National Institute for Health and Care Excellence

Final

Tobacco: preventing uptake, promoting quitting and treating dependence: update

[K] Evidence review for cessation and harm-reduction treatments

NICE guideline NG209

Evidence reviews underpinning recommendations 1.12.1 to 1.12.6, 1.12.13 to 1.12.17, 1.14.19, 1.22.1 to 1.22.2, 1.22.14, and research recommendations in the NICE guideline

November 2021

Final

These evidence reviews were developed by PH-IGD

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Cessation and harm reduction treatments

Review questions

This evidence report covers one review question with subsections.

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

i. Are e-cigarettes effective for cessation at 1-<6 months compared with e-cigarettes without nicotine (hereafter 'placebo e-cigarettes'), usual care or NRT?

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

[a] E-cigarettes refer throughout to any type of e-cigarette which contains nicotine unless stated otherwise.

Smoking cessation treatments

Review question

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

i. Are e-cigarettes effective for cessation at 1-<6 months compared with e-cigarettes without nicotine ('placebo e-cigarettes'), usual care or NRT?

Introduction

Electronic cigarettes (e-cigarettes) are a relatively new technology. Commonly used pharmacotherapies for cessation include NRT, varenicline and bupropion. The relative effectiveness of these treatments compared with e-cigarettes is unclear and may affect patient choice.

The main aim of this review is to establish which interventions are the most effective and cost effective for cessation at 6 months. The review will also separately consider the effectiveness of e-cigarettes for shorter term cessation (1-<6 months; question 1a.i.) to compare with the longer term results.

A Network Meta-Analysis (NMA) conducted by Thomas 2020[c] has been used for part of this review in order to provide information on relative effectiveness of smoking cessation treatments. This will allow judgements to be made about which treatments are likely to be most effective. The version of Thomas (2020) that was considered by the NICE guideline committee was based on a draft version of the manuscript dated July 2019. That version is yet to undergo a full peer and editorial review process in line with the NIHR Journals Library Policy.

Behavioural interventions are not the focus of this review question, which considers pharmacological treatments, NRT and e-cigarettes. Behavioural intervention-only arms were classed as "no drug treatment", along with arms where no intervention was given. Therefore the "no drug treatment" class represents a variety of different situations. There are also no "drug + behavioural intervention" nodes in the NMA, as the additive effect of behavioural interventions are not under investigation.

For most included studies, behavioural interventions are equal across arms with the only difference being the drug intervention. However, some studies investigated behavioural plus drug intervention vs no intervention. In these cases, the effect of the drug + behavioural intervention is attributed solely to the drug in the NMA

PICO table

The following table summarises the protocol for this review.

[b] E-cigarettes refer throughout to any type of e-cigarette which contains nicotine.

[c] Kyla H Thomas, Michael N. Dalili, Jose A. Lopez-Lopez, Edna Keeney, David Philippo, Marcus R Munafo et al. (2020) How do smoking cessation medicines compare with respect to their neuropsychiatric safety: a systematic review, network meta-analysis and cost effectiveness analysis. Health Technology Assessment 2020; in review.

Table 1: PICO inclusion criteria

Criteria	Detail
Population	Anyone aged 18 and over who smokes and wants to stop smoking. **Excluded**: People who do not smoke Pregnant and breastfeeding women People aged 17 and under People who want to stop using smokeless tobacco but not smoking.
Interventions	**Relative effectiveness:** Elements to be included in the NMA: • Varenicline • Bupropion • NRT single mode (use of either long-acting or short-acting NRT only) • NRT multi-mode (use of both a long-acting and short-acting NRT) • E-cigarettes (containing nicotine) • No intervention or usual care • E-cigarettes without nicotine ("placebo e-cigarettes"). These may be used as monotherapy or in combination with each other or with behavioural support. **Short follow-up**: E-cigarettes
Comparator	**Relative effectiveness:** Other interventions in the NMA **Short follow-up**: Placebo e-cigarettes, usual care, NRT. **Excluded**: Therapies not licensed in the UK. Alternative and complementary therapies. Psychotherapies (unless included as co-treatment with an included smoking cessation therapy). Therapies that are either smoked or contain tobacco.
Outcomes	**Critical outcomes** Cessation: Smoking status at 6 months follow-up. Measured as abstinence from smoking (relative risk). Where continuous abstinence is presented, this is preferred over point-prevalence abstinence. Point prevalence measures will only be used where no continuous measure is reported. Only biochemically validated measures will be accepted (i.e. saliva cotinine / carbon monoxide validation). **Important outcomes** • Adverse or unintended (positive or negative) effects of e-cigarettes when used for cessation or harm reduction at any time point, including: ○ Adverse effects such as headaches, nausea, throat irritation or dry mouth.

Criteria	Detail
	Health-related quality of life of using e-cigarettes for cessation or harm reduction (using validated patient-report measures, for example EQ-5D).

NMA: Network Meta-Analysis, NRT: Nicotine Replacement Therapy

For full details see the clinical review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods chapter for this guideline.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Included studies and tobacco organisations

The following studies included in the NMA had a link to tobacco organisations:

- Rose (2013): Funded by Philip Morris. Comparing bupropion + NRT long/short vs NRT long/short; varenicline + NRT long/short vs no drug treatment; varenicline + NRT long/short vs bupropion + NRT long/short.
- Caldwell (2014): Nicotine mouth spray provided by Niconovum. Study was not funded by Niconovum. Comparing NRT long / short vs NRT long & short.

The following study included in other parts of this review had a link to tobacco organisations:

- Cravo (2016) compared the adverse events of e-cigarettes to continued smoking. This study was funded by Fontem ventures.

Protocol deviations

A deviation from protocol has been made. The protocol stated that where biochemically validated measures were available, these would be preferred to self-reported measures. Self-reported measures would only be used where no validated measure is reported. This review will now exclude self-reported measures of smoking and only use validated measures. This is because self-report may show an underestimation in smoking prevalence and also an overestimation of abstinence due to reporting bias. While self-report measures have been accepted in some other reviews in this guideline due to paucity of data, this review contains a large number of studies, and so the restriction is judged to be reasonable. In addition, the work being undertaken by Thomas (2020) includes only studies with validated outcomes.

The NMA undertaken by Thomas (2020) investigated several different cessation outcomes. The cessation outcome that the committee decided to use for this review was *all bioverified abstinence,* defined as bioverified abstinence by any definition reported at 6 months. Where studies reported more than one cessation outcome, continuous/sustained abstinence was preferred, followed by prolonged abstinence, 30-day PPA, 7-day PPA and any other abstinence. This outcome was chosen as it balanced making good use of data by including a large number of studies with rigour by preferencing types of cessation known to be more robust. As this does not necessarily use the longest available follow up reported by the study, this is also a deviation from the protocol.

