. When used to aid cessation in current smokers, E-cigarettes resulted in £433 of healthcare savings and 0.13 QALYs gained per person (Table 21~~Table 21~~).

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The total number of people in the UK population who use e-cigarettes for smoking cessation was estimated to equal 1.6 million. This was based on: an ONS estimate for the total number of people who used e-cigarettes in the UK which was equal to roughly 3.2 million in 2018 (55); an assumption that 50% of this population use e-cigarettes for smoking cessation. Therefore, the total cost savings for e-cigarettes in this population is equal to roughly £700 million, that is, £433 in healthcare savings per person (Table 21~~Table 21~~) multiplied by the

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size of the population, 1.6 million. The total health benefits for e-cigarettes in this population versus placebo is equal to roughly 210,000 QALYs, that is, 0.13 QALYs per person (Table 21~~Table 21~~) multiplied by the size of the population, 1.6 million.

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Population harm following smoking uptake due to e-cigarettes

To estimate the population harm due to e-cigarette uptake we calculated the incremental lifetime healthcare savings and QALYs gained for non-smokers (including never smokers and ex-smokers) versus smokers and multiplied this by the number of people who take up smoking due to e-cigarettes. We assumed that quitters could be used as a reasonable approximation for the lifetime costs and QALYs of all non-smokers (i.e. both ex-smokers and never smokers). Therefore, we obtained the costs and QALYs per quitter versus smoker from the economic model.[e]

The total healthcare costs and QALYs gained per quitter were obtained from the economic model which was run for two scenarios. Firstly, the probability of quitting at 12-months was set equal to 100% meaning all 1,000 people in the population quit. Secondly the probability of quitting at 12-months was set equal to 0% meaning all 1,000 people in the population continued to smoke. The economic model predicted that each additional quitter (i.e. non-smoker) obtained at 12-months would result in lifetime healthcare savings equal to £3,523 and 1.05 additional lifetime QALY (both outcomes discounted at 3.5%).

The cost savings and QALYs gained between populations of quitters (i.e. non-smokers) and smokers is shown in Table 38~~Table 38~~.

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Table 38: Cost-effectiveness results (per person): Population of quitters versus population of smokers at 12-months.

	Quitter (i.e. non-smoker) P(quit) @12-months = 100%	**Smoker** P(quit) @12-months = 0%	**Incremental**
Intervention costs	N/A	N/A	N/A
Comorbidity costs (NHS)			
Stroke	£4,083	£5,413	-£1,330
Lung cancer	£591	£1,217	-£627
MI	£802	£1,268	-£466
CHD	£2,072	£2,349	-£277
COPD	£703	£1,525	-£822
Asthma	£15	£16	-£1
Total healthcare costs	£8,264	£11,787	-£3,523
QALYs	16.06	15.00	1.05
Net monetary benefit			£24,523
Productivity costs (work absenteeism)	£86	£1,211	-£1,125

[e] We assumed that quitters could be used as a reasonable approximation for the lifetime costs and QALYs for non-smokers including both never smokers and ex-smokers. However, we note that ex-smokers may have a lower health related quality of life, and increased risk of smoking related morbidities when compared to never-smokers. Consequently, this analysis is likely to slightly underestimate total population impact of taking up smoking due to e-cigarettes.

We investigated the total harm associated with the gateway effects of e-cigarettes in a two-way data table. The data table varied both the % of people in the UK non-smoking population who use e-cigarettes and the % of people who take up smoking following e-cigarette use. The population of non-smokers in UK was assumed to be equal to 54.5 million, estimated as the summed total of 54% never smokers and 28% ex-smokers reported in the HSE (2018) (49) and applying population size of 66.4 million (ONS) (13).

Net impact of e-cigarettes in the UK

The total positive budget impact of e-cigarettes due to promoting smoking cessation was summed with the harm of e-cigarettes due to increasing smoking uptake in previous non-smokers (including never smokers and ex-smokers). The net impact of e-cigarettes in these populations is displayed in the two-way data table in Figure 7~~Figure 7~~.

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For example, our results indicate that e-cigarettes would still likely have a positive budget impact if: 1.5% or fewer non-smokers (never smokers and ex-smokers) take up e-cigarettes *and* 20% of this population become regular tobacco smokers due to e-cigarette use; or alternatively, if 5% or fewer non-smokers (never smokers and ex-smokers) took up e-cigarettes *and* 5% or of this population become regular tobacco smokers due to e-cigarette use.

