Appendix A: National Institute for Health and Care Excellence

Draft for consultation

Tobacco: preventing uptake, promoting quitting and treating dependence

[P] Economic Model: Cessation During Pregnancy

NICE guideline NGxx

Economic Model

September 2020

Draft for Consultation

This report was developed by the NICE Economic and Methodological Unit

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ISBN:

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List of abbreviations

CHD	Coronary heart disease
COPD	Chronic obstructive pulmonary disease
DSA	Deterministic sensitivity analyses
ESIP	Economics of smoking in pregnancy
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
LC	Lung cancer
LSSS	Local stop smoking services
NCSCT	National Centre for Smoking Cessation and Training
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NRT	Nicotine replacement therapies
OTC	Over the counter
PHAC	Public Health Advisory Committee
PSA	Probabilistic sensitivity analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SNAP	Smoking nicotine and pregnancy

Plain Language Summary

Smoking in pregnancy can have a harmful impact on maternal and infant health. We conducted cost-effectiveness modelling to help the Public Health Advisory Committee (PHAC) develop recommendations on smoking cessation in pregnancy. The analysis used a published economic model, called the Economics of Smoking in Pregnancy (ESIP) model, which was previously developed by researchers at the University of Nottingham. The ESIP model uses the best-available information in order to understand how different smoking cessation interventions might affect the general health of mothers who smoke and their infant, as well as the impact interventions might have on the costs to the National Health Service (NHS).

The analysis evaluated the cost-effectiveness of three interventions to aid smoking cessation in pregnancy: Firstly, nicotine replacement therapy (NRT), either in the form of long acting patches, or shorter acting products such as gums and lozenges. Secondly financial incentives, for example shopping vouchers, with a maximum total value of £400 that would be provided to women if they could prove that they had quit smoking during GP appointments. And thirdly, carbon monoxide screening plus a digital opt-out referral pathway, which aimed to increase both the identification of smoking in pregnant women and their uptake of treatment to aid smoking cessation following identification.

We used evidence from NICE reviews, based on clinical trials, to calculate how effective the interventions were at promoting smoking cessation during pregnancy. Specifically, we used the evidence to calculate the total number of additional quitters that would be achieved if people received each intervention.

Once the number of additional quitters per intervention was calculated, the ESIP model estimated the likelihood that mothers who did / did not smoke would die or develop a range of health complications, including lung cancer, coronary heart disease, chronic obstructive pulmonary disease and stroke. Because we also know the NHS treatment costs associated with each of these complications, it was possible to calculate the costs per maternal smoker and non-smoker over their remaining lifetime. The ESIP model also measures health benefits for mothers 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 a mother that could be achieved by quitting smoking during pregnancy.

In addition, the ESIP model establishes the impact of maternal smoking cessation during pregnancy on their child's later outcomes across their lifetime, i.e. NHS costs and QALYs. Key childhood outcomes include an increased likelihood of surviving pregnancy, a reduction in health problems during early infancy, and a reduced risk of developing asthma later in childhood. The ESIP model also establishes the reduced NHS costs and additional QALYs for children who avoid taking up smoking later in life due to reductions in second-hand tobacco exposure during childhood if their mother quits smoking during pregnancy.

For each intervention, the overall health benefits in terms of QALYs and NHS treatment costs avoided, were calculated by summing outcomes for mother and child. These lifetime health benefits were compared to the upfront costs that would be incurred to deliver each intervention. The results of the analysis showed that, for NRT, financial incentives, and CO monitoring plus opt out provision, the lifetime QALYs and healthcare savings associated with reduced smoking during pregnancy outweighed the costs of the interventions. This means that the interventions were cost-effective and it would be beneficial to the NHS to provide these interventions to pregnant women.

In a hypothetical population of 1000 pregnant women who smoke, NRT was predicted to produce 16 additional mothers who quit smoking, which resulted in a combined mean of 0.018 additional QALYs, at a cost of £98 per mother and child. The ratio of NHS treatment

costs plus intervention costs per QALYs gained was equal to £5,281. As this is less than the NICE recommended threshold of £20,000, NRT was considered to be cost-effective. NRT was still cost-effective when we changed the ESIP model inputs to reflect a more pessimistic scenario, for example when increasing costs by 25% and when including potential safety impacts of nicotine of caesarean section. We also calculated the probability of NRT being cost-effective given the evidence that was available to inform the model which was equal to 83%, however, this also meant NRT was not cost-effective 17% of the time. The uncertainty in the cost-effectiveness result was because of uncertainty in the effectiveness of NRT: the intervention was associated with an increased number of quitters during pregnancy when compared with a control group, but this result was not statistically significant.

In the same hypothetical population of 1000 pregnant women who smoke, financial incentives were predicted to produce 177 additional mothers who quit smoking, which resulted in a combined mean of 0.205 additional QALYs, and NHS cost savings of £64 per mother and child which includes the cost of the incentives. Therefore, financial incentives were cost-effective to the NHS as they produced QALY benefits and saved the NHS money. Based on the available information to inform the ESIP model, there was almost no uncertainty regarding the results of financial incentives which had a probability of being cost-effective equal to 99.7%. In addition, the intervention was cost-effective for pessimistic scenarios where intervention costs were increased, and intervention effectiveness was decreased.

Finally, in a hypothetical population of 1000 pregnant women including both smokers and non-smokers, CO screening plus a digital opt-out referral pathway resulted in 21 additional mothers quitting smoking. The intervention resulted in a mean of 0.024 additional QALYs, and NHS cost savings of £19 per mother and child including the cost of delivering the intervention. Therefore, CO screening plus opt-out provision was considered cost-effective. The intervention remained cost-effective when increasing costs by 25% and for a scenario which substantially decreased the intervention's effectiveness.

As with any cost-effectiveness analysis, there were some factors that could be challenged, or alternative approaches that could have been taken. However, most areas that we left out of our analysis (for example due to being unable to find suitable evidence) would have meant that the interventions would have been even more cost-effective. For example, the ESIP model only includes health impacts on four smoking related conditions, and there are many other conditions that could potentially be avoided through quitting smoking. Had we included those factors, the benefits of each intervention would have been greater still. Because of this, we are confident that, as long as an intervention is effective at helping pregnant women quit smoking, then there is a high likelihood that it will also be cost-effective.

Introduction

Background

As stated in the NICE final scope, smoking is the main cause of preventable illness and premature death in England. Smoking is linked with many health problems, including circulation problems, heart disease (coronary heart disease (CHD) and heart attacks), stroke, lung cancer and chronic obstructive pulmonary disease (COPD) (1). Moreover, smoking during pregnancy can affect fetal health leading to an increased risk of birth complications (1), low birth weight and/or premature birth, and fetal mortality (2). Babies born prematurely are at increased risk of short and long term health complications, including respiratory problems (3). Furthermore, children with mothers who continue to smoke after birth are more likely to suffer from asthma and other serious illnesses that may need hospital treatment (4). Children brought up in environments where they are exposed to second hand tobacco are also more likely to take up smoking themselves later in life (5).

Despite the well-established health risks, many women struggle to stop smoking during pregnancy (6). Previous recommendations (2010) by NICE (7) were to monitor all women's smoking status throughout pregnancy by routine carbon monoxide measurement, to provide encouragement and support to quit smoking throughout the pregnancy, in addition to offering smoking cessation advice and referral to specialist behavioural interventions offered by local stop smoking services (LSSS).

Financial incentives (e.g. in the form of shopping vouchers) could provide an effective means to promote behavioural change in pregnant women (8). Previous NICE PH26 guidelines for smoking cessation in pregnancy suggested financial incentives were likely to be effective in other countries but additional evidence was required to determine whether they would work in the UK.

In addition to behavioural change interventions, LSSS also offer a variety of nicotine replacement therapies (NRT) via free prescription. Nicotine containing products to help people quit smoking, including electronic cigarettes (e-cigarettes), can also be privately purchased over the counter (OTC).

There are, however, some concerns regarding the impact of nicotine containing products on pregnant women and their unborn babies. The fetotoxic effects of tobacco smoking are well documented and some of these detrimental effects may be attributable to nicotine (9): Fetal exposure to nicotine may result in excessive stimulation of nicotinic receptors in the brain disrupting normal fetal development (10, 11). There are currently no long-term studies which investigate the negative health impacts of e-cigarettes on mothers or children. Arguably any safety concerns associated with nicotine containing products may be outweighed by the benefits of promoting smoking cessation thus reducing maternal and fetal harm from tobacco exposure (10).

Objectives

The current project conducts economic modelling to inform NICE's new tobacco guidelines on preventing update, promoting quitting and treating dependence. The following NICE guidelines will be updated and amalgamated:

- 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)

The focus of this report is exclusively on smoking cessation during pregnancy and, therefore, provides evidence towards the PH26 guideline update.

The PHAC prioritised questions in the NICE scope for further economic analysis. Research questions were not prioritised if there was sufficient cost-effectiveness evidence available in the published literature. Where cost-effectiveness evidence was insufficient, research questions were prioritised if there was updated and available effectiveness evidence since the publication of the previous guidelines or if economic modelling had previously not been conducted. The aim of this analysis was to conduct economic modelling and provide cost-effectiveness evidence to inform the prioritised questions in the NICE scope. Outcomes from the economic model will help to inform the committee's guidance decisions.

The key research questions from the NICE scope that were prioritised for economic modelling of tobacco cessation in pregnancy are listed below.

1. Are nicotine replacement therapies (NRT) or e-cigarettes effective and cost-effective at helping pregnant women who smoke to quit?
2. Are incentives effective and cost-effective for increasing smoking cessation among women who are pregnant?
3. Is opt-out provision of stop smoking support for pregnant women who smoke effective and cost effective in increasing uptake of the support and increasing smoking cessation?

Modelling Approach

The economic modelling was reliant on concurrent effectiveness reviews conducted by NICE. The NICE effectiveness review H: opt-out provision (12), I: financial incentives (13), and review J: NRT & e-cigarettes (14) identified relevant effectiveness evidence and informed the economic modelling for the related research question.

To answer the research questions regarding the cost-effectiveness of smoking cessation interventions in pregnant women, this analysis used a published economic model called the "economics of smoking in pregnancy" or *ESIP* model developed by the Division of Primary Care at the University of Nottingham (15). The ESIP model estimates the lifetime costs and benefits of maternal smoking cessation during pregnancy for both mother and child, from a health perspective including costs incurred by the NHS and health benefits measured as quality adjusted life years (QALYs).

A quality appraisal of the ESIP model was conducted by senior research staff at YHEC the results of which were discussed with the PHAC. The ESIP model was then updated to include relevant unit costs and effectiveness rates for each intervention and comparator.

Following further review a coding error was identified in the ESIP model, which, in some instances double counted intervention costs. The authors of the ESIP model subsequently updated the model to correct this coding error. Consequently, the results from this analysis may not be replicable in versions of the ESIP model dated prior to March 2020.

Methods

Overview

This section summarises the methods to answer the cost-effectiveness research questions related to smoking cessation in pregnancy. The following review questions in the NICE scope were identified as potentially relevant for economic modelling by the PHAC.

Review question:

- Are nicotine replacement therapies (NRT) or e-cigarettes effective and cost-effective at helping pregnant women who smoke to quit?

NICE evidence review J identified relevant evidence regarding the effectiveness of nicotine replacement therapy in pregnancy (14). The review identified one study evaluating the cost-effectiveness of NRT in pregnancy conducted alongside the smoking nicotine and pregnancy (SNAP) RCT (16). The single cost-effectiveness study had limitations including uncertainty around the effectiveness estimates, a truncated time horizon (equal to the duration of the RCT), and failure to use QALYs as the health outcome. The PHAC considered the evidence to be too uncertain to judge whether NRT was cost-effective. Therefore, further economic modelling was conducted to establish the cost-effectiveness of the intervention class listed below.

- NRT long or short acting (NRT l/s)

The NRT l/s intervention included any long or short acting NRT product administered as a monotherapy. The NRT/s intervention was compared to placebo NRT. Both NRT l/s and placebo were offered alongside behavioural support, which is available to all pregnant women who want to quit smoking through local stop smoking services (LSSS). From herein we condense the full description of this analysis (NRT l/s plus behavioural support versus placebo plus behavioural support) to NRT l/s versus placebo.

NRT combination therapy was excluded from the analysis as no effectiveness evidence was available from placebo-controlled trials for this population in NICE evidence review J (14). In addition, the NICE evidence reviews did not identify any studies designed to analyse the effectiveness of e-cigarettes for promoting smoking cessation in pregnant women (14). Consequently, and following discussion with the PHAC, exploratory economic modelling was conducted for e-cigarettes. In the absence of placebo-controlled trials, the exploratory analysis established the cost-effectiveness of e-cigarettes vs. placebo by approximating effectiveness estimates in pregnant women based on effectiveness evidence for e-cigarettes in the general population.

Review question:

- Are incentives effective and cost-effective for increasing smoking cessation among women who are pregnant?

NICE evidence review I (13) identified relevant evidence regarding the effectiveness of financial incentives in promoting smoking cessation pregnancy. One UK based cost-effectiveness study was identified for financial incentives, however the PHAC raised some concerns with the quality of the study, including potentially overestimating the impact of incentives due to additional treatment (i.e. telephone contact) being provided in the

intervention arm, that was not available in the comparator. Economic modelling was considered to be informative for this research question as cost-effectiveness results could be obtained using pooled effectiveness estimates across all relevant studies identified in NICE evidence review I (13).

Financial incentives were contingent on confirmed abstinence from tobacco smoking through biochemically validated measures (e.g. carbon monoxide readings). The base case analysis calculated the cost-effectiveness of staged financial incentives, where the intervention included incentives of increasing value provided according to duration of abstinence. The financial incentives intervention was delivered alongside usual care which included behavioural support and “free to the user” NRT. The comparator for the analysis was usual care without incentives. From herein we refer to this analysis as financial incentives versus no incentives.

Review question:

- Is opt-out provision of stop smoking support for pregnant women who smoke effective and cost effective in increasing uptake of the support and increasing smoking cessation?

NICE evidence review H (12) identified effectiveness evidence for three interventions which included opt-out provision of stop smoking support. The first two studies by Bauld (2012) (17) and Campbell (2017) (18) were uncontrolled before and after designs comparing a multifaceted intervention which combined carbon monoxide testing and opt-out provision of stop smoking support to the standard care pathway before implementation, this being opt-in provision with no CO testing. The third study was an interrupted time series analysis by Bell (2018) (19) comparing a complex intervention named “BabyClear” which combined CO testing, routine opt-out referral and a treatment follow up pathway versus usual care prior to intervention implementation.