Risk of bias

- This review addresses an intervention question. Only randomised studies are eligible for inclusion in this review. Question 1a.i of this review was conducted by NICE. The

evidence, which was all randomised, was assessed using the Cochrane Risk of Bias 2.0 tool, according to the NICE Manual.

- The part of this review conducted by Thomas (2020) (relative effectiveness, adverse events) used *Cochrane Risk of Bias (ROB) tool*, rather than the *Cochrane ROB 2.0 tool* recommended by NICE. As such, assessments of overall risk of bias of studies in this review were revised to align with judgments that would be derived from the use of the preferred tool as follows:
    - High risk of bias: The Cochrane ROB checklist contains a judgement for high risk of bias in at least one domain, or unclear risk for multiple domains in a way that substantially lowers confidence in the result.
    - Some concerns: The Cochrane ROB checklist contains a judgement for unclear risk in at least two domains, but not to be at high risk of bias for any domain.
    - Low risk of bias: The Cochrane ROB checklist contains no judgements of high risk of bias for any domain and is at unclear risk of bias in no more than one domain.
- All GRADE ratings start at 'high' and are downgraded as appropriate.
- Assessments for Risk of Bias in GRADE were drawn from the RoB tool assessment.

See appendix F for full GRADE tables.

See Methods document for details of rationale for GRADE judgements**.**

Classes of intervention

Interventions were grouped into classes as selected by the committee:

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

Subgroup analysis

Data was sufficient for subgroup analysis according to mental illness, as stated in the protocol.

After analysing all studies together (see the full NMA results, Appendix J), studies of people with mental illness were identified. For pairwise analysis (see forest plots in Appendix E), the full forest plots are subgrouped by mental health studies and studies of the general population. The exception to this is where the main analysis and the mental health

populations analysis required two different models (random effects and fixed effects). In this case the two are presented in separate forest plots with the relevant model applied.

Minimal Important Differences (MIDs)

The following MIDs were applied to the outcomes in this review.

Table 2: Minimal Important Differences (MIDs) agreed

Outcome	Importance	MID
Abstinence from smoking	Critical	Statistical significance
Adverse events of mortality	Important	Statistical significance
All other adverse events	Important	Default (RR 0.8-1.25)
Health-related quality of life (HRQoL) measures	Important	Published MIDs if available for individual measure, otherwise default.

Identification of public health evidence

Included studies

Section 1a of this review is made up of two separate parts:

1. relative effectiveness of treatments for cessation at 6 month follow-up
2. effectiveness of e-cigarettes for cessation at shorter follow-up of more than 1 month but less than 6 months.

Relative effectiveness at 6 month follow-up

The studies identified for inclusion in the Thomas (2020) NMA and which reported the outcome of interest (abstinence) were considered (n = 197). Studies investigating cessation from smokeless tobacco (n = 9) were removed. A total of 188 RCTs from Thomas (2020) were included. Of these, 13 were in populations with mental health conditions and so were included in the subgroup analysis. Rerun searches were carried out in November 2019. 1,137 items were identified. Twenty-six were requested for full-paper assessment. Four met the inclusion criteria for the NMA (none were in populations with mental health conditions). Additional rerun searches were carried out in July 2020. 1,382 articles were identified. Three studies were requested for full-paper assessment, none of these met the inclusion criteria for this review. A total of 192 studies were therefore included in the overall NMA for this review.

The NICE surveillance review for the Tobacco Update was checked. Four systematic reviews were consulted to check lists of included studies. Two studies were identified which matched the inclusion criteria (Bullen 2013, Caponnetto 2013) – these were already included in the Thomas (2020) NMA. A study which was ongoing at the time of the surveillance review (Hajek 2019) was not included by the Thomas (2020) study because it did not report bioverified abstinence at 6 months.

Adverse events

Nine RCTs were identified which provided data on adverse events of e-cigarettes compared to any of the interventions included in the NMA. The only comparisons used in the studies were NRT, placebo e-cigarette, and no drug treatment (definitions as per the above section on ‘classes of intervention’). Rerun searches were not conducted for this part of the review because the committee did not believe there to be substantial new evidence that would change the current results.

Relative effectiveness at short follow-up

Thomas (2020) identified 814 papers for inclusion in their wider review. Follow-up length was not a criterion for exclusion from this list, and so any studies investigating the relative effectiveness of e-cigarettes at 1-6 months follow-up would be included in this list. The full list of 814 papers was obtained and sifted at title and abstract stage. 13 papers from this search with potential to answer this review question were ordered for full-text review. Six studies met the inclusion criteria for this review.

The surveillance review for the Tobacco Update was also consulted. References were searched alongside the sift of the Thomas (2020) studies. One ongoing study – now published – identified in the surveillance review had already been identified.

Of the six studies meeting the inclusion criteria for this section of the review, two were also included in the NMA. Three were not included in the NMA due to follow-up times of less than 6 months, and one due to not measuring bioverified abstinence at 6 months. All six are RCTs, as specified in the review protocol. Only effectiveness data was used from these papers, as adverse event data from the Thomas (2020) review – which includes these studies and studies with longer follow-up – was used to assess adverse events of e-cigarettes. Rerun searches were not conducted for this part of the review because the committee did not believe there to be substantial new evidence that would change the current results.

Excluded studies

Studies excluded from the review and reasons for their exclusion are provided in appendix G for the short follow-up outcome, and for rerun searches.

Summary of public health studies included in the evidence review

Relative effectiveness at 6 months

192 studies were included for the NMA for cessation at 6 months (see references), with a total sample size of 92,067. Studies reported on ten active treatments (see Table 3) in addition to placebo, waiting list, usual care, and no drug treatment arms. Numbers of studies investigating each intervention or intervention combination are recorded below:

Table 3: Number of studies investigating each intervention or intervention combination in the NMA

Intervention	Number of studies investigating this intervention
NRT long/short acting	116 Ahluwalia 2006 Andrews 2016 Anthenelli 2016A Anthenelli 2016B Areechon 1988 Aubin 2008 Baker 2006 Baker 2016 Baldassarri 2018 Binnie 2007 Blondal 1997 Blondal 1999 Bullen 2013 Caldwell 2014