We do not know the precise number of people who take up smoking due to e-cigarettes in the UK. A meta-analysis by Khouja et al. (2020) (56) indicates that the risk of future tobacco smoking is 2.92 higher following e-cigarette use in young adult populations who had never previously smoked tobacco. This analysis indicates that e-cigarettes are likely to have net positive impact when assuming relatively low levels of e-cigarette use in non-smokers. The action on smoking and health (2019) (57) report indicates that regular e-cigarette usage in people aged between 11 to 18 years old is 1.6% (use e-cigarettes more than once per week); meanwhile any e-cigarette usage (usage more than once per week, and usage less than weekly) was equal to 4.9%.

Figure 7: E-cigarettes Uptake Analysis

Budget impact (£ millions)		% of new e-cig users who take up smoking								
		1.00%	2.50%	5.00%	7.50%	10.00%	15.00%	20.00%	25.00%	50.00%
% of non-smokers who take up e-cigarettes	1.00%	£4,719	£4,519	£4,185	£3,850	£3,516	£2,848	£2,180	£1,512	-£1,830
	1.50%	£4,652	£4,352	£3,850	£3,349	£2,848	£1,846	£843	-£159	-£5,171
	2.50%	£4,519	£4,017	£3,182	£2,347	£1,512	-£159	-£1,830	-£3,500	-£11,853
	5.00%	£4,185	£3,182	£1,512	-£159	-£1,830	-£5,171	-£8,512	-£11,853	-£28,560
	7.50%	£3,850	£2,347	-£159	-£2,665	-£5,171	-£10,183	-£15,195	-£20,207	-£45,266
	10.00%	£3,516	£1,512	-£1,830	-£5,171	-£8,512	-£15,195	-£21,877	-£28,560	-£61,972
	12.50%	£3,182	£676	-£3,500	-£7,677	-£11,853	-£20,207	-£28,560	-£36,913	-£78,679
	15.00%	£2,848	-£159	-£5,171	-£10,183	-£15,195	-£25,219	-£35,242	-£45,266	-£95,385
	20.00%	£2,180	-£1,830	-£8,512	-£15,195	-£21,877	-£35,242	-£48,607	-£61,972	-£128,798

Discussion

Key findings

Base case results

The objective of this economic analysis was to address a key question in the NICE scope. That is, to establish the most effective and cost-effective means of smoking cessation (including e-cigarettes). When comparing each intervention with one another, bupropion + NRT l&s was the most cost-effective strategy, across the base case and several deterministic scenarios. This finding was associated with high levels of uncertainty as the PSA indicated that bupropion + NRT l&s was cost-effective in 54% of PSA iteration but was not the most cost-effective strategy in the remaining 46% of iterations.

The uncertainty in the results was due to uncertainty in the effectiveness estimates. Bupropion + NRT l&s had relatively wide 95% confidence intervals around the RR parameter, meaning the interventions was not cost-effective for the analysis that applied the lower 95% confidence interval for the RR parameters. In addition, bupropion + NRT l&s was not the most cost-effective strategy for the scenario analysis where the effectiveness rates were updated with the NMA that included the Hajek et al. (2019) (17) study comparing e-cigarettes versus NRT l/s. When including evidence from the Hajek et al. (2019) study (17), e-cigarettes + NRT l/s replaced bupropion + NRT l&s as the most cost-effective strategy.

This economic evaluation confirmed previous analyses which demonstrated the general cost-effectiveness of the ten pharmaceutical smoking cessation interventions: NRT l/s, NRT l&s, bupropion, varenicline, e-cigarettes, bupropion + NRT l/s, bupropion + NRT l&s, varenicline + NRT l/s, varenicline + bupropion, and E-cigarettes + NRT l/s were all highly cost-effective interventions versus placebo. The results of the economic analysis assume pharmaceutical interventions are delivered alongside behavioural support which may be offered as usual care by LSSS.