NICE evidence review H (12) identified one cost-effectiveness study of interventions including opt-out provision. The single study was by Bell (2018) (19), this being the same study identified in the effectiveness review. The study by Bell (2018) (19) was not considered to provide sufficient evidence regarding the cost-effectiveness of opt-out provision as the intervention was complex including opt-out provision in combination with several other services. In addition, results were reported in terms of cost per quitter rather than cost per quality adjusted life year (QALY). Consequently, the PHAC agreed formal economic modelling was required to further establish the cost-effectiveness of opt-out provision of stop smoking support.

When considering all of the effectiveness evidence from NICE evidence review H (12) the PHAC and NICE team agreed that two studies by Campbell et al. (2017) (18) and Bell et al. (2018) (19) were likely to be associated with least uncertainties. The committee agreed that the that the study by Campbell et al. (2017) included an opt-out provision intervention that was relevant to the review question. In contrast, the PHAC indicated that the study by Bell et al. (2018) (19) contained a complex intervention that was less relevant to the review question. Therefore, the intervention study by Campbell et al. (2017) (18) informed the economic modelling.

The committee also discussed the quantitative study by Bauld (2012) (17) which showed reduced smoking abstinence rates for pregnant women following opt-out provision. The committee were concerned with several uncertainties in the study by Bauld (2012) (17) as it was unclear whether there had been errors in data collection and whether CO testing and the method of referring pregnant women had been implemented consistency. Due to these

uncertainties the committee preferred not to use the study by Bauld (2012) (17) to inform the economic modelling.

The opt-out provision intervention in Campbell et al. (2017) (18) included (i) self-reported smoking status at the first antenatal “booking” appointment, and (ii) carbon monoxide (CO) monitoring to establish maternal smoking status at the “dating appointment”, where expectant mothers receive their first ultrasound scan. CO monitoring was delivered to mothers at the dating appointment. Mothers who were identified as smokers (either through self-report or through CO testing) were referred to LSSS via a digital opt-out referral pathway. The only reason not to implement the opt-out referral was if the identified mother spontaneously refused the referral.

The intervention was compared to usual care before implementation. The comparator did not include CO monitoring. Instead, women confirmed their smoking status via self-report and were then referred to LSSS via digital opt-in pathways (18). In contrast to the opt-out referral, mothers who were identified as smokers were directly asked whether they wanted to be referred to LSSS or not. Consequently, the intervention and comparator under investigation in the primary economic modelling analysis was CO monitoring + opt-out referral versus no CO monitoring + opt-in referral.

The cost-effectiveness of opt-out provision versus opt-in provision was further investigated in a scenario analysis. The scenario analysis used the relative risk of cessation reported in the NICE effectiveness review. The numerator for the relative risk was the total number of quitters. The denominator for the RR was the number of referrals received by the stop smoking services. As a large proportion of the population in the opt-out referral pathway were identified as smokers via CO monitoring, whereas all of the population on the opt-in referral pathway were identified via self-report, the base for calculating the RR captures part of the impact of the intervention – specifically CO monitoring.

The specific opt-out versus opt-in provision analysis was included as a sensitivity rather than base case analysis due to the high risk of bias that is introduced when conflating part of the intervention effect (i.e. CO monitoring) within the relative risk calculation. A large proportion of the population in the opt-out referral pathway were identified as smokers via CO monitoring, whereas all of the population on the opt-in referral pathway were identified via self-report.

ESIP Model Structure

This analysis used the ESIP model developed by the Division of Primary Care at the University of Nottingham (15). The ESIP model was built to analyse the cost-effectiveness of several in-built smoking cessation interventions for a population of pregnant women who currently smoke. The ESIP model can also establish the cost-effectiveness of user defined interventions following user entry on intervention costs and effectiveness.

The ESIP model establishes the incremental cost-effectiveness ratio (ICER), expressed as the incremental cost per quality-adjusted life year (QALY), allowing for pairwise cost-effectiveness comparison between therapy alternatives. The model adopts an NHS and personal social services (PSS) perspective for costs and incorporates health outcomes as QALYs. The ESIP model also calculates cost-effectiveness of smoking cessation interventions separately for maternal outcomes only, infant outcomes only, and maternal & infant outcomes combined, each over several time horizons including pregnancy, childhood (<15 years), and lifetime (<100 years). Discount rates of 3.5% for both costs and benefits are applied as stipulated in the NICE methods manual (20).

A full description of the ESIP model, including model structure, input parameters, and methods to apply user defined inputs is provided in Jones et al. (2019) (21).

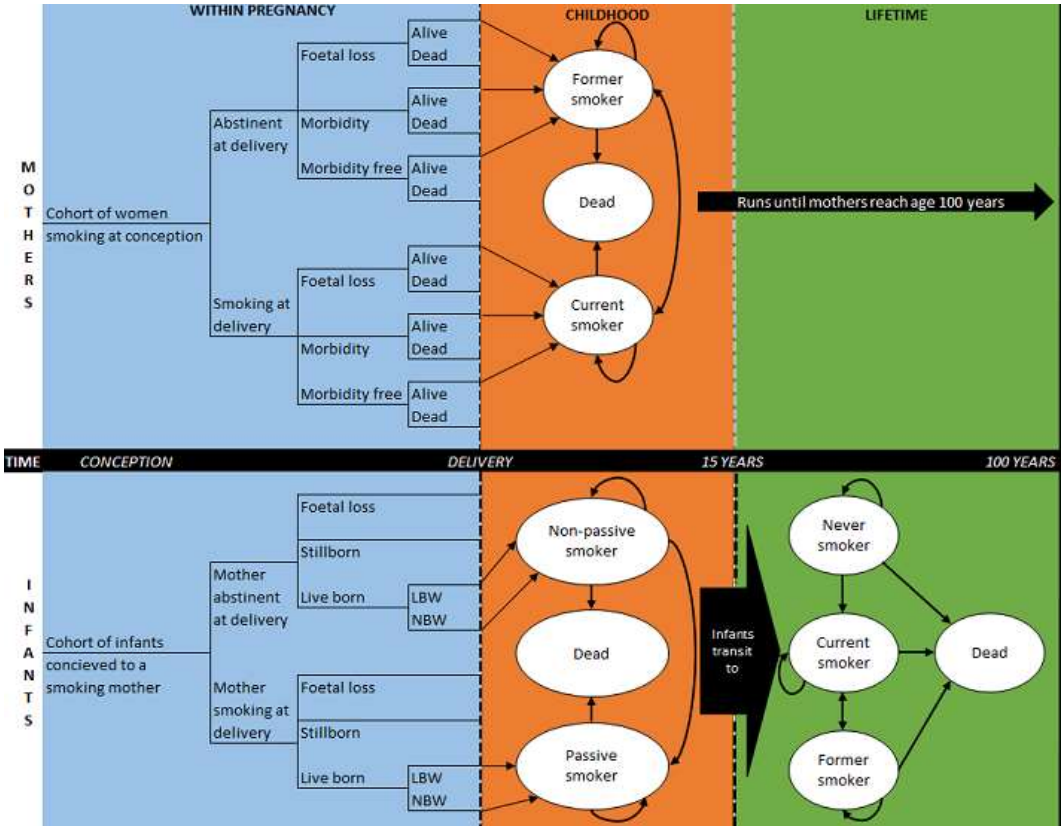
In brief, the ESIP model progresses a cohort of 1,000 pregnant women who smoke through an initial decision tree which maps maternal pregnancy outcomes. The cohort then enters a Markov model for the remaining time horizon. For mothers, the Markov component of the ESIP model contains health states related to smoking status, these being “current smoker”, “former smoker”, “dead”. Infants enter an initial Markov model during childhood where they are categorised as either passive or non-passive smokers according to their mothers smoking status. After the age of 15, infants’ transition to an adulthood Markov model which tracks their smoking status, assigning the population to “never smoker”, “current smoker”, “former smoker” and “dead” health states. Different transition probabilities are applied according to the effectiveness of each intervention.

Costs and QALYs are assigned in the ESIP model according to the following smoking related comorbidities:

- Eight pregnancy related comorbidities: ectopic pregnancy, miscarriage, placenta abruption, placenta previa, pre-eclampsia, still birth, low birth weight, and premature birth
- One childhood comorbidity associated with passive smoking: asthma
- Four smoking related comorbidities for mothers (and children when entering the adulthood component of the Markov model): COPD, CHD, lung cancer (LC), and stroke

The prevalence of the comorbidities by smoking status is used to calculate the number of people, in each health state, in each yearly cycle, who develop one of these comorbidities. Each health state has an associated utility value. Each comorbidity has an associated cost and disutility associated with the disease/pregnancy related event occurring. These costs and utilities are applied each 1-year cycle over the lifetime. The model structure of the ESIP model is depicted in Figure 1.

Figure 1: Model structure ESIP model.



The ESIP model captures the impact of smoking on fetal loss. Effective interventions that reduce the number of pregnant women who smoke reduce the number of fetal mortalities during pregnancy. Any change to the probability of fetal mortality has implications across the remaining lifespan as the cohort size for mothers and fetuses is not adjusted for after childbirth. Therefore, each fetal death is included in the mean lifetime costs calculation, effectively contributing 0 QALYs and £0 healthcare costs. The decision to include outcomes related to fetal loss was guided by discussions with the PHAC and is in line with other NICE guidelines. For instance, NICE has included discounted lifetime QALYs lost for stillbirth in NG137 guidelines for twin and triplet care in pregnancy (22).

Study Population

NRT l/s & Financial Incentives

The model generates average (or 'expected') outcomes for specific baseline characteristics. The population included a cohort of pregnant women who were current smokers and making a quit attempt. The cohort was set equal to 27 years of age, based on the mean age of pregnant women in the MiQuit trial, an RCT assessing the effectiveness of smoking cessation interventions in pregnancy. The age is similar to the ONS (2019) estimate (23) for the mean age of first-time mothers in England and Wales for 2017 (equal to 28.8 years). Note that the ONS estimate (23) was not used to inform the model as this contained both smokers and non-smokers.

CO monitoring + opt-out provision

The CO monitoring + opt-out provision intervention offers CO testing to all women during the 12-week dating appointment. Therefore, the eligible population includes both current

smokers and non-smokers. The ESIP model is designed to assess the cost-effectiveness of smoking cessation interventions that are delivered specifically to a population of current smokers. Consequently, it was not appropriate to directly use effectiveness estimates for the CO monitoring + opt-out provision analysis directly within the ESIP model.

Cost-effectiveness for CO monitoring + opt-out provision was instead calculated by establishing the total number of additional quitters achieved versus no CO monitoring + opt-in provision, as reported by Campbell et al. (2017) (18). The ESIP model was then used to calculate the mean health benefits (QALYs) and NHS savings per quitter, applying a mean population age equal to 27 years. Mean NHS savings and QALYs per quitter were obtained from the ESIP model by calculating outcomes for a cohort of current smokers who all continue to smoke (i.e. 0% chance of abstinence at delivery) vs. a cohort of current smokers who all quit (i.e. 100% chance of smoking abstinence at delivery).

The overall cost-effectiveness for the intervention was calculated by: (i) Identifying the incremental intervention cost of providing CO monitoring + opt out provision to a population of smokers and nonsmokers; (ii) estimating the total cost savings and QALYs gained due to quitting by multiplying the mean incremental costs and QALYs per quitter from the ESIP model by the total number of additional quitters attributable to CO monitoring + opt-out provision.

Model Input Parameters

Intervention Effectiveness

NRT l/s & Financial incentives

The ESIP model requires effectiveness estimates in terms of the absolute probability of smoking abstinence at delivery. However, intervention effectiveness was reported in NICE evidence reviews (13),(14) in terms of relative risk (RR) of smoking abstinence for NRT l/s and financial incentives vs. the relevant comparator. Therefore, it was necessary to convert the RR into absolute probabilities of smoking abstinence. Absolute rates of abstinence were obtained by multiplying the RR by a baseline probability of smoking abstinence for the control arm (i.e. the total number of quitters divided by the total number of participants in the control arm).

The RR for NRT l/s was vs. placebo was obtained from NICE evidence review J (14). The RR was calculated as a pooled effectiveness estimate across NRT l/s placebo-controlled studies, all of which included behavioural support in both intervention and control arms. The absolute probability of smoking abstinence for the placebo arm was set equal to 7.6%. This value was obtained from the smoking nicotine and pregnancy (SNAP) RCT by Cooper et al. (2014) (16), this being the most recent UK based study included in NICE evidence review J (14) and included placebo + behavioural support as the control arm.

The effectiveness of financial incentives was obtained from NICE evidence review I, this being the RR vs. no financial incentives, pooled across seven RCTs. The comparator in each of the seven studies was usual care without financial incentives. As there was potential for heterogeneity, NICE evidence review I conducted a quality appraisal where each of the seven ‘no incentives’ comparators were considered suitable for pooling (13). The absolute probability of smoking abstinence for the financial incentives comparator was obtained from NICE evidence review I (13) as the pooled rate of cessation across the seven RCT “no incentives” usual care control arms, equal to 9.0%.

The ESIP model requires probabilities of abstinence for the intervention and comparator at childbirth (40-weeks). Relative risks and absolute probabilities of cessation were only available at 20-weeks for the NRT l/s. Whilst mothers may relapse between the 20-week outcome measure and child birth, no published studies were identified which reported relapse rates specifically for pregnant women during this period. Consequently, the base case analysis assumed abstinence rates for NRT l/s were maintained from 20 weeks through to childbirth (i.e. no relapse). This assumption was investigated within a scenario analysis, which applied a 20% smoking relapse rate between weeks 20 and 40 in line with general population estimates reported in an HTA report by Coleman et al. (2010) (24). As all RR and probabilities of abstinence were obtained at childbirth for the financial incentives' intervention, no further adjustment for smoking relapse was required. The final effectiveness parameters included in the model are described in Table 1~~Table 1~~.

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Table 1: Intervention effectiveness

Intervention	RR of abstinence vs. control (95% CI)	P (quit) 20 weeks	P (quit) 40 weeks
NRT l/s base case analysis			
Placebo	N/A	7.60%	7.60%
NRT l/s [a]	1.21 (0.95, 1.55)	9.20%	9.20%
NRT l/s scenario analysis: 20% relapse			
Placebo	N/A	7.60%	6.08%
NRT l/s [a]	1.21 (0.95, 1.55)	9.20%	7.36%
Financial incentives analysis			
No incentives	N/A	N/A	9.02%
Financial incentives [b]	2.96 (2.22, 3.93)	N/A	26.68%

a: Effectiveness evidence obtained from NICE evidence review J for the Tobacco guidelines update (14)
b: Effectiveness evidence obtained from NICE evidence review I for the Tobacco guidelines update (13)

CO monitoring + opt-out provision

The effectiveness of CO monitoring + opt-out provision was calculated using results from Campbell et al. (2017) (18) who reported: 93 of 2293 women (4.06%) in the CO monitoring + opt-out provision pathway reported smoking abstinence 4-weeks after setting a quit date, whilst 46 of the 2287 (2.01%) participants in the no CO monitoring + opt-in provision pathway achieved smoking abstinence 4-weeks after setting a quit date.