Intervention	Number of studies investigating this intervention
	Caldwell 2016 Chan 2011 Cinciripini 1996 Cooney 2007 Cooney 2009 Cooper 2005 Cooperman 2017 Covey 2007 Cummins 2016 Cunningham 2016 Daughton 1991 Daughton 1998 Daughton 1999/TNSG 1991 Dautzenberg 2001 De Dios 2012 Ehrsam 1991 Evins 2007 Fagerstrom 1982 FernandezArias 2014 Fiore 1994A Fiore 1994B George 2008 Gifford 2004 Glavas 2003B GlaxoSmithKline 2009 Glover 2002 Gourlay 1995 Gross 1995 Hall 1985 Hall 1987 Hall 2006 Hanioka 2010 Harackiewicz 1988 Hays 1999 Herrera 1995 Heydari 2012 Hjalmarson 1984 Hjalmarson 1994 Hjalmarson 1997 Horst 2005 Hughes 1999 Hughes 2003 Hurt 1990 Jamrozik 1984 Jensen 1991 Jorenby 1999 Kalman 2006 Kalman 2011 Killen 1997 Killen 1999 Kornitzer 1995

Intervention	Number of studies investigating this intervention
	Leischow 1996 Lerman 2004 Lerman 2015 Lewis 1998 Llivina 1988 Malcolm 1980 Mori 1992 Nakamura 1990 Niaura 1994 Niaura 1999 Nides 2018 Okuyemi 2007 Perng 1998 Piper 2009 Pirie 1992 Puska 1995 QuilezGarcia 1989 Ratner 2004 Reid 2008 Richmond 1993 Richmond 1994 Rohsenow 2017 Rose 2013 Sachs 1993 Schneider 1983A Schneider 1983B Schneider 1995 Schneider 1996 Schnoll 2010 Schnoll 2010A Schnoll 2010B Segnan 1991 SelmaBozkurtZincir 2013 Sharma 2018 Shiffman 2009 Shiffman 2019 Stapleton 1995 Steinberg 2009 Sutherland 1992 Swanson 2003 Tonnesen 1993 Tonnesen 1999 Tonnesen 2000 Tonnesen 2006 Tønnesen 2012 Tulloch 2016 Uyar 2007 Vial 2002 Wallstrom 2000 Westman 1993 Wong 1999

Intervention	Number of studies investigating this intervention
NRT long&short acting	12 Blondal 1999 Bonevski 2018 Caldwell 2014 Caldwell 2016 Cooney 2009 Hand 2002 Heydari 2013 Joseph 2004 Kornitzer 1995 Puska 1995 Stein 2013 Stockings 2014
Bupropion	44 Ahluwalia 2002 Anthenelli 2016A Anthenelli 2016B Aryanpur 2016 Aubin 2004 Cinciripini 2013 Collins 2004 Covey 2007 Cox 2012 Dalsgarð 2004 Eisenberg 2013 Evins 2001 Evins 2005 Ferry 1992 Fossati 2007 Gonzales 2001 Gonzales 2006 Haggsträm 2006 Hall 2002 Hall 2011 Hatsukami 2004 Hertzberg 2001 Holt 2005 Jorenby 1999 Levine 2010 McCarthy 2008 Myles 2004 Nides 2006 Piper 2007 Piper 2009 Schmitz 2007 SelmaBozkurtZincir 2013 Siddiqi 2013 Simon 2009 SMK20001 Swanson 2003 Tashkin 2001

Intervention	Number of studies investigating this intervention
	Tonnesen 2003 Tonstad 2003 Uyar 2007 Wagena 2005 Zellweger 2005 Zernig 2008 ZYB40005
Varenicline	41 Anthenelli 2013 Anthenelli 2016A Anthenelli 2016B Ashara 2019 Aubin 2008 Baker 2016 Bolliger 2011 Carson 2014 Chengappa 2014 Cinciripini 2013 Cinciripini 2018 De Dios 2012 Dogar 2018 Ebbert 2014 Ebbert 2015 Ebbert 2017 Eisenberg 2016 Gonzales 2006 Gonzales 2014 Heydari 2012 Hughes 2011 Koegelenberg 2014 Lerman 2015 Nahvi 2014 Nakamura 2007 Niaura 2008 Nides 2006 Ramon 2014 Rennard 2012 Rigotti 2010 Rohsenow 2017 SelmaBozkurtZincir 2013 Stein 2013 Steinberg 2011 Tashkin 2011 Tonstad 2006 Tsai 2007 Tulloch 2016 Wang 2009 Westergaard 2015 Williams 2012
E-cigarette	4 Bullen 2013

Intervention	Number of studies investigating this intervention
	Caponnetto 2013 Halpern 2018 Holliday 2019
Bupropion + NRT long/short acting	10 Covey 2007 George 2008 Jorenby 1999 Kalman 2011 Piper 2007 Piper 2009 Rose 2013 Schnoll 2010 Swanson 2003 Winhusen 2014
Bupropion + NRT long&short acting	2 Evins 2007 Steinberg 2009
Varenicline + NRT long/short acting	3 Koegelenberg 2014 Ramon 2014 Rose 2013
Varenicline + bupropion	2 Cinciripini 2018 Ebbert 2014
E-cigarette + NRT long/short acting	2 Baldassarri 2018 Walker 2019

Possible intervention combinations where there were no studies identified:

- E-cigarette + NRT long&short acting
- E-cigarette + bupropion
- E-cigarette + varenicline
- Varenicline + NRT long&short acting
- Any combination of three treatments

Although nine studies were identified which reported on adverse events of e-cigarettes, only four of these met the inclusion criteria for the NMA, due to having shorter follow-up than 6 months.

Risk of bias

Of the studies included in the NMA, 44 were judged to be at low risk of bias. There were some concerns about 89 studies, and 59 studies were at high risk of bias:

Low risk	Some concerns	High risk
Ahluwalia 2002	Blondal 1997	Andrews 2016
Ahluwalia 2006	Carson 2014	Areechon 1988
Anthenelli 2013	Chengappa 2014	Aryanpur 2016
Anthenelli 2016A	Cinciripini 1996	Aubin 2008
Anthenelli 2016B	Cinciripini 2013	Baker 2006
Ashara 2019	Collins 2004	Baker 2016
Aubin 2004	Cooper 2005	Baldassarri 2018