The cost-effectiveness of the smoking cessation interventions was driven by the effectiveness parameters, which resulted in increased numbers of non-smokers at 12-months when compared with placebo. Increasing the number of quitters at 12-months reduced the number of smokers throughout the remainder of the economic model. Consequently, this reduced the health and economic burden associated with smoking, through reductions in the occurrence of smoking related diseases and smoking related mortality.

Across all base case and deterministic scenarios, when any intervention was more effective than placebo, it was also cost-effective. In the economic model, populations who continue 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 smoking cessation interventions outweighed the relatively modest upfront intervention costs.

The PSA identified very low levels of uncertainty regarding the cost-effectiveness of each intervention versus placebo. NRT l/s, NRT l&s, bupropion, varenicline, e-cigarettes, bupropion + NRT l/s, bupropion + NRT l&s, varenicline + NRT l/s, varenicline + bupropion, and E-cigarettes + NRT l/s were cost-effective in above to 99% of the PSA iterations versus placebo.

Similarly, the DSA results showed that the conclusions were robust to changes in inputs, indicating that each intervention was likely to be cost-effective versus placebo across a variety of scenarios and settings. This included several pessimistic scenarios such as reducing the effectiveness parameter equal to the 95% lower confidence interval, increasing intervention costs by 25%, increasing the discount rate to 5% for costs and QALYs, and even when reducing the time horizon to 5-years. The nine pharmaceutical interventions remained cost-effective when results were averaged across all population ages between 12 and 100, and when estimated specifically for populations aged 20 and 60.

Mental health subgroup

When compared with the base case analysis, the mental health subgroup model had a higher underlying prevalence of smoking related diseases, higher probabilities of smoking related diseases and lower absolute probabilities of smoking cessation at 12-months. As a consequence, each person in the economic model had decreased QALYs and increased costs across the lifetime.

When comparing each intervention with one another, bupropion + NRT l/s was the cost-effective strategy in the mental health subgroup. This result differed from the analysis in the base case population where bupropion + NRT l&s was cost-effective. Results in the mental health subgroup were uncertain: the PSA results indicated that bupropion + NRT l/s was cost-effective in around 62% of PSA iterations, but not cost-effective in 38% of PSA iterations.

In the pairwise comparisons, each of bupropion, NRT l/s, varenicline, NRT l&s, bupropion + NRT l/s and bupropion + NRT l&s were cost-effective and dominant versus placebo. As with the base case analysis, the cost-effectiveness results were driven by intervention effectiveness, i.e. where an intervention was more effective than placebo, it was always found to be cost-effective. There was some uncertainty associated with the effectiveness estimates for bupropion, NRT l&s, and bupropion + NRT l/s. The lower 95% confidence intervals for the RR parameter were below zero indicating that the NICE NMA (5) did not establish these interventions to be (statistically) significantly more effective than placebo. However, the PSA results suggested low levels of uncertainty in the cost-effectiveness results for each of the interventions versus placebo: NRT l/s, bupropion, varenicline, bupropion + NRT l&s, and bupropion + NRT l/s were almost always cost effective (>93%), and NRT l&s had a very high probability of cost-effectiveness (78%).

In general, there were higher levels of uncertainty in the point estimates for the mental health subgroup than for the base case population. For example, in the NICE NMA: in the mental health subgroup bupropion had a RR of 1.79 with 95% confidence intervals equal to 0.85 to 4.01 (see Table 21, NICE evidence review K (5)); in the general population bupropion had a RR of 1.73 with 95% confidence intervals equal to 1.52 to 1.95 (see Table 20, NICE evidence review K (5)). It is possible that the reduced certainty is related to true differences between the populations. However, such differences may be due to a reduction in the number of studies and participants for NMAs in the mental health subgroup when compared with the general population NMA. It is possible that the reduced number of studies impacted the reliability of the NMA which produced some logical inconsistencies for the mental health subgroup. For example, bupropion + NRT l/s was more effective and more cost-effective than bupropion + NRT l&s, which might be questionable given that: (i) bupropion is an effective intervention for smoking cessation; and (ii) NRT l&s was more effective and cost-effective than NRT l/s.

Uncertainty in effectiveness rates

The economic results consistently indicated that the most effective intervention was the most cost-effective. Further, the RR rank for each intervention was usually an exact indication for the interventions cost-effectiveness (NMB) rank. Therefore, the key area of uncertainty in the economic model related to the effectiveness rates obtained from the NMA in NICE evidence review K (5). As intervention effectiveness was the key determinate of cost-effectiveness, any methodological limitations associated with the NMA are also applicable to the results of the cost-effectiveness analysis.