Campbell et al. (2017) (18) indicated that quit dates were set following referral to local SSS (i.e. after the opt in or opt-out referral), but did not specify when 4-week abstinence was measured. For the economic analysis we assumed that the 4-week abstinence outcome was obtained at 20-weeks post conception. The assumption was made based on knowledge of the dating appointment in Campbell et al. (2017), which occurred at 12-weeks post conception. We assumed that quit dates would be set 4-weeks following the initial referral (i.e. at 16-weeks post conception). There was then an additional 4-week time period specified by Campbell et al (2017) (18) where the outcome is 4-week confirmed abstinence after setting a quit date. This meant the final outcome of smoking abstinence was assumed to occur at 20-weeks post conception.

Therefore, in a hypothetical population of 1000 pregnant women, including both smokers and non-smokers, CO monitoring + opt-out provision was calculated to achieve 20.5 additional quitters when compared to no CO monitoring + opt-in provision, i.e. 2.05%

(4.06%-2.01%).[1] As described previously, the denominator for the base case analysis included all mothers who attended the booking appointment, i.e. both current smokers and non-smokers.

Following the same methodology as described for NRT l/s, the base case analysis for CO monitoring + opt-out provision applied a 0% relapse rate between abstinence at 20-weeks and delivery at 40-weeks. Meanwhile, a scenario analysis was conducted applying a 20% relapse rate in line with general population estimates reported by Coleman et al. (2010) (24). Effectiveness estimates for the CO monitoring + opt-out provision analysis are displayed in Table 2~~Table 2~~.

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Table 2: Intervention effectiveness: CO monitoring + op-out provision

Intervention	Abstinence rate [a]	RR of abstinence vs. control [b]	Additional quitters per 1000 20-weeks	Additional quitters per 1000 40-weeks
Base case analysis				
No CO testing + opt-in provision	2.01%	N/A	N/A	N/A
CO testing + opt-out provision	4.06%	2.02	20.5	20.5
Scenario analysis: 20% relapse				
No CO testing + opt-in provision	2.01%	N/A	N/A	N/A
CO testing + opt-out provision	4.06%	2.02	20.5	16.4

a: Abstinence rates reported by Campbell et al. (2017) (18) where: the numerator equals the total number of women who set a quit date and have confirmed abstinence after 4-weeks; the denominator equal to all study participants eligible for opt-out provision, including smokers and non-smokers.

b: The relative risk of abstinence uses a base (denominator) that includes both smokers and non-smokers. Therefore, the RR in this table should not be directly compared to RR values for NRT l/s and financial incentives in Table 1~~Table 1~~ which use a base (denominator) of smokers *only*. The cost-effectiveness of CO monitoring + opt-out provision when applying a base of smokers only is investigated later in an exploratory scenario analysis.

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Intervention Costs

NRT l/s

The mean cost of behavioural support for the NRT l/s analysis was obtained from a follow up cost-effectiveness study of the SNAP trial conducted by Essex et al. (2015) (25). The average per person cost in the control arm reported by Essex et al. (2014) (25) was £47.75 and included: A behavioural support session at hospital with CO monitoring (£22.00); telephone support calls on quit date (£1.30), 3-days following quit (£1.94), and 4-weeks post quit (£2.91); a home visit for self-reported non-smokers at 4-weeks post quit (£9.46); training costs for midwives (£4.18); and costs to monitor CO levels at intervention delivery (£5.96). The total costs (£47.75) were uprated from 2009/2010 prices to 2019/2020 prices using the NHSCII pay and prices indexes reported in the PSSRU 2019 (26). The final cost of

[1] The economic modelling for CO monitoring + opt-out provision was conducted in a hypothetical population of 1,000 pregnant women including non-smokers and smokers. The number of additional quitters (20.5) is calculated in this population of 1,000. It does not represent the total number of additional quitters reported in the study by Campbell et al. (2017) where the number of participants was equal to 2,293 for CO monitoring + opt-our provision and 2,287 for no CO monitoring + opt-in provision. The size of the hypothetical population does not impact the results of the economic modelling which are reported per person.

behavioural support was equal to £53.64 and we applied this cost to both NRT l/s and placebo in the economic analysis.

The mean cost of NRT l/s was calculated as a weighted average based on the total number of participants who incurred costs across the multiple NRT products that informed the RR effectiveness estimate in NICE evidence review J (14). Weightings were NRT patch (74.7%), NRT gum (13.7%) and NRT inhalator (11.6%). Equivalent dosages were applied when costing each NRT product as recommended for the general population by the British National Formulary (BNF) online resource (27). This excluded products not indicated for use in pregnant women, including 24/hr nicotine patches and 4mg nicotine gums. The weighted cost across the NRT l/s products was equal to £119.07. As all NRT products are available as free prescriptions for pregnant women, we assumed that 0% of NRT would be purchased privately over the counter. The total costs of NRT l/s plus behavioural support was equal to £172.71 (£119.07 + £53.64). All intervention costs for the NRT l/s analysis are reported in Table 3~~Table 3~~.

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To address specific comments raised by the PHAC, an additional sensitivity analysis was conducted where intervention costs were reduced by 25% reflecting dosages applied in clinical trials. For example, the SNAP trial by Cooper et al. (2014) (16) provided pregnant women with 15mg patches over 8-weeks, which is roughly a quarter less than doses assumed in the general population (21mg patches for 7 weeks, 15mg for 2 weeks and 7mg for final two weeks).

Table 3: Intervention costs NRT l/s analysis

Intervention	NHS cost	Components	Unit Costs (per dose)	Source
Behavioural Support	£53.64	Mean cost incurred by the placebo arm of the SNAP trial. Behavioural support is comprised of telephone support, and home visits. The original cost [£47.75] was uprated from 2009/10 prices to 2018/19 prices using inflation indices reported in PSSRU (2019).	N/A	Essex (2015) (25)
NRT l/s [a]	£119.07	Weighted average: NRT patch (74.7%), NRT gum (13.7%), NRT Inhalator (11.6%)	NRT patch=£122.15 NRT gum=£90.72 NRT inhalator=£132.73	Weightings: NICE evidence review J (14)
NRT component costs				
NRT Patch	£122.15	High strength patch daily for 7 weeks, followed by medium strength patch for 2 weeks and low strength patch for 2 weeks. 16/hr patches indicated for use in pregnant women.	25 mg/16hr =£1.59 15mg/16hr=£1.59 10mg/16hr=£1.57	Drug costs and dosage: Joint Formulary Committee (2020) (27)
NRT Gum	£90.72	Ad lib [b] administration when cravings occur assumed equal to 12 gums per day (every 1.5 hours for 16 waking hours) 2mg NRT products indicated for use in pregnant women.	Per 2mg gum=£0.09	Drug costs and dosage: Joint Formulary Committee (2020) (27)
NRT Inhalator	£132.73	Ad lib [b] administration when cravings occur assumed equal to 2 cartridges per day (i.e. 30mg nicotine)	15mg = £1.22	Drug costs and dosage: Joint Formulary Committee (2020) (27)

a: Costs of NRT products are 100% prescribed as pregnant women receive free NRT prescriptions.
b: Ad lib administration assumed to occur for a period of 12 weeks unless otherwise stated.

Financial incentives

Intervention costs for the financial incentives analysis were obtained from a published study by Boyd et al. (2016), who investigated the cost-effectiveness of shopping voucher incentives using data from the phase II cessation in pregnancy incentives RCT (CPIT) in Glasgow, Scotland (8). The study by Boyd et al. (2016) was based on effectiveness estimates from the CPIT RCT by Tappin et al. (2015) (28). The study by Boyd et al. (2016) (8) was selected because it was the only study reporting intervention healthcare costs for financial incentives in the UK. Boyd et al. (2016) estimated the direct healthcare costs for CPIT participants individually for each trial arm. The cost for usual care included face-to-face and telephone behavioral support and any NRT prescriptions obtained by study participants in the "routine care" arm during the study period, with mean per participant costs equal to £85. This cost for usual care was applied to the no incentives control arm.

Boyd et al. (2016) estimated the mean cost per participant allocated to the financial incentives as equal to £243 (8). The cost of financial incentives included a maximum of £400 worth of shopping vouchers in addition to behavioral support and NRT. Incentives were contingent on mothers achieving biochemically validated abstinence through carbon monoxide measurements. The financial incentives were provided at the following pre-specified time points: £50 for initial quit, £50 4-weeks post quit, £100 at 12-weeks post quit, and £200 34-38 weeks post quit. Participants in the financial incentives arm of the CPIT study also had higher levels of NRT and behavioral support resource usage than the routine care arm, which was included as part of the overall cost reported by Boyd et al. (2016) (8).

The intervention in Boyd et al. (2016) (8) was similar to the interventions in the seven studies informing the pooled effectiveness estimate which each included financial incentives as vouchers contingent on continued abstinence. The total value of the vouchers available in Boyd et al. (2016) represented a reasonable midpoint of the values available from the seven effectiveness studies, which ranged between £150-£1,000. The final costs for financial incentives and usual care were uprated from 2013 to 2019/20 prices using the NHSCII pay and prices index (26) and are reported in Table 4~~Table 4~~.

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Table 4: Intervention costs financial incentives analysis

Intervention	NHS cost	Components	Source
Usual Care (i.e. no incentives)	£90.96	Behavioural support consisting of: one telephone first contact session (mean 10-minutes), one face-to-face support session (mean = 50 minutes), and up to five telephone support sessions (mean duration 15-minutes). All support sessions were costed based on time required for a smoke free pregnancy adviser (band 5) at unit cost of £35.00 per hour. NRT costs were a maximum of 3X 4-week prescription of 16-hour patch (unit costs = £9.97). Mean costs per person were equal to £85 and were uprated from 2013 to 2019 prices. Costs per individual components not reported.	Unit costs: Boyd (2016) (8) Uprating: Curtis & Burns (PSSRU 2019) (26)
Financial incentives + usual care	£260.05	Costs were incurred for financial incentives equal to £50 on 1st face to face contact, £50 4-weeks post quit, £100 12-weeks post quit and £200 at CO validated quit during weeks 34-38. Costs also included postage and packaging equal to £7.48 per participant. Participants receiving	Unit costs: Boyd (2016) (8) Uprating: Curtis & Burns (PSSRU 2019) (26)

Intervention	NHS cost	Components	Source
		financial incentives also incurred costs for behavioural support and NRT, as described for usual care. Mean costs per person were equal to £243 and were uprated from 2013 to 2019 prices. Costs per individual component not reported.	

CO monitoring + opt-out provision

The cost of CO monitoring + opt-out provision included three main components: intervention delivery including consumables and staff time, training costs, and costs associated with treatment provided by local SSS. All costs were applied for the CO monitoring + opt-out provision arm, whilst only local SSS treatment costs were applied for the no CO monitoring + opt-in provision arm.

Intervention consumables and unit costs for CO monitoring were identified through discussion with a National Centre for Smoking Cessation and Training (NCSCT) specialist consultant midwife. These included carbon monoxide monitors, mouthpiece adapters, disposable mouthpieces, calibrations kits, hand sanitizer for healthcare professionals and mothers during the test, and non-alcohol wipes to clean CO monitors after each test. We contacted Campbell et al. (2017) (18), who provided an estimated resource usage for the CO test consumables across all 2,293 study participants who received the intervention. In addition, as reported by Campbell et al. (2017), one healthcare assistant was hired for 20 hours per week over 6-months to cover time required by healthcare professionals for intervention delivery, and for electronic referrals to local SSS. The mean salary per healthcare assistant was obtained from a PSSRU report and was equal to £18,452 per full time year, i.e. £4,920.53 for all contracted hours. Intervention delivery costs were estimated per person by dividing total costs by the total number of study participants in the opt-out provision arm in Campbell et al. (2017) (n=2,293).

In total, six antenatal staff were involved in delivering the CO monitoring + opt-out provision intervention. All antenatal staff attended a full day of training delivered by the NCSCT, where content covered behavioral change techniques, identification of risks for smoking in pregnancy, instruction on how to deliver CO monitoring, interpretation of results, and instruction on electronic referral. Training costs were not available in Campbell et al. (2017). Instead, we obtained costs from Bell et al. (2018) (19) who estimated the total cost of training staff for a complex intervention which included opt out provision and CO monitoring in pregnant women. The costs of training reported by Bell were based on a contract with the Tobacco Control Collaborating Centre (TCCC), who provided training to 600 staff across 8 NHS trusts. The TCC 1-day training sessions covered multiple content including use of CO monitors and digital referral systems to LSSS. The total cost of the contract was £106,300, or £177.17 per staff member. The costs per staff member were uprated to 2019 prices using the NHSCII pay and prices index reported in the PSSRU (26), and were equal to £187.25. Total staff training costs for CO monitoring + opt-out provision were calculated by multiplying training costs per staff member by the number of people who attended training (n=6). Costs per pregnant woman were established by dividing this total by the number of study participants in the CO monitoring + opt-out provision arm in Campbell et al. (2017) who attended a booking appointment (n=2,293).

Campbell et al. (2017) (18) report that treatment following referral to local SSS included a maximum of one behavioral support session per week, and a full course of NRT. No information was provided on treatment uptake, duration of behavioral support, or the type of NRT provided. Therefore, we applied a conservative (higher costing) assumption, where all

women who set a quit date were assumed to consume a full course of NRT l/s, and attend behavioral support sessions consistent with the control arm of the SNAP trial [2](25), for a maximum of 12-weeks. Consequently, intervention costs per mother who received treatment were equivalent to those reported in Table 3~~Table 3~~ for the NRT l/s analysis, i.e. £172.71 (£119.07 for NRT l/s and £53.64 for behavioural support.