Low risk	Some concerns	High risk
Blondal 1999	Cox 2012	Binnie 2007
Bolliger 2011	Dalsgarð 2004	Bonevski 2018
Bullen 2013	Daughton 1991	Caldwell 2014
Caldwell 2016	Daughton 1998	Chan 2011
Campbell 1983	Daughton 1999/TNSG 1991	Cooney 2007
Caponnetto 2013	Dautzenberg 2001	Cooperman 2017
Cinciripini 2018	Ehrsam 1991	Covey 2007
Cooney 2009	Eisenberg 2013	Cummins 2016
Dogar 2018	Eisenberg 2016	Cunningham 2016
Ebbert 2014	Evins 2001	Ebbert 2017
Ebbert 2015	Evins 2005	FernandezArias 2014
Glover 2002	Evins 2007	Gifford 2004
Gonzales 2006	Fagerstrom 1982	Gross 1995
Hays 1999	Ferry 1992	Hall 1985
Hjalmarson 1997	Fiore 1994A	Hall 2002
Kornitzer 1995	Fiore 1994B	Hall 2006
Lerman 2004	Fossati 2007	Halpern 2018
Lewis 1998	De Dios 2012	Hand 2002
McCarthy 2008	George 2008	Harackiewicz 1988
Myles 2004	Glavas 2003B	Hatsukami 2004
Nahvi 2014	GlaxoSmithKline 2009	Hertzberg 2001
Piper 2007	Gonzales 2001	Heydari 2012
Ramon 2014	Gonzales 2014	Heydari 2013
Rennard 2012	Gourlay 1995	Holliday 2019
Rigotti 2010	Haggsträm 2006	Holt 2005
Schneider 1996	Hall 1987	Horst 2005
Schnoll 2010A	Hall 2011	Hughes 1999
Segnan 1991	Hanioka 2010	Jensen 1991
Shiffman 2019	Herrera 1995	Joseph 2004
Simon 2009	Hjalmarson 1984	Leischow 1996
Stapleton 1995	Hjalmarson 1994	Levine 2010
Steinberg 2011	Hughes 2003	Llivina 1988
Tonnesen 1993	Hughes 2011	Nakamura 1990
Tonnesen 1999	Hurt 1990	Nakamura 2007
Tønnesen 2012	Jamrozik 1984	Okuyemi 2007
Tonstad 2006	Jorenby 1999	Ratner 2004
Walker 2019	Kalman 2006	Reid 2008
	Kalman 2011	Richmond 1993
	Killen 1990	Schnoll 2010B
	Killen 1997	SelmaBozkurtZincir 2013
	Killen 1999	Sharma 2018
	Koegelenberg 2014	Siddiqi 2013
	Lerman 2015	Steinberg 2009
	Malcolm 1980	Stockings 2014
	Mori 1992	Swanson 2003
	Niaura 1994	Tulloch 2016
	Niaura 1999	Uyar 2007
	Niaura 2008	Vial 2002
	Nides 2006	Winhusen 2014
	Nides 2018	Wong 1999
	Perng 1998	Zernig 2008

Low risk	Some concerns	High risk
	Piper 2009 Pirie 1992 Puska 1995 QuilezGarcia 1989 Richmond 1994 Rohsenow 2017 Rose 2013 Sachs 1993 Schmitz 2007 Schneider 1983A Schneider 1983B Schneider 1995 Schnoll 2010 Shiffman 2009 SMK20001 Stein 2013 Sutherland 1992 Tashkin 2001 Tashkin 2011 Tonnesen 2000 Tonnesen 2003 Tonnesen 2006 Tonstad 2003 Tsai 2007 Wagena 2005 Wallstrom 2000 Wang 2009 Westergaard 2015 Westman 1993 Williams 2012 Zellweger 2005	ZYB40005

Table 4: Risk of bias in studies included in the NMA, by sources of bias

Source of bias	High risk	Some concerns	Low risk
Selection bias (random sequence generation)	1	89	102
Selection bias (allocation concealment)	4	102	85
Performance bias (participant and treatment administrator blinding)	43	73	76
Detection bias (blinding of outcome assessors)	18	84	90
Attrition bias (incomplete outcome data)	17	57	118
Reporting bias (selective reporting)	2	37	153
Other biases (adherence issues, lack of validation)	3	10	179

Of the studies included, 44 were judged to be at low risk of bias. There were some concerns about 89 studies, mainly due to unclear reporting on several the risk of bias domains. Fifty-nine studies were at high risk of bias for the outcome of cessation, due to being at high risk of bias in one or more of the domains (random sequence generation, allocation concealment, blinding of participants / personnel, blinding of outcome assessor, incomplete outcome data, selective reporting).

Adverse events

The Thomas (2020) group also conducted an NMA for serious adverse events, which included observational data. This is not included in the protocol for this review.

The randomised controlled trials included in this review investigated adverse events of e-cigarettes compared with any other included intervention at any time point. See table 4 for more detail. The studies reported results are reported as number of participants, not number of events.

Table 5: Summary of adverse event data

Adverse event	Studies reporting	E-cigarettes are compared with:
Abnormal Dreams	n = 3 Baldassarri 2018 Cravo 2016 Tseng 2016	• No drug treatment • NRT • Placebo e-cigarette
Anxiety	n = 2 Baldassarri 2018 Cravo 2016	• No drug treatment • NRT
Arrhythmia	n = 1 Cravo 2016	• No drug treatment
Cardiovascular Death	n = 3 Bullen 2013 Hajek 2019 *Tseng 2016*	• NRT • Placebo e-cigarette
Chronic Obstructive Pulmonary Disease (COPD)	n = 1 *Bullen 2013*	• NRT • Placebo e-cigarette
Death (All Causes)	n = 4 Bullen 2013 Cravo 2016 Hajek 2019 *Tseng 2016*	• No drug treatment • NRT • Placebo e-cigarette
Depression	n = 1 Hajek 2019	• NRT
Discontinued Treatment due to Adverse Events (AEs)	n = 2 *Carpenter 2017* *Tseng 2016*	• No drug treatment • Placebo e-cigarette
Dry Mouth	n = 1 Cravo 2016	• No drug treatment
Fatal Stroke	n = 1 *Tseng 2016*	• Placebo e-cigarette
Fatigue	n = 3 Baldassarri 2018	• No drug treatment • NRT

Adverse event	Studies reporting	E-cigarettes are compared with:
	Cravo 2016 Tseng 2016	• Placebo e-cigarette
Headache	n = 7 Baldassarri 2018 Carpenter 2017 Cravo 2016 Hajek 2019 Lee 2018 Masiero 2018 Tseng 2016	• No drug treatment • NRT • Placebo e-cigarette
Hospitalisation	n = 2 Bullen 2013 Hajek 2019	• NRT • Placebo e-cigarette
Insomnia	n = 4 Baldassarri 2018 Cravo 2016 Masiero 2018 Tseng 2016	• No drug treatment • NRT • Placebo e-cigarette
Irritability	n = 1 Cravo 2016	• No drug treatment
Nausea	n = 7 Baldassarri 2018 Carpenter 2017 Cravo 2016 Hajek 2019 Lee 2018 Masiero 2018 Tseng 2016	• No drug treatment • NRT • Placebo e-cigarette
Non-fatal Myocardial Infarction (MI)	n = 2 Bullen 2013 Hajek 2019	• NRT • Placebo e-cigarette
Non-fatal Stroke	n = 1 Bullen 2013	• NRT • Placebo e-cigarette
Palpitations	n = 4 Baldassarri 2018 Bullen 2013 Lee 2018 Tseng 2016	• NRT • Placebo e-cigarette
Pruritus	n = 1 Baldassarri 2018	• NRT
Serious Adverse Events	n = 6 Bullen 2013 *Caponnetto 2013* Cravo 2016 Hajek 2019 *Lee 2018* *Tseng 2016*	• No drug treatment • NRT • Placebo e-cigarette
Skin Rash	n = 2 Cravo 2016	• No drug treatment • NRT