The NICE NMA (5) pooled results across broad intervention classes, which may have differed in terms of the type of intervention provided. For example, the NMA did not require the pharmacological interventions to be delivered at the same dosage or for the same duration across the included studies. In addition, the NMA grouped studies which both included and excluded behavioural support as an addition to the pharmacological interventions and placebo. The type of behavioural support was consistent within studies but differed across studies. This may have influenced absolute probabilities of cessation for both arms of the RCT. However, as behavioural support was consistent within studies it would be unlikely to affect the RR parameters and therefore is likely to have had a minimal impact on the cost-effectiveness results.

There was also considerable uncertainty in the comparators included in the NICE NMA (5). For example, all placebo interventions were grouped as the same intervention class. However, the definition of placebo may differ across intervention categories, for instance the placebo e-cigarette may be substantially different to placebo tablets, and effect sizes may differ between the two. If, for example, placebo e-cigarettes are more effective than placebo tablets then the NMA may have underestimated the effectiveness of e-cigarettes. The PHAC discussed this limitation and agreed that it did not reduce their certainty in the usefulness of the estimates, but was borne in mind for their interpretation of the NMA results.

We included placebo as the comparator for the economic analysis as this was considered to be the most homogenous comparator, and had the largest number of participants across all comparators included in the NMA. The NICE NMA (5) reported results for three additional comparators: usual care, wait list and no drug treatment. Whilst there were some differences in the effectiveness values, all interventions in the NICE NMA were significantly more effective than both usual care and no intervention (excluding e-cigarettes which were non-significantly more effective than no drug treatment). If we had included usual care or no drug treatment as the comparator, all interventions would have still been cost-effective in the pairwise comparisons.

In contrast, many of the interventions were not significantly more effective than the waitlist control in the NICE NMA (5). If waitlist had been used as the comparator in the economic model then the probability of cost-effectiveness for each intervention would have been substantially reduced. However, waitlist was only used in three of the RCTs that informed the NMA. The reduced study number for the waitlist control is likely to be the key reason why interventions were not significantly effective when using this comparator. The selection of a different comparator (usual care, no drug treatment or waitlist) would not have influenced the cost-effectiveness results when establishing the most cost-effective intervention. This is because all comparators were included as part of the NMA, and therefore the RR for each intervention versus another intervention would remain consistent irrespective of the comparator that is selected.

Finally, given the limitations in the NICE NMA, there was substantial uncertainty in the absolute rate of cessation for placebo. In the base case analysis, the probability of cessation

in placebo was equal to 11.49% at 6-months. Due to the high level of uncertainty, this value was varied to a low estimate of 9.77% and a high estimate of 13.22% (-/+ 15% of mean value). The base case results were consistent for both deterministic scenarios which applied the lower and higher estimate. We applied a substantially larger range for this parameter in the DSA than is indicated by the associated 95% CI where the lower 95% CI for the rate of cessation for placebo was equal to 11.12% whilst the higher 95% CI was equal to 11.86%. Therefore, the impact of uncertainty in this parameter on the cost-effectiveness findings is likely to be minimal.

E-cigarette health harms and uptake

In the base case analysis, E-cigarettes were found to be highly cost-effective and dominant versus placebo. However, the PHAC had concerns regarding the base case cost-effectiveness results as there is currently no evidence to indicate whether E-cigarettes are safe over the long term. The safety analysis suggests that e-cigarettes would need to cause very high number of adverse outcomes before they were considered not to be cost-effective versus placebo. For example, e-cigarettes would remain cost-effective if: over 25% of users had an adverse event costing £10,000, similar to 12 years maintenance cost for treating COPD [NG115]; up to 10% of users had an adverse event costing £25,000, which is similar to the 5-year treatment costs for stoke [NICE CG92]; and up to 5% of users had an adverse event costing £50,000, which is similar to the estimated lifetime cost of treating coronary heart disease [Walker].