Treatment costs were only applied to pregnant women who set a quit date for both the CO monitoring + opt out (n=121) and no CO monitoring + opt-in (n=57) referral pathways. The costs per person were then established by dividing this total by the number of study participants in the opt out (n=2,293) and opt in (n= 2,287) arms in Campbell et al. (2017). The resultant treatment costs per pregnant woman (including smokers and non-smokers) for CO monitoring + opt-out provision was equal to £6.28 for NRT l/s and £2.83 for behavioral support. The treatment cost per pregnant woman across smokers and non-smokers for no CO monitoring + opt-in provision was equal to £2.97 for NRT l/s and £1.94 for behavioral support.

The total intervention cost (including consumables, training and treatment costs) per pregnant woman at booking (smokers and non-smokers) was equal to £12.58 for the CO monitoring + opt-out provision pathway, and for £4.30 for the no CO monitoring + opt-in provision pathway. A detailed cost breakdown is provided in Table 5~~Table 5~~ and Table 6~~Table 6~~.

Table 5: Intervention costs CO monitoring + opt-out provision

Resource Item	Quantity	Unit cost	Total cost [a]	Cost per person [b]	Source (quantity; unit costs)
Consumables					
Baby CO Monitor	4	£174.00	£696.00	£0.30	(18); NCSCT [c]
Mouthpiece adaptor (x10)	2	£25.96	£51.92	£0.02	
Mouthpiece (x200)	8	£45.00	£360.00	£0.16	
Calibration kit	6	£98.00	£588.00	£0.26	
Hand Sanitiser (100ml)	30	£5.00	£150.00	£0.07	
Non-alcohol wipes (x25)	12	£5.00	£60.00	£0.03	
Healthcare assistant Annual salary	0.27	£18,452.00	£4,920.53	£2.15	(18); (26)
1-day NCSCT training session	6	£187.25[c]	£1,123.50	£0.49	(18); (19)
NRT l/s (standard course) [e]	121	£119.07	£14,407.47	£6.28	(18); Table 3~~Table 3~~
Behavioural support [e]	121	£53.64	£6,490.44	£2.83	(18); (25); Table 3~~Table 3~~
Total opt-out provision			£28,847.86	£12.58	

a: Total cost is quantity multiplied by unit costs
b: Cost per person in the CO testing + opt-out provision arm (n=2,293) in Campbell et al. (2017) including current smokers and non-smokers. Calculation is total costs/ n=2,293.
c: Unit costs and resource items for CO testing obtained through discussion with NCSCT specialist consultant midwife.
d: Unit costs calculated from Bell et al. (2018) based on contract for training 600 healthcare staff by the Tobacco Control Collaborating Centre.
e: Treatment costs are only applied to women who set a quit date (n=121). Unit costs are assumed to be identical to the NRT l/s analysis: all women who receive treatment uptake a full course of NRT l/s

[2] See NRT l/s costing section for details of the SNAP trial.

and receive behavioral support through telephone and home visits in line with the mean costs observed in the SNAP trial (25).

Table 6: Intervention costs No CO monitoring + opt-in provision

Resource Item	Quantity	Unit costs	Total cost [a]	Cost per person [b]	Source (quantity; unit costs)
NRT l/s (standard course) [c]	57	£119.07	£6,786.99	£2.97	(18); Table 3~~Table 3~~
Behavioural support [c]	57	£53.64	£3,057.48	£1.34	(18); (25); Table 3~~Table 3~~
Total opt-in provision			£9,844.47	£4.30	

a: Total cost is quantity multiplied by unit costs.
b: Cost per person across all pregnant women at booking in the opt-in provision arm (n=2,287) including current smokers and non-smokers. Calculation is Total cost/ n=2,287.
c: Treatment costs are only applied to women who set a quit date (n=121). Unit costs are assumed to be identical to the NRT l/s analysis: all women who receive treatment uptake a full course of NRT l/s and receive behavioral support through telephone and home visits in line with the mean costs observed in the SNAP trial (25).

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Epidemiological/comorbidity parameters

No additional changes were made to the model input parameters included in the original ESIP model. Further details on parameters including the prevalence and relative risk of smoking related comorbidities, comorbidity costs, utility values, and mortality rates are described in detail in the original publication, Jones et al. (2019) (21).

Model Version

It is noted that the results of this analysis were obtained from an updated version of the ESIP model. The updated version removed a coding error which, in some cases, previously double counted intervention costs. Therefore, the results from this analysis may not be replicable in versions of the ESIP model dated prior to March 2020.

Economic Evaluation

Decision Rule

Cost-effectiveness models are used to assess the relative benefits of a given treatment using patient outcomes and the costs incurred in achieving those outcomes. Economic evaluations use decision rules to identify the cost-effective intervention. This was an incremental analysis involving pairwise comparisons for each intervention vs. the relevant comparator. The key outcome for this analysis was the incremental cost-effectiveness ratio (ICER) which is calculated by dividing incremental costs by incremental effects as shown in the formula below.

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

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

Discounting

Future costs and outcomes were discounted in the model at a rate of 3.5% per year, in line with the values suggested in the NICE methods manual (20).

Time horizon

In the base case, the time horizon of the model was the lifetime of mother and child, which was set to a maximum of 100 years. The ESIP model also allows cost-effectiveness to be calculated at two additional time horizons, these being during pregnancy only, and covering the “childhood” portion of the model (pregnancy and 15 years immediately after birth). Deterministic scenario analyses were conducted across these additional time horizons.

Perspective

The ESIP model facilitates cost-effectiveness analysis, from a healthcare perspective, including health outcomes measured as QALYs and healthcare costs incurred by the NHS and PSS.

Tobacco smoking is a known teratogen and increases the likelihood of fetal death, fetal malformation, and subsequent developmental disorders in surviving infants (29). Therefore, smoking cessation interventions during pregnancy could have a direct effect on fetal and infant health if they effectively reduce the number of pregnant women who smoke. As stated in the reference case in the NICE methods manual (20), economic evaluations should include all “direct health effects whether for people using the services, or when relevant, other people”. Therefore, the primary analysis included both maternal and child lifetime healthcare costs and QALYs within the perspective. The childhood outcomes included those occurring within pregnancy, the 15-year markov model for passive smoking status, and lifetime outcomes based on children’s smoking status during adulthood. Cost-effectiveness results were also obtained when including maternal outcomes only, however, these were for illustrative purposes and should not be viewed as the primary outcome of this analysis.

Sensitivity and Scenario Analyses

Deterministic Sensitivity Analysis

Different deterministic sensitivity analyses (DSA) were performed by manually changing relevant input parameters in the ESIP model and re-estimating the model results. Key input parameters included effectiveness estimates which were varied across the reported 95% confidence interval, and intervention costs which were increased and decreased by 25%. DSA was also conducted for: the time horizon which was reduced to include outcomes for pregnancy only; the mean age of the population which was both decreased and increased from a mean age of 27 in the base case model to ages of 21 and 38 years respectively; utility values which were set equal for smokers and non-smokers, and disutility and cost per smoking related comorbidities which were increased/decreased by 25%.

We also conducted a single threshold analysis for the financial incentives analysis. Threshold analyses are a type of deterministic sensitivity analysis where a single model

parameter is varied to establish a parameter value where the decision would be altered. In this case the threshold analysis was conducted around the effectiveness parameter to establish the minimum number of quitters at 12-months for financial incentives to be considered cost-effective versus no incentives. The threshold analysis was conducted to address a specific concern raised by the PHAC: the pooled effectiveness estimates for financial incentives had a RR of cessation equal to 2.24 (95% CI equal to 1.75 to 2.88) at 6-months versus no incentives. The PHAC were concerned that the pooled estimate may have been inflated by a single study by Tappin et al. (2015) (28) which had a relatively large and imprecise effect size with the RR being equal to 3.88 and the 95% CI equal to 2.10 to 7.16.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis is a technique used in economic modelling that allows the modeller 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 ESIP model contains in-built functionality to conduct PSA. Information on the parameters and distributions used in the PSA within the ESIP model are reported in Jones et al. (2019) (21). The PSA was conducted by entering standard errors for relative risks estimates as reported in NICE evidence reviews I and J (13, 14). Standard errors for cost parameters were not available, and were therefore assumed to equal 10% of mean costs. This analysis conducted PSA for the NRT l/s and financial incentives analysis, by calculating the number of times each intervention was cost-effective versus the comparator across 10,000 iterations.

PSA could not be conducted for the CO monitoring + opt-out provision analysis as cost-effectiveness was calculated using outputs from the model (i.e. by estimating the cost and QALYs per quitter). This was in contrast to the NRT l/s and financial incentives analysis where the population was exclusively made up of current smokers and effectiveness rates were used directly as parameters within the ESIP model.

Scenario Analyses

Several scenario analyses were conducted to explore key issues identified by the PHAC. Each of the scenario analyses were not included as the base case results due to lack of relevant evidence or the high risk of bias associated with the available evidence. Therefore, the results of the scenario analyses should be viewed as illustrative.

NRT safety

NICE evidence review J (14) included an assessment of the safety of NRT l/s on a variety of pregnancy related outcomes. The reviews did not identify any statistically significant safety issues. However, the PHAC expressed some concerns regarding the impact of NRT on fetal loss and delivery mode (i.e. the increased requirement for caesarean section during birth) as

both of these outcomes had a mean RR in excess of 1 for NRT vs. placebo. The current structure of the ESIP model does not include options to differ safety effects by intervention type but does model fetal loss/caesarean section based on smoking status. Therefore, we investigated the impact of NRT safety issues in a scenario analysis.

The safety analysis was conducted as a threshold analysis which determined the total number of mothers with NRT dependent fetal loss/caesarean section that would be required to make the NRT l/s intervention not cost-effective vs. placebo.

The lifetime QALYs lost and healthcare costs associated with caesarean section per mother were identified directly from parameter values used in the ESIP model. The lifetime QALYs and healthcare costs associated with caesarean section per child were equal to zero as the ESIP model assumes caesarean section has no positive or negative impact on birth outcomes (i.e. survival) and childhood morbidities.

The lifetime QALYs lost and reduced healthcare costs due to fetal loss were calculated by running the ESIP model for scenarios where (i) the probability of fetal loss was equal to 100%, and (ii) the probability of fetal loss was equal to 0%. The incremental QALYs and costs between scenarios with 100% and 0% fetal loss represents the mean lifetime costs per child who is born vs. child who is not born. Fetal loss resulted in cost savings of -£1,434 for mothers as healthcare costs were not required for delivery. Fetal loss also resulted in 0.1 QALYs worth of disutility for mothers due to the mental and physical health problems associated with unsuccessful pregnancies.

For every successful birth, the ESIP model calculated total discounted lifetime QALYs equal to 26.38, meanwhile lifetime healthcare costs were equal to £8,770. The healthcare costs are not reflective of all the NHS costs that a child would be expected to incur across their lifetime. This is because the ESIP model only includes costs associated with *smoking* related comorbidities, that is asthma, COPD, lung cancer, stroke and coronary heart disease. As children will incur costs for many other non-smoking related health conditions, lifetime costs per fetal loss are underestimated in this analysis. All costs and QALYs for the adverse safety events are summarised in Table 7~~Table 7~~.

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Table 7: Cost and QALY impact per adverse safety event from the ESIP model

Adverse Event	Cost impact	QALYs impact per AE	Cost & QALYs impact
Fetal loss (mother) [a]	-£1,434	-0.1	£566
Caesarean section (mother) [b]	£1,284	0	£1,284
Fetal loss (child) [a]	-£8,770	-26.38	£518,830
Caesarean section (child)	£0	0	£0.00

a: calculated by comparing incremental costs and QALYs from the ESIP model for scenarios with 100% fetal loss and 0% fetal loss.
b: Costs obtained directly from parameter values in the original ESIP model.

The safety analysis was conducted, first by estimating results for the base case analysis i.e. comparing the cost-effectiveness of NRT l/s vs. placebo. Next, the cost and QALY loss associated with each adverse safety event was multiplied by x%, that is the proportion of mothers who have the adverse outcome due to NRT l/s. Then the product (QALYs and costs multiplied by x%) was subtracted from the NRT intervention arm and cost-effectiveness was re-estimated. If the new ICER was above the £20,000 threshold then NRT l/s was not cost-effective vs. placebo assuming NRT l/s results in x% of caesarean sections/fetal losses.

The safety analysis investigated a range of different “x” values, by varying the percentage of mothers who had each safety outcome within a two-way data table in Microsoft Excel. The two-way table included 0% values for both outcomes, allowing the impact of both safety issues to be analysed independently and simultaneously. The data table established a threshold “x” proportion for which NRT l/s would become not cost-effective vs. placebo.

Maximum value of incentives

In addition to the analysis of contingent, stepped financial incentives, the PHAC were interested in establishing, in theory, the maximum value of incentive that could be provided per pregnant woman who successfully quit smoking. Consequently, a threshold analysis was conducted to determine the maximum value of financial incentives before the intervention became not cost-effective vs. no incentives.

The scenario analysis estimated the mean lifetime costs and QALYs per quitter in the ESIP model, that is the incremental difference in costs and QALYs for a cohort of mothers who all quit vs. a cohort of mothers who all continued to smoke at delivery. Lifetime costs and QALYs were estimated by running the ESIP model with a 100% (quitters) and 0% (smokers) probabilities of smoking abstinence at childbirth.

The maximum value of financial incentives was estimated by calculating the net monetary benefit (NMB) per successful quitter. The NMB is a summary statistic that represents the value of an intervention in monetary terms, at a stated willingness-to-pay threshold per QALY. The NMB was calculated by multiplying incremental lifetime QALYs by the cost-effectiveness threshold, £20,000, and subtracting incremental lifetime costs. The value of the NMB in the threshold analysis represented the maximum mean cost afforded per successful quitter in the ESIP model. Therefore, this represented the maximum possible value per financial incentive that could be paid per mother who successfully quit, to produce an ICER = £0, where the intervention is no better or worse than placebo. This is only a theoretical value likely to overstate the maximum value of financial incentives: the costs of financial incentives in practice would need to incorporate the value of financial incentives per successful quitter, administration costs, and any costs per incentives that may be provided to women who later relapse.

Cost-effectiveness of e-cigarettes

Electronic cigarettes were not included in the base case analysis because NICE evidence review (J) (14) did not identify any appropriate studies which established effectiveness specifically in populations of pregnant women. Consequently, the cost-effectiveness of e-cigarettes was investigated in an exploratory scenario analysis.