Adverse event	Studies reporting	E-cigarettes are compared with:
	Lee 2018	
Sleep Disorders	n = 2 Cravo 2016 Hajek 2019	• No drug treatment • NRT
Suicidal Ideation	n = 1 Hajek 2019	• NRT
Transient Ischemic Attack	n = 2 Bullen 2013 Hajek 2019	• NRT • Placebo e-cigarette
Unstable Angina	n = 1 *Bullen 2013*	• NRT • Placebo e-cigarette
Withdrew from study due to Adverse Event (AE)	n = 3 *Carpenter 2017* Cravo 2016 *Tseng*	• No drug treatment • Placebo e-cigarette

Italics denotes 0 events in both arms, therefore not included in analysis

Mental health subgroup – relative effectiveness

In addition to the main analysis of the effectiveness of the treatments in the general population, a subgroup analysis was conducted for studies in populations with mental health conditions.

Thirteen studies in populations with mental health conditions were identified (see Table 5). These formed a connected network.

Possible interventions where there were no studies identified;

- E-cigarettes
- Waitlist

Of the interventions included, possible combinations where there were no studies identified:

- NRT long/short acting + varenicline
- Bupropion + varenicline
- NRT long & short acting with any other active treatment
- Any combinations of three treatments

Table 6: Details of mental health studies in subgroup analysis

Study	Participants studied	Comparisons	Risk of bias
Anthenelli 2013	Smokers with current or past depression (major depressive disorder)	• Varenicline • Placebo	Low risk
Anthenelli 2016B	Smokers with psychiatric disorders	• Varenicline • Bupropion • NRT long / short acting • Placebo	Low risk
Baker 2006	Smokers with a non-acute psychotic disorder	• NRT long / short acting • Usual care	High risk
Chengappa 2014	Smokers with bipolar disorder	• Varenicline • Placebo	Some concerns

Study	Participants studied	Comparisons	Risk of bias
Evins 2001	Smokers with schizophrenia	• Bupropion • Placebo	Some concerns
Evins 2005	Smokers with schizophrenia or schizoaffective disorder depressed type	• Bupropion • Placebo	Some concerns
Evins 2007	Smokers with schizophrenia	• NRT long/short acting • Bupropion + NRT long & short acting	Some concerns
George 2008	Smokers with schizophrenia or schizoaffective disorder	• NRT long/short acting • Bupropion + NRT long / short acting	Some concerns
Hall 2006	Smokers with unipolar depression	• NRT long / short acting • No drug treatment (brief contact control)	High risk
Hertzberg 2001	Male veteran smokers with PTSD	• Placebo • Bupropion	High risk
Horst 2005	Smokers with a diagnosis of schizophrenia or schizoaffective disorder who successfully quit tobacco use after 90 days (open label phase)	• NRT long / short acting • Placebo	High risk
Stockings 2014	Inpatient psychiatric patient smokers	• NRT long & short acting • Usual care	High risk
Williams 2012	Smokers with schizophrenia/schizoaffective disorder	• Varenicline • Placebo	Some concerns

Sensitivity analysis by risk of bias was not undertaken. This is because Thomas (2020) concluded that removing high risk of bias studies from the NMA did not change the results.

Relative effectiveness at short follow-up

Six studies were identified which reported the effectiveness of e-cigarettes for cessation vs. comparators defined in the protocol (placebo e-cigarette, usual care, or NRT) at more than one but less than 6 months. A brief summary of these studies is in Table 6.

Table 7: Summary of e-cigarette studies for short follow-up

Study	Population	Intervention	Comparator	Outcome(s)
Baldassarri 2018 RCT USA, outpatient smoking clinic	Smokers 18+ years old, 1+ CPD 40 participants	E-cigarette (second generation) (24mg/ml, 2.4% nicotine), plus NRT patch plus counselling. People smoking 10+CPD received higher dose NRT patch than those smoking ≥10.	Non-nicotine e-cigarette (second generation) plus NRT plus counselling. 8 week duration.	Validated smoking abstinence (point prevalence) (eCO ≤6ppm) at 8 weeks.

Study	Population	Intervention	Comparator	Outcome(s)
		8 week duration.		
Bullen 2013 RCT New Zealand, community setting	Smokers 18+, 10+CPD for past year 657 participants	E-cigarette (first generation) (16mg/ml, 1.6% nicotine) plus Quitline referral. 1 week pre-quit date, 12 weeks post-quit date.	1. Non-nicotine e-cigarette (second generation) plus Quitline referral 2. NRT patch (21mg/24hr) plus Quitline referral 1 week pre-quit date, 12 weeks post-quit date.	Validated smoking abstinence (continuous) (eCO ≤10ppm) at 1 month and 3 months.
Hajek 2019 RCT UK, stop smoking services	Adult smokers 886 participants	E-cigarette (second generation) (18mg/ml, 1.8% nicotine) plus behavioural support. 4 weeks behavioural support, e-cig until e-liquid finished.	NRT of choice plus behavioural support. 4 weeks behavioural support, up to 3 months NRT.	Validated smoking abstinence (point prevalence) (eCO <8ppm) at 4 weeks.
Halpern 2018 RCT USA, workplace setting	Employed smokers 18+ 2012 participants	E-cigarette (generation unclear) (10-15mg/ml, 1.0-1.5% nicotine) plus usual workplace care plus text messaging service. 6 months e-cigarette duration.	Usual workplace care plus text messaging service. Unclear duration.	Validated smoking abstinence (continuous) (usual care: cotinine <20ng/ml; e-cig <20ng/ml and if positive, blood carboxyhaemoglobin level <4%) at 1 month and 3 months.
Lee 2018 RCT USA, preoperative clinic [not included in NMA]	Smokers of >2 CPD, presenting to preoperative clinic 30 participants	E-cigarette (first generation) decreasing dose (4.5% to 2.4% to 0%) plus brief counselling, brochure, referral to Quitline. 6 weeks duration.	NRT patch decreasing dose (21mg/day [for smokers of >10CPD] to 14mg/day to 7mg/day to 0mg/day) plus brief counselling, brochure, referral to Quitline. 6 weeks duration.	Validated smoking abstinence (point prevalence) (eCO ≤10ppm) at 8 weeks.
Masiero 2018 RCT	Adults 55+ years, ≥10 CPD for past 10 years	E-cigarette (second generation) (8mg/ml, 0.8%	Non-nicotine e-cigarette (second generation) plus	Validated smoking abstinence (continuous)

Study	Population	Intervention	Comparator	Outcome(s)
Italy, screening programme, outpatient [not included in NMA]	210 participants	nicotine) plus telephone counselling 1 week pre-quit date, 11 weeks post-quit date.	telephone counselling 1 week pre-quit date, 11 weeks post-quit date.	(eCO ≤5ppm) at 3 months.