The PHAC also had concerns regarding the potential for e-cigarettes to promote smoking uptake if they were made available by local stop smoking services, for example, by acting as a gateway to tobacco smoking in non-smoking populations. The results of the exploratory analysis indicated that e-cigarettes would have a net positive impact on health and healthcare resources if acting as a gateway to tobacco smoking in up to 0.25% on the non-smoking UK population. This value is equivalent to 2.5% of non-smokers taking up e-cigarettes and up to 10% of this population subsequently taking up tobacco smoking.

According to the HSE (2018) (49) report, the total number of e-cigarette users in the UK is equal to 3.2 million. The same report indicates that 82% of people in the UK are classified as non-smokers, which equate to around 54.5 million given an ONS UK population estimate of 66.4 million. Therefore, the uptake of tobacco smoking due to e-cigarettes would need to be equal to 136,000 (i.e. 2.5% of 54.5 million) for e-cigarettes to be considered to do more harm than good. This would represent around 5% of the total population who currently use e-cigarettes. The percentage would rise further when accounting for the likely substantial proportion of e-cigarette users who are current smokers attempting to quit.

The exploratory analysis for tobacco smoking uptake has several limitations and any conclusions should be treated with caution. We are not aware of any published evidence that establishes how many non-smokers in the UK increase uptake of tobacco smoking directly due to e-cigarettes. In addition, the analysis was conducted for a population of non-smokers including both ex-smokers and never smokers. It is possible that the gateway effect is most relevant for younger populations of never smokers. Had the analysis been limited to younger populations of never smokers then the overall population size where e-cigarettes do harm would have been substantially reduced. This would have allowed for a much larger gateway impact associated with e-cigarettes. Finally, the analysis was not intended to be a full budget impact assessment relating to the impact of offering e-cigarettes in LSSS. It is likely that many non-smokers who uptake tobacco smoking due to e-cigarettes would do so via private purchases and irrespective of whether e-cigarettes are recommended for use in LSSS.

Costs to the Local Authority

Stop smoking services are funded by the local authority (LA). The PHAC questioned whether the smoking cessation interventions would be cost saving to the LA assuming that the LA incurred all of the intervention costs. The benefits of stopping smoking included in the economic model were related to reductions in smoking related diseases, and therefore represented savings that would be recouped by the NHS, rather than the LA. Therefore, it was not possible to directly address the question raised by the PHAC within the economic model.

In addition to the health benefits and NHS treatment costs included in the economic model, tobacco smoking is associated with social care costs. For example, smoking is associated with an increased risk of stroke and dementia, which are associated with substantial personal and private costs for care. A report by Landman Economics, estimated the costs of smoking to the social care system for older people in the England. According to the report, the relative risk of receiving LA funded domiciliary care was equal to 3.93 for smokers versus nonsmokers. Furthermore, the report estimated that LA funded domiciliary care due to smoking could be in excess of £720 million per year. Based on HSE (2018) estimates, there are around 860,000 current smokers aged 65 and over in England. Therefore, each smoker aged 65 or over is estimated to cost the LA £840 per year (i.e. £720 million/ 860,000).

In the cost-effectiveness analysis, the least effective smoking cessation intervention (bupropion) increased smoking cessation versus placebo by roughly 8%, whereas the most effective intervention (bupropion + NRT l&s) increased the absolute percentage of smoking cessation by around 25% versus placebo. Consequently, the estimated saving per person to the LA due to the smoking cessation interventions would range from £67 per year to £210 per year (8% and 25% of £840 respectively). The cost of the pharmaceutical smoking cessation interventions ranged from a low of £48 (bupropion) to a high of £205 (varenicline + bupropion) per person. These approximations indicate that any LA expenditure to fund smoking cessation interventions may be recouped in as little as 2-years due to savings from reduced need for domiciliary care.

Comparison to other models

Results from this economic modelling report were comparable to results reported by studies in the existing literature. The BENESCO model is a Markov model that is used to estimate the lifetime cost and benefits of smoking. The BENESCO model has been applied across a variety of populations including the USA, the Caribbean, central America, and Europe (58-60). In keeping with a running theme across all of the economic modelling results in the smoking cessation and harm reduction literature, all of the results using the BENESCO model found that effective interventions are highly cost-effective when compared to placebo or usual care. As demonstrated in this economic analysis, smoking cessation 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 analysis.