The exploratory analysis assumed the efficacy of e-cigarettes in pregnancy populations vs. the general population would be similar to the efficacy of NRT l/s in pregnancy populations vs. the general population. The RR of smoking abstinence for NRT l/s vs. placebo in the general population was obtained from a network meta-analysis in NICE evidence review (K) in the Tobacco guidelines updates (30). The RR of 2.64 in the general population (30) compared with a RR of 1.21 as applied for the pregnancy population in this analysis (14). Similarly, the RR of smoking abstinence for e-cigarettes vs. placebo in the general population was obtained from the NMA in NICE evidence review (K), and was equal to 3.96 (30). Therefore, the RR of smoking abstinence for e-cigarettes in pregnancy populations applied in the exploratory analysis was approximated as equal 3.96*(1.21/2.64) = 1.82. This resulted in an absolute probability of quitting at childbirth equal to 13.10%. The probability of smoking cessation for placebo was 7.6%, equivalent to cessation rates for pregnant women who received placebo plus behavioural support in the control arm for the NRT l/s analysis.

The exploratory analysis was conducted assuming e-cigarettes obtained an NHS licence and would be available via free prescriptions for pregnant women, as with NRT. No published literature was identified which reported costs for e-cigarettes in pregnant women. Consequently, costs were applied as per the general population by uprating cost and resource usage items reported in a cost-effectiveness study by Li et al. (2020) (31). Costs by Li et al. (2020) included the new One Kit 2016 e-cigarette starter pack for each participant, 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]. Li et al. (2020) also calculated the mean costs per participant for e-liquid refills over a 12-month period, which were halved to estimate e-liquid costs over 6-months, equal to £80.33 after uprating. All costs were uprated 2019 prices using the NHSCII pay and prices index reported in the PSSRU (26). The total cost of the e-cigarette's intervention was £133.97 which included the cost of behavioural support (equal to £53.64).

There is currently no evidence available regarding the safety issues associated with e-cigarettes for mothers and children. The safety of e-cigarettes was incorporated in the economic modelling using a threshold analysis, in the same way as described previously for NRT I/s intervention, similarly including safety outcomes for fetal loss and caesarean section. The scenario analysis established the threshold cost required for each safety issue that would result in e-cigarettes not being cost-effective vs. placebo. The threshold cost was estimated in two-way data tables which varied the rate of fetal loss and c-section due to e-cigarettes.

Cost effectiveness per smoker: Co monitoring + opt-out provision vs. no CO monitoring + opt-in provision

The final scenario analysis was specifically requested by the NICE team. The analysis evaluated the cost-effectiveness of CO monitoring + opt-out provision vs. no CO monitoring + opt-in provision exclusively for a population of expectant mothers who were current smokers. The exploratory scenario differed from the base case analysis which established cost-effectiveness in a population of both smokers and non-smokers, i.e. the population who received the CO monitoring intervention in the study by Campbell et al. (2017) (18).

The effectiveness estimate for the exploratory scenario was obtained from NICE evidence review H which reported a RR of smoking abstinence of 1.39 (95% CI = 1.01, 1.92). The RR of smoking abstinence was calculated by NICE by dividing the total number of participants in Campbell et al. (2017) who achieved 4-weeks continued abstinence after their quit date by the total number of participants who had been identified as smokers in each treatment arm. For CO monitoring + opt-out provision 93 expectant mothers achieved 4-week abstinence out of 421 smokers identified. For No CO monitoring + opt-in provision 46 expectant mothers achieved abstinence out of 290 identified. Consequently, the RR was equal to (93/421)/(46/290).

The absolute probabilities of smoking abstinence for the exploratory scenario are displayed in Table 8~~Table 8~~. As with the base case analysis, the probability of abstinence for CO monitoring was assumed to be reported at 20 weeks post conception. This assumption was based on the CO monitoring intervention being delivered at 12-weeks post conception, an assumed 4-week time required between smoking identification and setting a quit date with LSSS, and the 4-weeks abstinence required between quit date and final abstinence measure, (18).

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The probability of smoking abstinence at 20 weeks post conception for no CO monitoring + opt-in provision was equal to 15.9%, i.e. 46 out of 290 smokers who achieved the 4-week abstinence outcome in the control arm of Campbell et al. (2017). The probability of smoking

abstinence for CO monitoring + opt-out provision at 20-weeks post conception was 22.1%, calculated by multiplying the associated RR by the probability of abstinence in the control arm (i.e. 1.39 X 15.9%). Similar to analyses for each of the other interventions, results are reported for scenarios applying 0% and 20% relapse rates between probabilities of abstinence at 20-weeks and 40-weeks post conception.

Table 8: Intervention effectiveness CO monitoring + opt-out versus no Co monitoring + opt-in provision, smokers only.

Intervention	RR of abstinence vs. comparator	P (quit) 20 weeks	P (quit) 40 weeks
Scenario 1: No relapse			
No CO monitoring + opt-in provision	N/A	15.86%[a]	15.86%
CO monitoring + opt-out provision	1.39	22.04%	22.04%
Scenario 2: 20% relapse			
No CO monitoring + opt-in provision	N/A	15.86%	12.69%
CO monitoring + opt-out provision	1.39	22.04%	17.64%

A: probability of abstinence at 20-weeks calculated as total number of abstainers (n=46) divided by the total number of smokers identified in the opt-in provision arm (n=290) in Campbell et al. (2017) (18).

Intervention costs for the exploratory analysis were identical to the costs applied for the base case analysis, but to reflect the change in population were converted to a cost per smoker, rather than costs per smoker and non-smoker as applied in the base case.

The total cost for CO monitoring + opt-out provision including consumables, staff costs, and treatment with NRT + behavioural support across all participants (smokers and non-smokers) in Campbell et al. (2017) (18) was equal to £28,847.86 (see previous Table 5~~Table 5~~). The total cost per smoker identified was equal to £68.52 (i.e. £28,848 divided by 421 smokers identified for the CO monitoring + opt-out pathway).

The total cost for no CO monitoring + opt-in provision, including treatment costs for NRT and behavioural support for all those who set a quit date across all participants in Campbell et al. (2017) (18) was equal to £9,844.47 (see previous Table 6~~Table 6~~). The total cost per smoker identified was equal to £33.95 (i.e. £9,844.47 divided by 290 smokers identified for the no CO monitoring + opt-in pathway). Intervention costs for the exploratory analysis are summarised in Table 9~~Table 9~~.

Table 9: Intervention costs per smoker: CO monitoring + opt out provision vs. no CO monitoring + opt-in provision .

Intervention	Total costs (ref)	Smokers identified (ref)	Cost per smoker
No CO monitoring + opt-in provision	£9,844.47 (Table 6~~Table 6~~)	290 (18)	£33.95
CO monitoring + opt-out provision	£28,847.86 (Table 5~~Table 5~~)	421 (18)	£68.52

Results

Base Case Results

NRT l/s

At a threshold of £20,000 per QALY, the results of the base case analysis identified NRT l/s as cost-effective vs. placebo with an ICER equal to £5,281. In a population of 1000 pregnant women, the ESIP model estimated NRT l/s would produce 16 additional quitters, resulting in a mean of 0.019 additional QALYs per mother *and* child vs. placebo. The predicted increase in health benefits occurred due to the combined impact of fewer fetal related mortalities (mean = -0.56 per 1000), fetal morbidities (mean = -0.92 per 1000), and a reduction in the number of maternal smoking related morbidities (mean = -1.89 per 1000). NRT l/s incurred additional lifetime healthcare costs vs. placebo, equal to £98 per person. The difference in healthcare costs between NRT l/s and placebo was primarily due to the upfront intervention costs (i.e. costs of NRT l/s treatment).

For the maternal only analysis, NRT l/s was not cost-effective vs. placebo with an ICER equal to £30,056, which exceeds the £20,000 cost-effectiveness threshold stated in the NICE methods manual (20). The difference in cost-effectiveness results across the two perspectives was due to the additional lifetime health benefits in children, where mean incremental QALYs increased substantially from 0.004 per mother to 0.019 per mother and child.

The inclusion of a 20% relapse rate between 20 and 40 weeks increased the ICERs for NRT l/s vs. placebo, but did not impact on the findings, with the intervention remaining cost-effective for the maternal plus child analysis and not cost-effective for the maternal only analysis. All results for the base case analysis are reported in Table 10~~Table 10~~.

Table 10: Cost-effectiveness results: NRT l/s

	Absolute Costs		Absolute QALYs		Incremental		
	NRT l/s	Placebo [a]	NRT l/s	Placebo [a]	Costs	QALYs	ICER
Base case analysis: 0% relapse between weeks 20 and 40 of pregnancy							
Mother + child [b]	£21,011	£21,110	46.85	46.83	£98	0.019	£5,281
Mother [c]	£10,228	£10,117	23.20	23.20	£111	0.004	£30,056
Scenario: 20% relapse between weeks 20 and 40 of pregnancy							
Mother + child [b]	£21,134	£21,032	46.83	46.82	£102	0.015	£6,884
Mother [c]	£10,237	£10,124	23.19	23.20	£113	0.003	£38,101

a: Intervention and placebo arm include behavioural support
b: Outcomes reported *per mother and child dyad*
c: Outcomes reported per mother only

Financial Incentives

The stepped financial incentives intervention was cost-effective for the mother plus child analysis (dominant) and for the mother only analysis (ICER equal to £2,005), Table 11. Financial incentives were associated with lifetime healthcare savings of £64 per mother and child. However, the intervention had slightly increased costs when compared with no

incentives, equal to £82 for the mother only analysis. The increase in costs was due to the cost of administering and providing financial incentives. The slight increase in healthcare costs was more than offset by the substantial health benefits, where mean incremental QALYs were equal to 0.04 per mother, and 0.21 per mother and child vs. no incentives. Results for the base case mother and child analysis were driven by a substantial increase in the number of quitters (177 per 1000) causing: a decrease in the number of smoking related comorbidities per mother (20.87 per 1000), a reduction in fetal mortalities (6.28 per 1000) and a reduction in the number of children who become smokers during adulthood (1.3 per 1000).

Table 11: Cost-effectiveness results: Financial incentives

	Absolute Costs		Absolute QALYs		Incremental		
	Incentives	N.I. [a]	Incentives	N.I. [a]	Costs	QALYs	ICER
Mother + child [b]	£20,966	£21,030	47.05	46.85	-£64	0.205	Dominant
Mother [c]	£10,229	£10,147	23.24	23.19	£82	0.041	£2,003

N.I. No incentives
a: Incentives and no incentives arm includes behavioural support and NRT l/s
b: Outcomes reported *per mother and child dyad*
c: Outcomes reported per mother only

CO monitoring + opt-out provision

The CO monitoring + opt-out provision intervention was cost-effective for both the maternal only, and the maternal and child analyses. For both analyses the intervention was dominant, being cost saving and resulting in additional QALYs versus no CO monitoring + opt in provision.

CO monitoring + opt-out provision resulted in 20.5 additional quitters per 1,000 (including both smokers and non-smokers). Results from the ESIP model established the mean incremental lifetime costs and QALYs per each additional quitter were equal to -£492.71 and 0.232 (mother only) and -£1,318.74 and 1.163 (mother and child), Table 12~~Table 12~~.

Table 12: Lifetime costs and QALYs per quitter

Population	Mother		Child		Mother + Child	
	Costs	QALYs	Costs	QALYs	Costs	QALYs
Quitters [a]	£9,607.77	23.410	£10,131.56	24.493	£19,739.33	47.903
Smokers [b]	£10,100.48	23.178	£10,957.59	23.562	£21,058.07	46.740
Incremental	-£492.71	0.232	-£826.03	0.931	-£1,318.74	1.163

a: Abstinence rate = 100%, where all current smokers in the ESIP model quit by delivery.
b: Abstinence rate = 0%, where all current smokers in the ESIP model continue to smoke at delivery.

The intervention costs for CO monitoring + opt-out provision was £12.58 per person, meanwhile the intervention costs for no CO monitoring + opt-in provision was £8.28 per person. Therefore, the incremental intervention costs of CO monitoring + opt-out provision vs. opt-in provision in a hypothetical cohort of 1,000 pregnant women was £8,280 or £8.28 per woman (including both smokers and non-smokers).

When including intervention costs, and the costs for 20.5 quitters, the incremental cost of CO monitoring + opt-out provision vs. No CO monitoring + opt-in provision for a hypothetical population of 1,000 pregnant women was equal to -£1,821 (mother only) and -£18,754 (mother and child outcomes). In addition, incremental QALYs for CO monitoring + opt-out provision vs. opt-in provision due to an additional 20.5 quitters per 1,000 were equal to 4.756

(mother only) and 23.842 (mother and child outcomes). As CO monitoring + opt-in provision was cost saving and achieved health benefits the intervention was cost-effective with a dominant ICER. A full breakdown of cost-effectiveness results is provided in Table 13~~Table 13~~.

Table 13: Incremental cost-effectiveness results opt-out vs. opt-in provision

	Incremental population outcomes (n=1,000)				Incremental cost-effectiveness results (per person)		
	Intervention Costs	No. of quitters	Costs all quitters	QALYs all quitters	Total Costs	Total QALYs	ICER
Base case: 0% relapse							
Mother + child	£8,280.00	20.5	-£27,034	23.842	-£18.75	0.0238	Dominant
Mother	£8,280.00	20.5	-£10,101	4.756	-£1.82	0.0048	Dominant
Scenario: 20% relapse between weeks 20 and 40 of pregnancy							
Mother + child	£8,280.00	16.4	-£21,627	19.073	-£13.34	0.0191	Dominant
Mother	£8,280.00	16.4	-£8,080	3.805	£0.20	0.0038	£52.45

Cost-effectiveness results obtained for opt-out vs. opt-in provision of stop smoking support in a hypothetical population of 1,000 pregnant women, including smokers and non-smokers.

The inclusion of a 20% relapse rate between weeks 20 and 40 of pregnancy decreased the number of additional quitters attributable to CO monitoring+ opt-out provision from 20.5 to 16.4 per 1,000. This resulted in costs across all quitters equal to -£8,080 (mother only) and -£21,627.34 (mother and child) and QALYs equal to 3.805 (mother only) and 19.073 (mother and child). As intervention costs exceeded cost savings per quitter, the associated ICER for the mother only analysis was not dominant, but remained cost-effective, being equal to £52.45, substantially less than the £20,000 threshold. The ICER for CO monitoring + opt-out provision remained dominant when including maternal and child outcomes, Table 13~~Table 13~~.

Uncertainty Analysis

Deterministic Sensitivity Analysis Results

One-way deterministic sensitivity analysis (DSA) was conducted for intervention effectiveness, intervention costs, time horizon, mean age of the population, utility for smokers and non-smokers, disutility per comorbidity and cost per comorbidity. Results are reported for the analysis including both maternal and child outcomes, and with relapse between weeks 20 and 40 equal to 0%. All results of the DSA are reported in Table 14~~Table 14~~ **Error! Reference source not found.**(NRT l/s), Table 15~~Table 15~~ (financial incentives) and Table 16~~Table 16~~ (opt-out provision).