CPD: Cigarettes per day

See appendix D for full evidence tables.

Studies were combined into meta-analysis for e-cigarettes vs placebo e-cigarette (abstinence at 1-<3 months and 3-<6 months) and for e-cigarettes vs NRT (abstinence at 1-<3 months). There were no clear differences between studies in presence of mental illness, cardiovascular disease, COPD, diabetes, heavy smoking (defined as smoking more than 20 cigarettes per day [CPD] at baseline), previous quit attempts or the generation of e-cigarette used. Therefore, subgroup analysis was not possible for this section of the review.

Sensitivity analysis removing studies at high risk of bias was not able to be conducted for e-cigarettes vs placebo e-cigarette (abstinence at 1-<3 months) despite serious inconsistency because neither study was at high risk of bias.

Economic evidence

Included studies

3576 records were assessed against the eligibility criteria for review question (RQ) 6.1a.

3409 records were excluded based on information in the title and abstract for RQ 6.1a. Both reviewers assessed all of the record. The level of agreement between the two reviewers was 100%.

The full-text papers of 166 documents were retrieved and assessed and 13 studies were assessed as meeting the eligibility criteria for RQ 6.1a. Both reviewers assessed all of the full texts. The level of agreement between the two reviewers was 100%. For RQ 6.1a, 13 studies were included.

One of the studies included (Li, 2019) was identified by a member of committee. Although the study was published after completion of the cost effectiveness searches it was agreed it should be included because it covered an intervention for which no other cost effectiveness evidence had been identified.

Excluded studies

154 full text documents were excluded for this question. The documents and the reasons for their exclusion are listed in Appendix G – Excluded studies. Documents were excluded for the following reasons: ineligible study design (n=44), ineligible year (n=36), ineligible intervention (n=29), ineligible outcomes (n=15), ineligible country (n=14), ineligible comparator (n=6), ineligible language (n=4), ineligible patient population (n=4), paper not found (n=1), and ineligible setting (n=1). The selection process is shown in Appendix G.

Summary of studies included in the economic evidence review

Varenicline interventions

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Annemans 2015 (Belgium) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Current smoker willing to quit **Population size:** 1,000 (hypothetical) **Time horizon:** Lifetime (100 years or dead) **Study aim:** To evaluate the cost-effectiveness of re-treatment with varenicline compared with	Minor limitations [b]	Partly applicable [c]	Similar model to Kautianen (2017) but in a Belgium context	**Total population costs (€):** Not reported **Total cost per person (€):** Not reported **Currency & cost year:** EUR (€); 2013	**Total population QALYs:** Not reported **QALYS per person:** Not reported **% abstinent at 12 months 1st attempt (2nd attempt):** Varenicline 21.1% (20.1%) Bupropion 15.7% (15.7%) NRT 14.9% (14.9%) Placebo 9.3% (3.3%)	**Incremental costs (total population) (€):** 2QA varenicline compared with: 2QA NRT - 275,000 2QA bupropion - 118,000 2QA placebo - 316,000 1QA varenicline - 237,000 **Incremental costs per person (€):**	**Incremental QALYs (total population):** 2QA varenicline compared with: 2QA NRT 74 2QA bupropion 63 2QA placebo 193 1QA varenicline 111 **Incremental QALYs per person:** *CALCULATED BY YHEC* [d]	**Incremental cost per QALY (€):** 2QA varenicline dominates all other interventions. This means it is both less costly and results in better health outcomes than each comparator.	Both one-way univariate analyses and probabilistic sensitivity analysis (PSA) were performed. Univariate sensitivity analyses found discount rates, cost of NRT and relative risks of smoking related diseases in long term quitters were the most influential parameters. However, changes to these parameters did not affect the conclusions. PSA indicated that the conclusions are robust. For every treatment

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
other smoking cessation interventions **Intervention** [a]**:** 2QA varenicline: 1QA with varenicline followed by varenicline re-treatment in case of failure or relapse **Comparators** [a]**:** 2QA NRT: 1QA with NRT followed by NRT re-treatment in case of failure or relapse 2QA bupropion: 1QA with bupropion followed by bupropion re-treatment in case of failure or relapse 2QA placebo: 1QA with placebo followed by placebo re-						*CALCULATED BY YHEC* [d] 2QA varenicline compared with: 2QA NRT - 275 2QA bupropion - 118 2QA placebo - 316 1QA varenicline - 237	2QA varenicline compared with: 2QA NRT 0.074 2QA bupropion 0.063 2QA placebo 0.193 1QA varenicline 0.111 **Incremental LYs (total population):** Compared with 2QA varenicline 2QA NRT 56 2QA bupropion 48 2QA placebo 146		comparison, the PSA results confirmed that varenicline significantly dominated comparators.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
treatment in case of failure or relapse 1QA varenicline: 1QA with varenicline followed by 1QA with placebo							1QA varenicline 84		
Data sources									
Health outcomes: Abstinence rates were derived from Cahill et al. (2013) as well as RCTs. Second line treatment efficacy for NRT and bupropion conservatively used the same value as first line treatment due to lack of evidence. **Quality-of-life weights:** Utility weights for health states are from published data sources. These are the same as those reported in a previous BENESCO model (Annemans et al., 2009). **Cost sources:** Hospitalization costs of smoking-related diseases were obtained from the Belgium TCT database Annual follow-up costs were taken from literature. Drug costs were taken from the RIZIV/INAMI database and the CBIP. All cost prior to 2013 were inflated.									
Abbreviations: ICER: Incremental cost-effectiveness ratio; LY: Life years NRT: Nicotine replacement therapy; QA: quit attempt; QALY: Quality-adjusted life year									
a) The length of treatment is not specified within the study. A 12-week treatment length is assumed in line with the cost per intervention.									
b) The model includes all important, and relevant, costs and outcomes. It is assumed that the first and second quit attempts for NRT and bupropion cessation have equal efficacy; however, varying this in PSA did not change the conclusions. The model considers only five smoking related diseases keeping co-morbidities to a minimum. Finally, the impact of possible adverse events is not considered									
c) The interventions considered are relevant to the UK context, but caution is required when transferring the results of the study given the difference in prices and healthcare systems between the UK and Belgium.									
d) Assumed to be incremental costs/QALYS (total population) divided by population size (1000).									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Athanasakis 2012 (Greece) **Economic analysis:**	Minor limitations [a]	Partly applicable [b]	Similar model to Knight (2012) but in a Greek context	**Total population costs (€, thousands):** Varenicline (12 weeks)	**Total population QALYs:** Varenicline (12 weeks) 11,610,664	**Incremental costs (total population) (€, thousands):**	**Incremental QALYs (total population):** Varenicline (12 weeks)	**Incremental cost per QALY:** Varenicline dominates all other	Both probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA)