The model structure, resource constraints and a lack of data made it impossible to categorize 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 multiple quit attempts beyond the initial intervention in the first year. However, the incorporation of a background 'net' quit rate into the model addresses this limitation. Sensitivity analysis showed that this input has some impact on the results but would need to change significantly in order for the direction of results to change.

Model estimates for the effectiveness of interventions were provided by NICE and obtained from the updated NMA by Thomas et al. (2020). These results were obtained from RCTs and therefore didn't account for the impact of patient choice, and how intervention effectiveness may translate from a clinical to a real-world setting. For example, the economic modelling established bupropion + NRT I&s was cost-effective across all pharmaceutical alternatives given to trial participants in the studies informing the NMA. It is possible that bupropion + NRT I&s would not be cost-effective if provided to LSSS for people who prefer, say, varenicline or e-cigarettes. Given that intervention effectiveness was such a key driver of cost-effectiveness, any small differences in effectiveness through patient choice, and access to smoking cessation services have the potential to impact the overall cost-effectiveness findings.

The model included productivity estimates based on the average age of retirement being equal to 63. However, the Pensions Act 2014 brought an increase in the state pension age to 67. Therefore, the economic model potentially underestimates the productivity benefits associated with more effective interventions as people would now be expected to work for a longer duration. The impact of this limitation on the cost-effectiveness findings is minimal as (i) productivity costs were not included in the base case results and (ii) the additional 4 years of pension covers only a small percentage of a person's total working years.

We included disutilities associated with both smoking and smoking related comorbidities. It is possible that the disutilities between current smokers and ex-smokers could be derived as a result of one, or both, of two factors: Firstly, ex-smokers feeling better than smokers simply because they do not smoke; secondly ex-smokers feeling better than smokers because they experience fewer co-morbidities. If the latter is the greater driver of differences in quality of life, then potential double-counting will be occurring in the model as disutilities are already assigned to each comorbidity. Double counting disutility is unlikely to have influenced the cost-effectiveness findings as the difference in utility (equal to 0.015) between smokers and ex-smokers was relatively small and was not a key driver of the cost-effectiveness.

The model doesn't include any age adjustment for utility values as this was not available from the sources in the published literature. Whilst it is possible that utilities decline generally with age it is unclear whether the disutilities associated with the comorbidities would increase decrease or stay the same. Therefore, the economic model applied a simplifying base case assumption of constant utility with respect to age. This assumption is not likely to have influenced the cost-effectiveness findings as indicated in the DSA where varying the utility values by 25% did not alter the cost-effectiveness results for any intervention (Appendix 1, Table 46, Table 47).

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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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Appendix 1: DSA Results

Table 39: Cost-effectiveness results (per person): DSA, intervention costs increased by 25%

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£11,523	15.11	£0	11	11
Bupropion	1.95	192	£11,325	15.18	£1,712	10	10
NRT l/s	2.01	198	£11,297	15.19	£1,948	9	9
Bupropion + NRT l/s	2.46	242	£11,317	15.20	£2,135	8	8
Varenicline	2.55	251	£11,284	15.24	£2,873	7	7
E-cigarettes	3.58	352	£11,090	15.24	£3,026	6	6
Varenicline + NRT l/s	3.7	364	£11,238	15.27	£3,563	5	5
Varenicline + bupropion	4.05	398	£11,173	15.29	£3,980	4	4
NRT l&s	3.4	335	£11,061	15.29	£4,009	3	3
E-cigarettes + NRT l/s	4.8	472	£10,916	15.31	£4,611	2	2
Bupropion + NRT l&s	5.59	642	£10,839	15.37	£5,891	1	1

Table 40: Cost-effectiveness results (per person): DSA, intervention costs decreased by 25%

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£11,523	15.11	£0	11	11
Bupropion	1.95	192	£11,303	15.18	£1,734	10	10
NRT l/s	2.01	198	£11,272	15.19	£1,973	9	9

Bupropion + NRT l/s	2.46	242	£11,271	15.20	£2,182	8	8
Varenicline	2.55	251	£11,204	15.24	£2,954	7	7
E-cigarettes	3.58	352	£11,090	15.24	£3,026	6	6
Varenicline + NRT l/s	3.7	364	£11,133	15.27	£3,667	5	5
NRT l&s	3.4	335	£11,009	15.29	£4,061	4	3
Varenicline + bupropion	4.05	398	£11,071	15.29	£4,083	3	4
E-cigarettes + NRT l/s	4.8	472	£10,891	15.31	£4,635	2	2
Bupropion + NRT l&s	5.59	642	£10,765	15.37	£5,965	1	1