For the NRT l/s analysis, cost-effectiveness results were highly sensitive to changes in the relative risk of smoking cessation (i.e. intervention effectiveness): when applying the upper 95% CI RR (equal to 1.55) there was a substantial decrease in the ICER from £5,381 to £1,315; In contrast when applying the lower 95% CI RR (equal to 0.95) NRT l/s was not cost-effective being dominated by placebo (costlier and less effective). Similarly, results were sensitive to changes in the time horizon, where NRT l/s was not cost-effective when limiting the analysis to pregnancy only (ICER vs. placebo =£130,000). Cost-effectiveness results

were robust across all other DSA, which included variations to intervention costs, disease costs, and utility values.

Table 14: Results of deterministic sensitivity analysis: NRT l/s

DSA Scenario	DSA Parameter Value	Absolute (NRT l/s)		Incremental (NRT l/s vs. placebo)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£21,110	46.85	£98.02	0.019	£5,281
Effectiveness	Lower 95% CI RR (0.95)	£21,136	46.82	£124.08	-0.004	Dominated
	Upper 95% CI RR (1.55)	£21,075	46.88	£63.95	0.049	£1,315
Intervention costs	Increase by 25%	£21,153	46.85	£127.79	0.019	£6,884
	Decrease by 25%	£21,066	46.85	£68.26	0.019	£3,677
Time horizon	Limit to pregnancy	£6,458	0.69	£59.81	0.0005	£130,311
Mother's age	Mean age 21	£19,831	48.02	£100.59	0.018	£5,570
	Mean age 38	£24,241	44.30	£90.80	0.020	£4,536
Utility	Same QoL for smokers and non-smokers	£21,110	47.20	£98.02	0.017	£5,766
Disease costs	Decrease by 25%	£15,875	46.85	£103.28	0.019	£5,564
	Increase by 25%	£26,344	46.85	£92.76	0.019	£4,997
Disease disutility	Decrease by 25%	£21,110	36.80	£98.02	0.007	£14,083
	Increase by 25%	£21,110	45.77	£98.02	0.021	£4,668

The financial incentives intervention remained cost-effective for the DSA which applied the lower 95% confidence interval for the RR (equal to 2.22) of smoking cessation vs. no incentives. Financial incentives were also cost-effective vs. no incentives for all other scenario analyses, including when limiting the time horizon to pregnancy, which resulted in an ICER equal to £17,232. Increasing the age of the cohort from 27 to 38 resulted in increased incremental healthcare savings and QALYs gained due to an increased prevalence of comorbidities at the starting age for the cohort and consequently less discounting applied to comorbidity costs and QALYs. Decreasing the age of the cohort from 27 to 21 had the opposite effect, i.e. increasing healthcare costs and reducing QALYs gained due to a reduced prevalence of comorbidities at the starting age of the cohort and therefore additional discounting.

Table 15: Results of deterministic sensitivity analysis: Financial Incentives

DSA Scenario	DSA Parameter Value	Absolute (incentives)		Incremental (incentives vs. no incentives)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£20,966	47.05	-£64.05	0.205	Dominant
Effectiveness	Lower 95% CI RR (2.22)	£21,054	46.97	£23.97	0.128	£187
	Upper 95% CI RR (3.93)	£20,851	47.15	-£179.44	0.251	Dominant
Intervention costs	Increase by 25%	£21,031	47.05	£0.96	0.205	£5
	Decrease by 25%	£20,901	47.05	-£129	0.205	Dominant
Time horizon	Limit to pregnancy	£6,504	0.69	£87.61	0.005	£17,232
Mother's age	Mean age 21	£19,716	48.21	-£35.64	0.200	Dominant
	Mean age 38	£24,018	44.52	-£144.01	0.222	Dominant
Utility	Same QoL for smokers and non-smokers	£20,966	47.38	-£64.05	0.187	Dominant
Disease costs	Decrease by 25%	£15,789	47.05	-5.77	0.205	Dominant

	Increase by 25%	£26,143	47.05	-£122.34	0.205	Dominant
Disease disutility	Decrease by 25%	£20,966	36.87	-£64.05	0.078	Dominant
	Increase by 25%	£20,966	46.00	-£64.05	0.235	Dominant

We also conducted a threshold to address specific concerns from the PHAC regarding the effectiveness estimate. The threshold analysis established the minimum number of quitters required for financial incentives to still be considered cost-effective. When considering maternal and child outcomes, financial incentives needed to result in at least 7 additional quitters per 1,000 to be considered cost-effective versus no financial incentives (or a RR= 1.08). When considering maternal outcomes only, financial incentives needed to result in at least 33 additional quitters per 1,000 (or a RR = 1.38) to be considered cost-effective versus no financial incentives. The threshold is substantially less that the base case parameters where financial incentives resulted in 177 additional quitters per 1,000.

Cost-effectiveness results for the CO monitoring + opt-out provision analysis were robust in all deterministic scenario analyses. CO monitoring + opt-out provision remained cost-effective vs. no CO monitoring + opt-in provision for pessimistic effectiveness scenario where the number of additional quitters was reduced to 5 (the lower 95% CI value for opt-out provision and the upper 95% CI value for opt-in provision). Similarly, the intervention remained cost-effective when increasing intervention costs by 25%; when including mean cost and QALYs per quitter for both mothers and children; and when increasing and decreasing the mean age of mothers to 38 and 21 respectively. Furthermore, CO monitoring + opt-out provision was cost-effective when limiting the time horizon to the pregnancy period only. CO monitoring + opt-out provision only became not cost-effective vs. opt-in provision when: incremental quitters were reduced to fewer than 0.4 per 1000; and when intervention costs exceeded £500 per person (including costs for both smokers and non-smokers). The DSA results for the opt-out provision analysis are displayed in Table 16~~Table 16~~.

Table 16: Deterministic sensitivity analysis: CO monitoring + opt-out provision

DSA Scenario	DSA Parameter Value	Incremental (opt-out vs. opt-in provision)					
		No. quitters	Cost per quitter	QALYs per quitter	Total costs per person	Total QALYs per person	ICER
Base Case	N/a	20.50	-£1,319	1.163	-£18.75	0.024	Dominant
Effectiveness	Lowest estimate	6.00	-£1,319	1.163	£0.37	0.007	£52.67
	Highest estimate	34.00	-£1,319	1.163	-£36.56	0.040	Dominant
Intervention costs	Increase by 25%	20.50	-£1,319	1.163	-£16.68	0.024	Dominant
	Decrease by 25%	20.50	-£1,319	1.163	-£20.82	0.024	Dominant
Time horizon	Pregnancy only	20.50	£18.00	0.029	£8.65	0.001	£14,649
Mother's age	Mean age 21	20.50	-£1,158	1.131	-15.46	0.023	Dominant
	Mean age 38	20.50	-£1,771	1.254	-£28.03	0.026	Dominant
Utility	Same QoL for smokers and non-smokers	20.50	-£1,319	1.057	-£18.75	0.022	Dominant
Disease costs	Increase by 25%	20.50	-£1,648	1.163	-£25.50	0.024	Dominant
Disease disutility	Decrease by 25%	20.50	-£1,319	1.219	-£18.75	0.025	Dominant

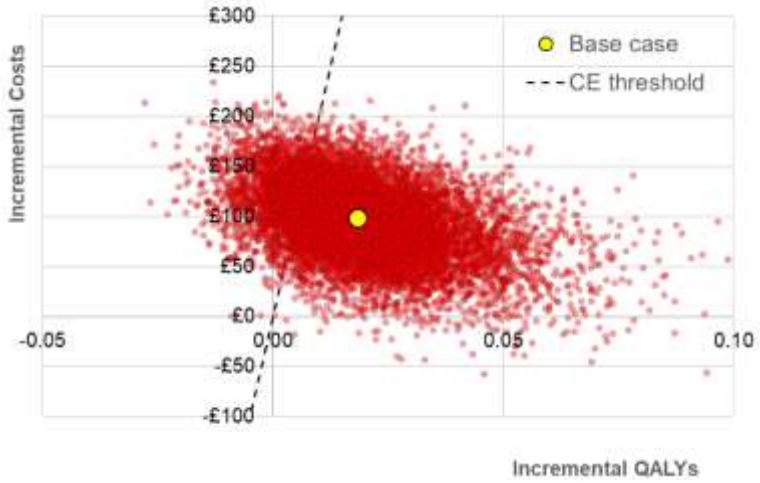
Probabilistic Sensitivity Analysis

NRT l/s was identified as the cost-effective strategy in 83.1~~73.7~~% of PSA iterations, with placebo being cost-effective in the remaining 16.9~~26.3~~%. The results of the PSA are illustrated in Figure 2. The figure plots PSA results on a cost-effectiveness plane, each point

(in red) represents one PSA iteration. PSA was conducted across a total of 10,000 iterations. 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.

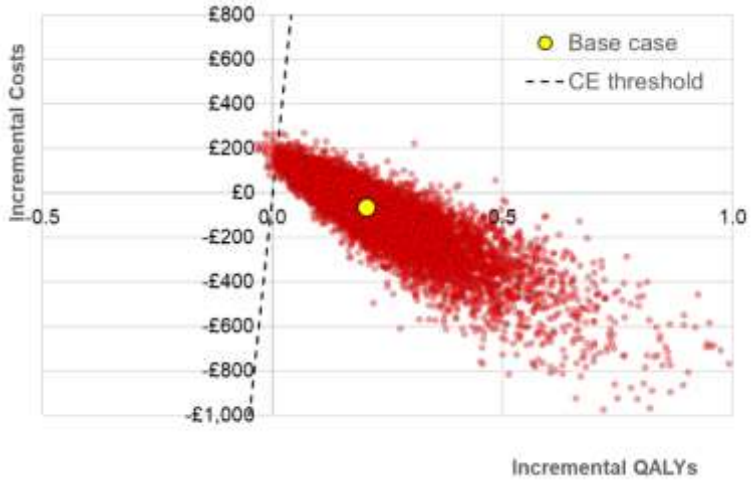
The PSA results reflected results from the NICE effectiveness reviews where the lower 95% confidence interval for the RR of smoking cessation for NRT l/s vs placebo was equal to 0.95, falling below the line of no effect. PSA iterations with a RR parameter value <1 resulted in NRT l/s being less effective than placebo and, consequently, fewer non-smokers and fewer lifetime QALYs. In addition, whilst NRT l/s was usually costlier than placebo, the uncertainty around the effectiveness parameters impacted on the size of incremental costs, which ranged between -£50 and £250.

Figure 2: PSA Results NRT l/s



The financial incentives intervention was cost-effective in 99.7% of the 10,000 iterations, meaning no incentives were only cost-effective 0.3% of the time , Figure 3. The difference in PSA results were driven by increased certainty around the effectiveness parameter. As the lower 95% CI RR for financial incentives was greater than 1 (equal to 2.22), across all PSA iterations, the intervention was always effective and incremental QALYs always positive vs. no incentives.

Figure 3: PSA Results Financial Incentives



It was not possible to conduct PSA for the CO monitoring + opt -out provision analysis as the intervention was delivered to a population of smokers and non-smokers. This meant cost-effectiveness was analyzed indirectly using outputs from the ESIP i.e. estimating incremental mean lifetime costs and QALYs per additional quitter.

Scenario Analyses

Exploratory analysis: Cost-effectiveness of E-cigarettes

The exploratory analysis, applying assumed effectiveness rates[c] and costs of a starter park plus refills for 12 months, found e-cigarettes were cost-effective for both the mother and child and mother only analyses, with ICERs equal to £39 and £3,748, respectively. The e-cigarettes intervention was associated with slightly increased costs when compared with placebo, equal to £3 (per mother and child) and £51.26 (per mother only). The analysis assumed e-cigarettes would have received an NHS licence, and therefore the increased costs were driven by intervention costs. E-cigarettes were associated with a health benefit, where mean incremental lifetime QALYs were equal to 0.069 per mother and child and 0.014 per mother vs. placebo. All results for the e-cigarettes analysis are displayed in Table 17.

Table 17: Results of E-cigarette exploratory analysis [a]

	Absolute Costs		Absolute QALYs		Incremental		
	E-cigs	Placebo	E-cigs	Placebo	Costs	QALYs	ICER
E-cigarettes vs. placebo							
Mother and child	£21,019	£21,016	46.89	46.82	£2.67	0.069	£39
Mother only	£10,170	£10,119	23.21	23.19	£51.26	0.014	£3,748

a: Exploratory analysis applied assumptions regarding for e-cigarettes, including a proportional relative risk for smoking cessation and equivalent costs as observed in general populations. Parameter values are *not* specific for pregnancy populations.

The DSA results for the e-cigarettes analysis are reported in Table 18. Because this was an exploratory analysis where effectiveness estimates were approximated based on adjusted effectiveness rates for the general population[2], a large range was investigated for the effectiveness parameters. E-cigarettes remained cost-effective when reducing the approximated relative risk of smoking cessation by 33%, but with an ICER which increased

[c] Assumed effectiveness rates were calculated by applying effectiveness rates for e-cigarettes in the general population and adjusting these rates for pregnant women. The adjusted rates were calculated by obtaining the ratio of effectiveness for NRT l/s in the general population: NRT l/s in pregnant women. The same ratio was assumed for the effectiveness of e-cigarettes in the general population: e-cigarettes in pregnant women.

from £39 to £3,304. Similarly, cost-effectiveness results remained robust when increasing and decreasing intervention costs by 50%, indicating that e-cigarettes may be cost-effective vs. placebo for a range of plausible parameter values in a population of pregnant women. Cost-effectiveness results were also robust when varying several other parameter values including increasing and decreasing the mean age of pregnant women, the utility and disutility values, and the cost of the comorbidities. However, e-cigarettes were not cost-effective when limiting the model time horizon to pregnancy only.

Table 18: Results of deterministic sensitivity analysis: E-cigarettes [a]

DSA Scenario	DSA Parameter Value	Absolute		Incremental (vs. placebo)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£21,019	46.89	£3	0.069	£39
Effectiveness	RR decreased by 33%	£21,076	46.84	£59	0.018	£3,304
	RR increased by 33%	£20,962	46.94	-£55	0.119	Dominant
Intervention costs	Increase by 50%	£21,153	46.89	£136	0.069	£1,978
	Decreased by 50%	£20,855	46.89	-£131	0.069	Dominant
Time horizon	Limit to pregnancy	£6,372	0.69	£81	0.002	£47,946
Mother's age	Mean age 21	£19,747	48.06	£12	0.067	£180
	Mean age 38	£24,133	44.35	-£24	0.074	Dominant
Utility	Same QoL for smokers and non-smokers	£21,019	47.24	£3	0.062	£43
Disease costs	Increase by 25%	£26,241	46.89	-£17	0.069	Dominant
Disease disutility	Increase by 25%	£21,019	50.21	£3	0.072	£35

a: Base case exploratory analysis applied assumptions regarding for e-cigarettes, including a proportional relative risk for smoking cessation and equivalent costs as observed in general populations. Parameter values are *not* specific for pregnancy populations.