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Cost-utility analysis (CUA) **Population:** Individuals making a single quit attempt **Population size:** 819,709 (hypothetical) **Time horizon:** Lifetime **Study aim:** To evaluate the cost-effectiveness of a 12-week course of varenicline for smoking cessation **Intervention:** Varenicline (12 weeks) **Comparator(s):** Bupropion (12 weeks) NRT (12 weeks)				15,485,564 Bupropion (12 weeks) 15,654,958 NRT (12 weeks) 15,711,867 Unaided cessation 15,883,032 **Total cost per person:** *CALCULATED BY YHEC* [c] Varenicline (12 weeks) 18,891 Bupropion (12 weeks) 19,098 NRT (12 weeks) 19,167 Unaided cessation 19,376	Bupropion (12 weeks) 11,582,961 NRT (12 weeks) 11,582,803 Unaided cessation 11,541,803 **QALYs per person:** *CALCULATED BY YHEC* [c] Varenicline (12 weeks) 14.2 Bupropion (12 weeks) 14.1 NRT (12 weeks) 14.1 Unaided cessation 14.1 **% abstinent at 12 months:**	Varenicline (12 weeks) compared with: Bupropion (12 weeks) -169,394 NRT (12 weeks) -226,302 Unaided cessation -397,468 **Incremental costs per person (€):** *CALCULATED BY YHEC* [e] Varenicline (12 weeks) compared with: Bupropion (12 weeks) -207 NRT (12 weeks) -276	compared with: Bupropion (12 weeks) 27,703 NRT (12 weeks) 27,861 Unaided cessation 68,861 **Incremental QALYs per person:** *CALCULATED BY YHEC* [e] Varenicline (12 weeks) compared with: Bupropion (12 weeks) 0.034 NRT (12 weeks) 0.034 Unaided cessation	interventions and unaided cessation. **Cost per additional quitter (strategy costs only) (€) :** Varenicline vs. bupropion 2,659 Varenicline vs. NRT 1,015	were performed. For an implicit €30,000 threshold, varenicline was cost-effective for 82.3%, 86.6%, and 85.2% of the Monte-Carlo iterations versus bupropion, NRT, and unaided cessation respectively. DSA found utilities after smoking-related events, the discount rate, costs of events, and effectiveness of varenicline to be of significant influence but did not change the conclusions. Varenicline remained dominant in a shorter timeframe of 20 years.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Unaided cessation				**Intervention costs per person [d]:** NR **Currency & cost year:** EUR (€); 2011	Varenicline (12 weeks) 22.4% Bupropion (12 weeks) 15.4% NRT (12 weeks) 15.4% Unaided cessation 5%	Unaided cessation -485	0.084		

Data sources
Health outcomes: 1-year quit rates from two head to head RCTs, pooled in analysis by Nides (2008) for varenicline and bupropion. 1-year quit rates for NRT taken from 2 meta-analyses of trials, and for unaided cessation taken from Foulds et al. **Quality-of-life weights:** Utility weights for health states are taken from various published data sources, baseline utilities from Fiscella and Franks. **Cost sources:** Medication cost were taken from the Greek National Formulary, the cost of a physician's visit was based on official social security tariff and healthcare costs are taken from recent economic evaluation in the Greek healthcare setting.
Abbreviations: DSA: Deterministic sensitivity analysis; ICER: Incremental cost- effectiveness ratio; NRT: Nicotine replacement therapy; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life year
(a) The model includes all important, and relevant, costs and outcomes. Some parameter values are taken from published data sources without detailed methodology on how these were derived.
(b) The interventions considered are relevant to the UK context, but caution is required when transferring the results of the study given the difference in prices and healthcare systems between the UK and Greece.
(c) Assumed to be total population costs/QALYS divided by population size (819,709).
(d) Intervention costs included 12 weeks of medication and the cost of a single physicians visit at the initiation of treatment. These figures were not reported.
(e) Assumed to be incremental costs/QALYS (total population) divided by population size (819,709).