Table 41: Cost-effectiveness results (per person): DSA, natural cessation rate increased from 2% to 5%

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£10,467	15.40	£0	11	11
Bupropion	1.95	192	£10,342	15.46	£1,166	10	10
NRT l/s	2.01	198	£10,324	15.46	£1,328	9	9
Bupropion + NRT l/s	2.46	242	£10,345	15.47	£1,449	8	8
Varenicline	2.55	251	£10,334	15.49	£1,945	7	7
E-cigarettes	3.58	352	£10,178	15.49	£2,073	6	6
Varenicline + NRT l/s	3.7	364	£10,311	15.52	£2,410	5	5
Varenicline + bupropion	4.05	398	£10,267	15.53	£2,697	4	4
NRT l&s	3.4	335	£10,176	15.53	£2,732	3	3
E-cigarettes + NRT l/s	4.8	472	£10,070	15.54	£3,152	2	2
Bupropion + NRT l&s	5.59	642	£10,035	15.58	£4,014	1	1

Table 42: Cost-effectiveness results (per person): DSA, discount rate = 1.5% costs, 1.5% QALYs

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£17,606	21.13	£0	11	11
Bupropion	1.95	192	£17,301	21.25	£2,630	10	10
NRT l/s	2.01	198	£17,258	21.26	£2,991	9	9
Bupropion + NRT l/s	2.46	242	£17,255	21.28	£3,313	8	8
Varenicline	2.55	251	£17,160	21.33	£4,491	7	7
E-cigarettes	3.58	352	£17,009	21.33	£4,578	6	6
Varenicline + NRT l/s	3.7	364	£17,061	21.38	£5,577	5	5
NRT l&s	3.4	335	£16,893	21.40	£6,159	4	3
Varenicline + bupropion	4.05	398	£16,975	21.41	£6,205	3	4
E-cigarettes + NRT l/s	4.8	472	£16,733	21.44	£7,020	2	2
Bupropion + NRT l&s	5.59	642	£16,555	21.53	£9,045	1	1

Table 43: Cost-effectiveness results (per person): DSA, discount rate = 5% costs, 5% QALYs

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£8,982	12.35	£0	11	11
Bupropion	1.95	192	£8,818	12.41	£1,328	10	10
NRT l/s	2.01	198	£8,794	12.42	£1,512	9	9
Bupropion + NRT l/s	2.46	242	£8,810	12.43	£1,655	8	8

Varenicline	2.55	251	£8,781	12.45	£2,227	7	7
E-cigarettes	3.58	352	£8,626	12.45	£2,350	6	6
Varenicline + NRT l/s	3.7	364	£8,742	12.48	£2,761	5	5
Varenicline + bupropion	4.05	398	£8,689	12.49	£3,085	4	4
NRT l&s	3.4	335	£8,599	12.49	£3,111	3	3
E-cigarettes + NRT l/s	4.8	472	£8,481	12.51	£3,580	2	2
Bupropion + NRT l&s	5.59	642	£8,416	12.55	£4,571	1	1

Table 44: Cost-effectiveness results (per person): DSA, comorbidity costs increased by 25%

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£14,383	15.11	£0	11	11
Bupropion	1.95	192	£14,111	15.18	£1,786	10	10
NRT l/s	2.01	198	£14,073	15.19	£2,032	9	9
Bupropion + NRT l/s	2.46	242	£14,074	15.20	£2,239	8	8
Varenicline	2.55	251	£13,994	15.24	£3,024	7	7
E-cigarettes	3.58	352	£13,842	15.24	£3,134	6	6
Varenicline + NRT l/s	3.7	364	£13,909	15.27	£3,752	5	5
Varenicline + bupropion	4.05	398	£13,830	15.29	£4,183	4	4
NRT l&s	3.4	335	£13,747	15.29	£4,183	3	3
E-cigarettes + NRT l/s	4.8	472	£13,596	15.31	£4,790	2	2
Bupropion + NRT l&s	5.59	642	£13,444	15.37	£6,145	1	1