Safety Analysis: NRT l/s & E-cigarettes

The results of the safety analysis for NRT l/s vs. placebo are reported in Figure 4. The analysis demonstrates that cost-effectiveness results are somewhat sensitive to changes in caesarean section and highly sensitive to changes in fetal loss. The NRT l/s intervention would need to increase caesarean section in mothers by over 18% before NRT l/s became not cost-effective. However, any increase in fetal loss would mean NRT l/s was not cost-effective vs. placebo.

Figure 4: Safety Analysis NRT l/s

NMB [a]		Absolute % increase in fetal loss (NRT)										
		0%	0.1%	0.2%	0.3%	0.4%	0.5%	0.6%	0.7%	0.8%	0.9%	1.0%
Absolute % increase in c-section (NRT)	0%	£252	-£267	-£787	-£1,306	-£1,826	-£2,345	-£2,864	-£3,384	-£3,903	-£4,423	-£4,942
	2%	£226	-£293	-£812	-£1,332	-£1,851	-£2,371	-£2,890	-£3,409	-£3,929	-£4,448	-£4,968
	4%	£201	-£319	-£838	-£1,358	-£1,877	-£2,396	-£2,916	-£3,435	-£3,955	-£4,474	-£4,993
	6%	£175	-£344	-£864	-£1,383	-£1,903	-£2,422	-£2,941	-£3,461	-£3,980	-£4,500	-£5,019
	8%	£149	-£370	-£889	-£1,409	-£1,928	-£2,448	-£2,967	-£3,486	-£4,006	-£4,525	-£5,045
	10%	£124	-£396	-£915	-£1,435	-£1,954	-£2,473	-£2,993	-£3,512	-£4,032	-£4,551	-£5,070
	12%	£98	-£421	-£941	-£1,460	-£1,980	-£2,499	-£3,018	-£3,538	-£4,057	-£4,577	-£5,096
	14%	£72	-£447	-£967	-£1,486	-£2,005	-£2,525	-£3,044	-£3,567	-£4,083	-£4,602	-£5,122
	16%	£47	-£473	-£992	-£1,512	-£2,031	-£2,550	-£3,070	-£3,589	-£4,109	-£4,628	-£5,147
	18%	£21	-£499	-£1,018	-£1,537	-£2,057	-£2,576	-£3,095	-£3,615	-£4,134	-£4,654	-£5,173
	20%	-£5	-£524	-£1,044	-£1,563	-£2,082	-£2,602	-£3,121	-£3,641	-£4,160	-£4,679	-£5,199

The figure depicts cost effectiveness results for NRT I/s vs. placebo, which have been re-estimated assuming that the intervention results in an x% increase in fetal loss and a y% increase in c-section loss.

a: 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.

In contrast, e-cigarettes would still be considered cost-effective even if resulting in a 100% of mother's requiring a caesarean section. E-cigarettes would not be cost-effective if they resulted in an increase in fetal mortality in more than or equal to 0.3% of the population receiving the intervention. The impact of fetal mortality is so pronounced due to the extremely high QALY loss per each fetal death, this being equal to the mean QALYs across the entire life expectancy of surviving infants. The joint impact of both adverse events is depicted in Figure 5, which indicates that e-cigarettes may still be cost-effective versus placebo if they caused up to 20% of mothers to have c-sections and up to 0.2% of mothers to suffer fetal loss.

Figure 5: Safety Analysis E-cigarettes

NMB [a]		Absolute % increase in fetal loss (e-cigs)										
		0%	0.1%	0.2%	0.3%	0.4%	0.5%	0.6%	0.7%	0.8%	0.9%	1.0%
Absolute % increase in c-section (e-cigs)	0%	£1,365	£845	£326	-£193	-£713	-£1,232	-£1,752	-£2,271	-£2,790	-£3,310	-£3,829
	10%	£1,236	£717	£198	-£322	-£841	-£1,361	-£1,880	-£2,399	-£2,919	-£3,438	-£3,958
	20%	£1,108	£589	£69	-£450	-£970	-£1,489	-£2,008	-£2,528	-£3,047	-£3,567	-£4,086
	30%	£980	£460	-£59	-£579	-£1,098	-£1,617	-£2,137	-£2,656	-£3,176	-£3,695	-£4,214
	40%	£851	£332	-£188	-£707	-£1,226	-£1,746	-£2,265	-£2,785	-£3,304	-£3,823	-£4,343
	50%	£723	£203	-£316	-£835	-£1,355	-£1,874	-£2,394	-£2,913	-£3,432	-£3,952	-£4,471
	60%	£594	£75	-£444	-£964	-£1,483	-£2,003	-£2,522	-£3,041	-£3,561	-£4,080	-£4,600
	70%	£466	-£53	-£573	-£1,092	-£1,612	-£2,131	-£2,650	-£3,170	-£3,689	-£4,209	-£4,728
	80%	£338	-£182	-£701	-£1,221	-£1,740	-£2,250	-£2,779	-£3,298	-£3,818	-£4,337	-£4,856
	90%	£209	-£310	-£830	-£1,349	-£1,868	-£2,388	-£2,907	-£3,427	-£3,946	-£4,465	-£4,985
	100%	£81	-£439	-£958	-£1,477	-£1,997	-£2,516	-£3,036	-£3,555	-£4,074	-£4,594	-£5,113

The figure depicts cost effectiveness results for E-cigarettes vs placebo, which have been re-estimated assuming that the intervention results in an x% increase in fetal loss and a y% increase in c-section loss.

a: 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.

Maximum value of Financial Incentives

The ESIP model was used to estimate the lifetime costs and QALYs per mother and child if a mother quit smoking vs. if a mother continued to smoke during pregnancy, by setting effectiveness rates equal to 100% and 0% respectively. A cohort of mothers who quit smoking, after discounting, were predicted to have 0.232 additional lifetime QALYs, and decreased healthcare costs of £493 *per mother* when compared with a cohort who continued to smoke. In addition, quitting smoking would result in 0.931 additional discounted QALYs, and a reduction of £826 in discounted healthcare costs *per child*. If applying a cost-effectiveness threshold of £20,000 per QALY, the summed net monetary benefit across mother and child was equal to £24,580, Table 19. The NMB represents the mean maximum value of financial incentive per person before the intervention becomes not cost-effective vs. no incentives. The analysis assumes that incentives would only be given to mothers who successfully quit and would only be provided following a confirmed quit (i.e. no stepped incentives). The analysis did not factor in any additional costs associated with intervention delivery e.g. administration and marketing fees.

Table 19: Maximum value of financial incentives

	Absolute Costs		Absolute QALYs		Incremental Analysis [a] [quitters vs. smokers]		
	Quitters	**Smokers**	**Quitters**	**Smokers**	**Costs**	**QALYs**	**NMB**
Mother + Child	£19,739	£21,058	47.903	46.740	-£1,319	1.163	£24,580
Mother	£9,607	£10,100	23.410	23.178	-£493	0.232	£5,129
Child	£10,132	£10,958	24.493	23.562	-£826	0.931	£19,446

a: The incremental analysis between quitters and smokers is used to estimate the maximum value of financial incentives if incentives were paid only to mother's with confirmed smoking abstinence. The maximum value of incentives per mother is equal to the net monetary benefit (NMB).

Exploratory analysis: Cost-effectiveness of opt-out versus opt in provision

The final exploratory analysis assessed the cost-effectiveness of CO monitoring + opt-out provision vs. no CO monitoring + opt-in provision for the population of mothers who were identified as smokers. This contrasted to the base case analysis which assessed the cost-effectiveness in the study population which included both smokers and non-smokers.

The exploratory analysis, in a population of smokers, found CO monitoring plus opt-out provision to be cost-effective when compared with no CO monitoring + opt-in provision. The intervention was dominant when including both mother and child outcomes: CO monitoring + opt-out provision was associated with decreased costs equal to -£47 and increased QALYs of 0.072 per mother who smokes. Cost-effectiveness results were also consistent for the mother only perspective, where the ICER for the intervention was equal to £288, substantially below the £20,000 cost-effectiveness threshold. Results were also consistent for the scenario which applied a 20% relapse to smoking between the outcome measure at week 20 and delivery at week 40 post conception. All cost-effectiveness results for exploratory scenario analysis are displayed in Table 20.

Table 20: Cost-effectiveness results in a population of maternal smokers: CO monitoring + opt-out provision vs. no CO monitoring + opt-in provision.

	Absolute Costs		Absolute QALYs		Incremental		
	CO + Opt-out	No CO +Opt-in	CO + Opt-out	No CO +Opt-in	Costs	QALYs	ICER
Scenario 1: No relapse between weeks 20 and 40							
Mother and child	£20,836	£20,883	47.00	46.92	-£47	0.072	Dominant
Mother only	£10,060	£10,056	23.23	23.21	£4	0.014	£288
Scenario 2: 20% relapse between weeks 20 and 40							
Mother and child	£20,894	£20,925	46.95	46.89	-£31	0.058	Dominant
Mother only	£10,071	£10,082	23.22	23.21	£10	0.012	£887

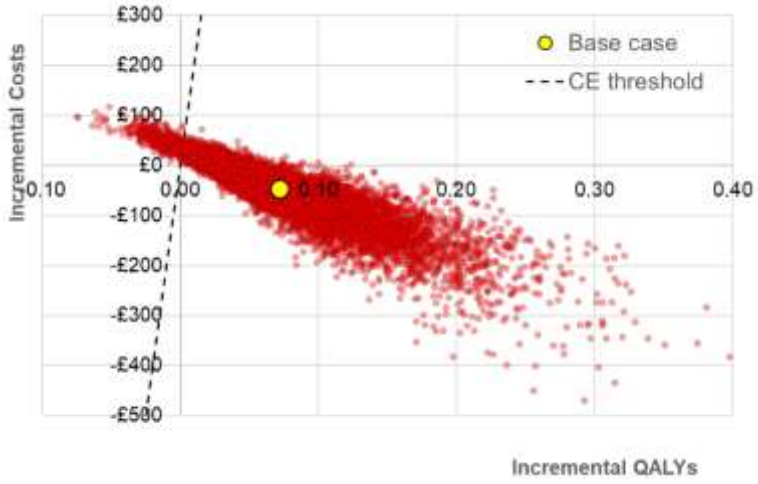
The DSA results for the CO monitoring + opt-out scenario analysis in a population of current smokers is reported in Table 21. There was considerable variability in the results when varying the RR parameters. However, CO monitoring + opt-in provision remained cost-effective even from the lower effectiveness estimate: The ICER was equal to £17,433 and was dominant when applying the lower 95% CI RR and upper 95% CI RR respectively. Similarly, cost-effectiveness results remained robust when: increasing and decreasing intervention costs by 25%; increasing and decreasing the mean age of mothers; increasing the utility and disutility values; increasing and decreasing the cost of the comorbidities. CO monitoring + opt-out provision was not cost-effective when limiting the model time horizon to pregnancy only, resulting in an ICER of £21,326 per QALY, slightly above the £20,000 per QALY threshold.

Table 21: Results of deterministic sensitivity analysis: Opt-out provision.

DSA Scenario	DSA Parameter Value	Absolute		Incremental (vs. opt-in)		
		Costs	QALYs	Costs	QALYs	ICER
Base Case	N/a	£20,836	47.00	-£47	0.072	Dominant
Effectiveness	Low 95% CI RR (1.01)	£20,915	46.93	£32	0.002	£17,443
	Up 95% CI RR (1.92)	£20,721	47.10	-£162	0.173	Dominant
Intervention costs	Increase by 25%	£20,853	47.00	-£30	0.072	Dominant
	Decreased by 25%	£20,819	47.00	-£64	0.072	Dominant
Time horizon	Limit to pregnancy	£3,188	0.69	£37	0.002	£21,326
Mother's age	Mean age 21	£19,578	48.16	-£37	0.070	Dominant
	Mean age 38	£23,909	44.46	-£75	0.078	Dominant
Utility	Same QoL for smokers and non-smokers	£20,836	47.99	-£47	0.065	Dominant
Disease costs	Decrease by 25%	£15,644	47.00	-£26	0.072	Dominant
	Increase by 25%	£26,028	47.00	-£67	0.072	Dominant
Disease disutility	Decrease by 25%	£20,836	50.33	-£47	0.075	Dominant
	Increase by 25%	£20,836	43.66	-£47	0.068	Dominant

The NICE team also requested that PSA analysis was conducted for the exploratory scenario. In a population of smokers, CO monitoring + opt-out provision was cost-effective across 95.2% of the 10,000 PSA iterations vs. no CO monitoring + opt-in provision, Figure 6. The PSA results were driven by high confidence around the effectiveness parameter, where the lower 95% CI RR for the intervention was greater than 1 (equal to 1.01). Therefore, across almost all PSA iterations, the intervention was effective and incremental QALYs always positive vs. no CO monitoring + opt-in provision.

Figure 6: PSA Results CO monitoring + opt-out provision (exploratory scenario)


£300
£200
£100
£0
-£100
-£200
-£300
-£400
-£500
Incremental Costs
0.10
0.00
0.10
0.20
0.30
0.40
Incremental QALYs
Base case
CE threshold

Discussion

Key findings

This economic evaluation demonstrated that NRT l/s plus behavioral support is likely to be cost-effective for promoting smoking cessation in pregnant women vs placebo plus behavioral support. In addition, the analysis suggested that e-cigarettes would be cost-effective versus placebo if e-cigarettes were prescribed by the NHS and achieved the assumed effectiveness rate[d]. Further, financial incentives were highly likely to be cost-effective versus no incentives when provided in addition to usual care which included behavioral support and pharmacotherapy. Finally, a referral pathway including CO monitoring plus opt-out provision to LSS during the antenatal dating appointment was found to be highly cost-effective vs. an intervention where women self-reported their smoking status and were referred to LSSS via an opt-in provision pathway.

The results of the ESIP model were driven by intervention effectiveness which determined the number of smokers and non-smokers in the model and the lifetime impact of smoking. Mothers who continue to smoke during (and after) pregnancy are at an increased risk of serious disease later in life, including lung cancer, stroke and myocardial infarction. In addition, tobacco smoking is a known teratogen and increases the likelihood of fetal death, fetal malformation and subsequent developmental disorders in surviving infants.

The healthcare costs and health impact of tobacco smoking were equal to roughly £1,300 and 1.16 QALYs per mother and child, which substantially exceed the upfront costs associated with typical stop smoking services and interventions. Consequently, stop smoking interventions can be cost-effective, even when achieving only a modest number of additional quitters, as demonstrated in this analysis for the NRT l/s and CO monitoring + opt-out provision interventions which were cost-effective when achieving 16 and 20 additional quitters per 1000 respectively.

Due to increased effectiveness and a much larger number of additional quitters achieved (177 per 1000), stepped financial incentives in the form of shopping vouchers, were highly cost-effective to the NHS, generating substantial population health benefits, at a relatively small financial cost. The intervention cost per mother was a maximum of £400 in shopping vouchers assuming women achieved abstinence at all follow up points. The PHAC were interested in investigating the maximum cost-effective value of a (onetime) incentive per successful quit, which was estimated as the net monetary per mother and child if a mother quit smoking vs. if a mother continued to smoke. The NMB was equal to roughly £25,000 indicating that very large incentives are, in theory, cost-effective vs. no incentives and usual care.

The maximum value per incentive identified in this analysis should not, however, be interpreted as the cost-effective value of a financial incentive: Firstly, if the value of financial incentives were set to equal to the NMB (i.e. £25,000) per successful quitter, the associated net health benefit would be equal to zero as the benefit from one mother stopping smoking would be equivalent to the value paid per incentive. Secondly, the value per incentive would need to account for any administrative costs, and any incentives paid prior to the final clinical endpoint in women who quit and then relapsed during each study's time horizon. Thirdly, there is likely to be diminishing returns on the value per incentive: For example, it is questionable whether pregnant women who will not quit smoking when offered a £5000 incentive would be more likely to quit if offered, say £6000. If there are no differences in

[d] Assumed effectiveness rates were calculated by applying effectiveness rates for e-cigarettes in the general population and adjusting these rates for pregnant women. The adjusted rates were calculated by obtaining the ratio of effectiveness for NRT l/s in the general population: NRT l/s in pregnant women. The same ratio was assumed for the effectiveness of e-cigarettes in the general population: e-cigarettes in pregnant women.

effectiveness then lower value incentives would be cost-effective vs. any higher value incentive as they would achieve the same health benefit at a lower intervention cost. The analysis does, however, provide justification for increasing the maximum value of incentives beyond £400 if this were to achieve an additional number of quitters. There is likely to be an optimum maximum value per incentive between £0 and £25,000. Further research is required to establish effectiveness and cost-effectiveness across a range of incentive values.

Uncertainty

The analysis suggests that NRT l/s was very likely to be cost-effective, as the results were subject to only a small degree of uncertainty. The PSA results indicated that NRT l/s was cost-effective in 83.1% of iterations, but not cost-effective in 16.9% of iterations. The results of the DSA suggest that uncertainty was driven by the effectiveness of the smoking cessation interventions. For example, when parameter values were set to the lower 95% confidence interval NRT l/s was dominated by placebo, whereas the upper 95% confidence interval resulted in NRT l/s being cost-effective with a very favorable ICER below £1500.

In contrast, there was almost no uncertainty regarding the analysis of financial incentives. Results from the PSA identified financial incentives as cost-effective vs. no incentives in 99.7% of the 10,000 PSA iterations. The increased certainty of financial incentives was due to increased significance in the effect sizes identified in NICE evidence review I (13): The 95% lower confidence interval for the RR of smoking cessation was equal to 2.22, which is substantially greater than the value for no effect (RR=1) and this resulting in a substantial number of additional quitters vs. no incentives. Furthermore, the results of the DSA were robust, with financial incentives remaining dominant (more effective and less costly) vs. no incentives in the majority of cases. The threshold analysis indicated that financial incentives would need to result in as few as 7 additional quitters per 1,000 to be considered cost-effective versus no incentives, which is substantially less than the base case where financial incentives resulted in 177 additional quitters at 12-months. These results indicate that financial incentives are highly likely to be cost-effective even when applying pessimistic effectiveness estimates.

In general, the results of the uncertainty analysis illustrate the effectiveness parameters as being key drivers of cost-effectiveness in the ESIP model: There is little uncertainty that substantial costs and health detriments will occur for mothers and children through continued tobacco use, therefore, whenever interventions are more effective than the comparator (including in all PSA iterations) they were also cost-effective.

The results of the exploratory modelling for e-cigarettes were robust when varying intervention cost and effectiveness across a wide range of parameter values in the DSA. It is plausible that e-cigarettes are effective in promoting cessation in pregnant women given findings from NICE evidence review K (30) which identified higher quit rates associated with e-cigarettes than for NRT in the general population. If similar effectiveness rates are identified in pregnant women, then e-cigarettes are likely to be cost-effective given the findings that NRT l/s was likely to be cost-effective. Whilst there are limitations in the availability of clinical evidence in relevant populations, the analysis indicates that e-cigarettes may be cost-effective for smoking cessation in pregnant women, and may provide a benefit to population health if offered as a free prescription by LSSS.

The results of the CO monitoring + opt-out provision analysis was robust across all DSA, including when reducing effectiveness estimates to 0.4 additional quitters per 1000 mothers. The consistency of cost-effectiveness results is perhaps unsurprising given the known cost-effectiveness of smoking cessation interventions, and the additional benefits that can be achieved in children when promoting cessation in pregnant women. Results are, however, dependent on CO monitoring + opt-out provision providing a positive effect (i.e. increasing

quit rates) vs. opt in provision. The reliability of the effectiveness estimates informing this analysis could be questioned as these were obtained from a single uncontrolled before and after study by Campbell et al. (2017) (12, 18).

There was also considerable uncertainty around the value of intervention costs for the CO monitoring + opt-out provision analysis as key information on resource usage and unit costs were not available from Campbell et al. (2017) (18). Therefore, a conservative estimate was made where all women who set a quit date were assumed to incur costs for a full course of NRT *and* behavioral support. Nevertheless, the intervention was cost-effective even when applying a 25% increase in costs on top of the conservative estimate, and remained cost-effective when increasing mean intervention costs up to £500 per person. The total cost of CO monitoring + opt-out provision is considered very unlikely to exceed £500 per pregnant woman given (i) the relatively insubstantial costs associated with CO testing and electronic referrals and (ii) the minimal impact on staff time if CO testing is incorporated into the regular antenatal dating appointment.

Furthermore, the final exploratory scenario analysis indicated that CO monitoring + op-out provision was cost-effective versus no CO monitoring + opt-in provision using effectiveness estimates per identified smokers. The NICE team requested this analysis to aid comparison with other smoking cessation interventions such as NRT l/s and financial incentives which were provided to a population of expectant mothers who currently smoke. The results from the exploratory analysis indicated that CO monitoring + opt-out provision was highly likely to be cost-effective, with the PSA results equal to 95.2%.

Given the relatively modest cost associated with CO monitoring and a digital referral, the base case and exploratory scenario analysis indicate that the opt-out provision pathway is almost certainly cost-effective versus opt-in referrals without CO monitoring if it is effective in promoting smoking abstinence during pregnancy.

Inclusion of Child Outcomes

The inclusion of children's outcomes within the analytical perspective had an impact on cost-effectiveness results for NRT l/s, as the intervention was not cost-effective when including maternal outcomes only. In contrast, financial incentives, e-cigarettes and CO monitoring + opt-out provision were consistently cost-effective across both perspectives. The decision to include both maternal and child outcomes in the primary perspective is consistent with recommendations in the NICE methods manual which states that economic evaluations should include all "direct health effects whether for people using the services, or when relevant other people" (20). It follows that the inclusion of maternal and child outcomes is the appropriate perspective for this analysis given that tobacco smoking is a known teratogen and interventions to reduce smoking act directly to lessen these effects.

The results of the economic evaluation suggest that child outcomes are a stronger determinant of cost-effectiveness than maternal outcomes. For example, in the NRT l/s analysis, the incremental difference in QALYs quadrupled when moving from a maternal only to a maternal plus child. Children's outcomes were predominantly driven by the negative impact of tobacco smoking on fetal survival. The ESIP model treats each fetal loss as a "death", where healthcare costs and QALYs per fetal loss are equivalent to the mean lifetime outcomes for surviving infants. After discounting, surviving children incurred a mean of £8,770 in healthcare costs and 26.38 QALYs in the ESIP model. The decision to include outcomes related to fetal loss was guided by discussions with the PHAC and is in line with other NICE guidelines. For instance NICE has included discounted lifetime QALYs lost for stillbirth in NG137 guidelines for twin and triplet care in pregnancy (22).

Safety

The safety analysis indicated that NRT l/s was not likely to be cost-effective if the intervention increased the chance of fetal loss vs. placebo, due to the substantial loss in lifetime QALYs associated with each unsuccessful birth. In contrast, increases in caesarean section were less impactful, with NRT l/s remaining cost-effective even when resulting in an absolute increase in c-section of 10%. The underlying absolute probability of c-section in the UK is equal to 26% (32), therefore the associated relative risk required to achieve an *absolute* increase of 10% in this outcome would be equal to 1.38. Based on the findings from this analysis, NRT l/s is cost-effective, when incorporating safety impacts from c-section as the RR of 1.38 exceeds the RR observed for NRT l/s vs. placebo in NICE evidence review J (RR=1.24) (14).

The true safety impact of NRT l/s on fetal loss and c-section is unclear. The increased relative risk of fetal loss and c-section for NRT vs. placebo were not statistically significant (14), and therefore may have been due to chance. The results from the economic modelling support the need for future research investigating the safety impact of NRT l/s particularly on fetal loss which is a key determinant of cost-effectiveness.

Comparison with Other Models

Results from the ESIP model were comparable to results from previously published NICE guidelines on tobacco cessation and harm reduction (33-35) and associated updates (36, 37), in the sense that effective interventions were generally found to be cost-effective. However, if applying the same intervention effectiveness rates in the ESIP model and in a model of smoking cessation in the general population, interventions had more favorable cost-effectiveness outcomes (i.e. reduced ICER) for the general population model. The results suggest that the ESIP model places a lower value on the long-term benefits of smoking cessation which is not intuitive given the inclusion of both maternal and child outcomes.

There are several reasons why the ESIP model may place a lower than expected value on smoking cessation. Firstly, the ESIP model includes only pregnant women meaning the starting age of the cohort is relatively young (equal to 27), whereas the general population model includes people of all ages between 12 to 80. The majority of smoking related diseases, for example lung cancer, stroke and coronary heart disease typically occur later in life. Consequently, many additional years of discounting are applied to the benefits of smoking cessation in younger cohorts, reducing the present-day value of QALYs and healthcare costs associated with treating smoking related comorbidities.

Secondly, the rate of postpartum relapse is much higher than annual relapse rates for the general population. Relapse rates applied in the year after delivery in the ESIP model were equal to 47%. Consequently, around half of women who quit smoking during pregnancy fail to achieve the lifetime health benefits that are associated with sustained abstinence.

Finally, the ESIP model may underestimate the benefits of smoking cessation as it does not include myocardial infarction as a smoking related comorbidity: The comorbidities included in the general population model include asthma, CHD, COPD, lung cancer, MI, and stroke whereas the ESIP model includes asthma, CHD, COPD, lung cancer, MI, and stroke.

Limitations

As with any economic evaluation, there are a number of limitations inherent in this analysis. The ESIP model measures intervention effectiveness as smoking abstinence at delivery. Therefore, it does not account for when smoking cessation occurred. The time at which mothers quit smoking may be important, as: (i) different levels of smoking harm may be

associated with different periods of fetal development; and (ii) the effects of tobacco smoking on fetal health are likely to be cumulative (38). The NICE effectiveness reviews which informed the analysis measured cessation at 20-weeks post-partum.

The ESIP model considered two scenarios regarding smoking relapse between weeks 20 and delivery. The first scenario applied an assumption of no relapse whilst the second applied relapse rates consistent with those identified for the general population. Cost-effectiveness results may have been overestimated in this analysis *if* relapse rates during pregnancy exceed relapse rates of 20% i.e. those observed in the general population.

The results of the exploratory analysis for CO monitoring + opt-out provision should be interpreted with caution due to the considerable selection issues brought about by the nature of the intervention. CO monitoring directly increases the identification of smokers. The relative risk for the exploratory analysis was calculated as the ratio of expectant mothers who quit smoking divided by the total number of smokers identified. Ideally, we would have known of the number of smokers in both arms. However, smokers were identified by Campbell et al. (2017) (18): via a combination of self-report and CO monitoring for the opt-out referral pathway; and exclusively via self-report for the opt-in pathway. This meant there were considerably less women identified as smokers in the opt-in provision pathway, with likely many additional unconfirmed smokers in the population. The difference in the population introduces both a risk of selection bias, and problems with the arithmetic as the RR base (number of smokers) is artificially deflated for the no CO monitoring + opt-in pathway.

High rates of smoking relapse during pregnancy may have resulted in further overestimation of cost-effectiveness if the benefits of smoking cessation on fetal health occur predominantly after the first trimester. There is, however, evidence of generally decreasing smoking prevalence rates across pregnancy: In a cross-sectional study of around 4,000,000 live births in the USA, Kondracki et al. (2019) (39) identified higher smoking prevalence in the first trimester (7.2%), than in the second (6.1%) and third (5.7%) trimesters. This may indicate that relapse rates are likely to be relatively insubstantial up to delivery in pregnant women who have successfully quit smoking.

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

- Reduction in other smoking-related adulthood diseases (apart from the four long-term comorbidities and asthma exacerbations) for example myocardial infarction.
- Reduction in smoking-related childhood diseases. Members of the PHAC indicated that smoking is likely to impact on outcomes such a glue-ear which have implications on health and healthcare resource use.
- Reduction in developmental abnormalities. Smoking during pregnancy may be related to cognitive, physical, social and emotional development deficiencies. Developmental deficiencies are associated with health and economic outcomes, including earnings, later in life (40).
- Impact on other people’s smoking behavior. Children’s second-hand smoking status and likelihood of smoking during adulthood was dependent on maternal smoking only. The smoking status of other family members e.g. fathers is also likely to determine children’s outcomes and may be reduced by maternal smoking behavior.
- Level of tobacco consumption.
- Improved recovery from other healthcare interventions such as surgery.

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

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