Table 45: Cost-effectiveness results (per person): DSA, comorbidity costs decreased by 25%

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£8,663	15.11	£0	11	11
Bupropion	1.95	192	£8,518	15.18	£1,660	10	10
NRT l/s	2.01	198	£8,496	15.19	£1,888	9	9
Bupropion + NRT l/s	2.46	242	£8,515	15.20	£2,078	8	8
Varenicline	2.55	251	£8,494	15.24	£2,803	7	7
E-cigarettes	3.58	352	£8,338	15.24	£2,918	6	6
Varenicline + NRT l/s	3.7	364	£8,462	15.27	£3,478	5	5
Varenicline + bupropion	4.05	398	£8,413	15.29	£3,880	4	4
NRT l&s	3.4	335	£8,323	15.29	£3,887	3	3
E-cigarettes + NRT l/s	4.8	472	£8,210	15.31	£4,456	2	2
Bupropion + NRT l&s	5.59	642	£8,159	15.37	£5,710	1	1

Table 46: Cost-effectiveness results (per person): DSA, comorbidity utility increased by 25%

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£11,523	15.76	£0	11	11
Bupropion	1.95	192	£11,314	15.82	£1,449	10	10
NRT l/s	2.01	198	£11,285	15.83	£1,648	9	9
Bupropion + NRT l/s	2.46	242	£11,294	15.84	£1,809	8	8
Varenicline	2.55	251	£11,244	15.87	£2,436	7	7
E-cigarettes	3.58	352	£11,090	15.87	£2,556	6	6
Varenicline + NRT l/s	3.7	364	£11,186	15.90	£3,021	5	5

Varenicline + bupropion	4.05	398	£11,122	15.91	£3,374	4	4
NRT l&s	3.4	335	£11,035	15.91	£3,393	3	3
E-cigarettes + NRT l/s	4.8	472	£10,903	15.93	£3,898	2	2
Bupropion + NRT l&s	5.59	642	£10,802	15.98	£4,985	1	1

Table 47: Cost-effectiveness results (per person): DSA, comorbidity utility decreased by 25%

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)
Placebo	1	98	£11,523	13.97	£0	11	11
Bupropion	1.95	192	£11,314	14.08	£2,297	10	10
NRT l/s	2.01	198	£11,285	14.09	£2,613	9	9
Bupropion + NRT l/s	2.46	242	£11,294	14.11	£2,889	8	8
Varenicline	2.55	251	£11,244	14.16	£3,911	7	7
E-cigarettes	3.58	352	£11,090	14.15	£4,008	6	6
Varenicline + NRT l/s	3.7	364	£11,186	14.20	£4,857	5	5
NRT l&s	3.4	335	£11,035	14.22	£5,379	4	3
Varenicline + bupropion	4.05	398	£11,122	14.22	£5,406	3	4
E-cigarettes + NRT l/s	4.8	472	£10,903	14.25	£6,140	2	2
Bupropion + NRT l&s	5.59	642	£10,802	14.33	£7,900	1	1

Table 48: Cost-effectiveness results (per person): DSA, smokers and former smokers assigned the same utility [a]

Intervention	RR	Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	NMB vs. placebo	CE rank DSA	CE rank (base case)

Placebo	1	98	£11,523	15.26	£0	11	11
Bupropion	1.95	192	£11,314	15.32	£1,507	10	10
NRT l/s	2.01	198	£11,285	15.33	£1,714	9	9
Bupropion + NRT l/s	2.46	242	£11,294	15.34	£1,883	8	8
Varenicline	2.55	251	£11,244	15.37	£2,537	7	7
E-cigarettes	3.58	352	£11,090	15.37	£2,656	6	6
Varenicline + NRT l/s	3.7	364	£11,186	15.40	£3,147	5	5
Varenicline + bupropion	4.05	398	£11,122	15.41	£3,513	4	4
NRT l&s	3.4	335	£11,035	15.41	£3,529	3	3
E-cigarettes + NRT l/s	4.8	472	£10,903	15.43	£4,051	2	2
Bupropion + NRT l&s	5.59	642	£10,802	15.48	£5,184	1	1

a: Utility decrements are applied per comorbidity. Smokers have a lower utility than former smokers only due to an increase in the prevalence of smoking related comorbidities.