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Coward 2014 (Canada) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Smokers between the age of 18 and 35, who are newly diagnosed with Crohn's disease (CD) and are naïve to antitumor necrosis factor (anti-TNF) [a] **Population size:** Not reported **Time horizon:** 5 years **Study aim:** to evaluate the cost-effectiveness of a 12-week course of varenicline for	Major limitations [e]	Partly applicable [f]	None	**Total population costs:** Not reported **Total cost per person (CAD$) (95% CI):** Varenicline (12 weeks) 55,614 (52,755 – 58,474) NRT + counselling 58,878 (56,050 – 61,706) NRT 59,540 (56,732 – 62,347) Counselling 61,029 (58,246 – 63,812) No program 63,601 (60,865 – 66,337)	**Total population QALYs:** Not reported **QALYs per person (95% CI):** Varenicline (12 weeks) 3.70 (3.68 – 3.73) NRT + counselling 3.69 (3.66 – 3.72) NRT 3.69 (3.66 – 3.71) Counselling 3.68 (3.65 – 3.71) No program 3.67 (3.64 – 3.69) **% abstinent at 12 months:** Varenicline (12 weeks)	**Incremental costs per person (CAD$):** *CALCULATED BY YHEC* [g] Varenicline (12 weeks compared with:) NRT + counselling - 3,264 NRT - 3,926 Counselling - 5,415 No program - 7,987	**Incremental QALYs per person:** *CALCULATED BY YHEC* [g] Varenicline (12 weeks compared with:) NRT + counselling 0.01 NRT 0.01 Counselling 0.02 No program 0.03	**Incremental cost per QALY:** Varenicline dominated all other interventions **Cost savings (5 years) compared with no program:** Varenicline (12 weeks) $16,116,169 NRT + counselling $9,530,069 NRT $8,194,286 Counselling $5,189,782	Probabilistic sensitivity analysis was conducted to account for variation in effectiveness of smoking cessation programs. Varenicline remained the most cost-effective strategy until its effectiveness was reduced below 17.7%. In addition, a 10% decrease in anti-TNF effectiveness among smokers and a 0.3 decrease in utilities for flares leading to surgery and the health state "surgery" were assessed. The finding did not substantially change results.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
smoking cessation for patients with CD **Intervention:** Varenicline (12 weeks) **Comparator(s):** NRT [b] + counselling [c] NRT Counselling No program [d]				**Intervention costs per person (CAD$):** Varenicline (12 weeks) 293.33 NRT + counselling 458.58 NRT 267.78 Counselling 190.80 No program 0.00 **Currency & cost year:** CAD ($); 2013	27.87% NRT + counselling 18.17% NRT 15.95% Counselling 10.96% No program 3.00%				
Data sources									
Health outcomes: Effectiveness data was taken from published data sources. **Quality-of-life weights:** Utility estimates were derived from Gregor (1997). **Cost sources:** Drug costs relating to CD were taken from the Alberta Blue Cross Interactive Drug Benefit List. Drug costs relating to smoking cessation were taken from published data sources. Surgery cost were taken from studies but the studies were not referenced.									
Abbreviations: CD: Crohn's disease; NRT: nicotine replacement therapy; QALY: quality adjusted life years									
a) This is not described by the author. Anti-TNF drugs are used to treat CD. It is assumed to mean a person who has not received an anti-TFN previously.									
b) A nicotine patch is used; however, the dose and length of use is not specified.									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
c) Individual counselling once a week for six weeks led by a healthcare professional.									
d) Recommendation to quit smoking without any direct counselling or prescription of smoking cessation medication.									
e) The study focused on CD population and did not consider long-term health states relating to smoking. Effectiveness data for smoking cessation interventions is taken from multiple source without the use of meta-analysis. Some parameter values are taken from published data sources without detailed methodology on how these were derived. Utilities relating to CD health states were not varied for smokers and non-smokers.									
f) The interventions considered are relevant to the UK context, but caution is required when transferring the results of the study given the difference in prices and healthcare systems between the UK and Canada.									
g) Assumed to be costs/QALYS per person for varenicline (12 weeks) subtract comparator costs/QALYs per person.									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Hagen 2010 (Norway) **Economic analysis:** Cost-effectiveness analysis (CEA) **Population:** Current smoker of the Norwegian population **Population size:** Not reported **Time horizon:** Lifetime (100 years or dead)	Minor limitations [b]	Partly applicable [c]	None	**Total population costs (kr):** Not reported **Total cost per person (kr):** Varenicline 863,650 Bupropion 859,706 NRT 858,118 No treatment 853,977 **Intervention costs per**	**Total population LYs:** Not reported **LYs per person:** Varenicline 14.74 Bupropion 14.69 NRT 14.62 No treatment 14.60 **Efficacy in relative risks (95%**	**Incremental costs per person (kr):** Compared with placebo NRT 4,141 Bupropion 5,729 Varenicline 9,672	**Incremental LYs per person:** Compared with placebo NRT 0.02 Bupropion 0.09 Varenicline 0.14	**Incremental cost per LY (kr):** Compared with placebo NRT 207,050 Bupropion 63,656 Varenicline 69,086 **Net health benefit:** Compared with placebo Varenicline 0.121	Both one-way and probabilistic sensitivity analysis was conducted. Results are most sensitive to changes in age (20 to 80), the price of varenicline (0 to 2,324), average healthcare expenses per person per year (0 to 60,000) and choice of discount rate (0 to 0.08). However, changes to these parameters will not bring the

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Study aim: to evaluate the effectiveness and cost-effectiveness of varenicline, bupropion and nicotine replacement therapy for smoking cessation **Intervention [a]:** Varenicline **Comparators [a]:** Bupropion NRT No treatment				**person (kr) [d]:** Varenicline (105 days) 2,456 Bupropion (56 days) 1,103 NRT (90 days) 3,150 **Annual healthcare cost [e] (kr):** 45,544 Last year of life 73,306 **Currency & cost year:** NOK (kr); 2009	**CI):** NRT vs placebo 1.58 (1.50 – 1.66) Bupropion vs NRT 1.45 (0.50 – 4.18) Varenicline vs bupropion 1.46 (1.18 – 1.81)			Bupropion 0.079 NRT 0.012	ICER above the willingness to pay per life year of NOK 500,000. Probabilistic sensitivity analysis showed varenicline was the optimal choice when willingness to pay per life year was above NOK 116,000.
Data sources									
Health outcomes: Efficacy estimates were taken from a systematic review (no further details as this was in Norwegian). **Quality-of-life weights:** N/A. **Cost sources:** Cost data used from published data sources.									
Abbreviations: CI: Confidence interval; ICER: Incremental cost-effectiveness ratio; LY: Life years; NRT: Nicotine replacement therapy; QALY: quality-adjusted life years									
a) The dosage and treatment length for the intervention and comparators is not specified in the study. Length of treatment is specified when calculating costs; however, it is unclear whether the same length of treatment is used when calculating efficacy.									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
b) The model includes all important, and relevant, costs and outcomes. The study calculates LYs but not QALYs. Only health states necessary to capture costs and health effects of being dead or alive are considered. The model did not consider long-term health states relating to smoking									
c) The interventions considered are relevant to the UK context, but caution is required when transferring the results of the study given the difference in prices and healthcare systems between the UK and Norway.									
d) It is assumed that patients treated with varenicline and bupropion will have one visit to a GP in order to get a prescription. NRT is available over-the-counter.									
e) It is assumed that annual healthcare costs are the same for smokers and non-smokers, and that healthcare costs are constant across age. A higher healthcare cost is applied to the last year of life for all persons, a cost of dying. This assumption was investigated in sensitivity analysis. A scenario analysis was constructed where smokers had higher annual health care costs than ex-smokers and where annual costs varied across age. This did not affect the conclusions.									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Hettle, 2012 (Europe) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Three groups: patients with CHD, patients with a history of stroke, patients with PVD **Population size:**	Minor limitations [b]	Partly applicable [c]	Similar population and interventions to Wilson, 2012 but in three different countries	**Total population costs (€):** Austria Varenicline 17,730,771 Placebo 16,970,528 Germany Varenicline 32,278,318 Placebo 31,423,185 Hungary Varenicline 6,110,250 Placebo 5,771,339	**Total population QALYs (millions):** Austria Varenicline 5,316 Placebo 5,172 Germany Varenicline 5,243 Placebo 5,098 Hungary Varenicline 4,511	**Incremental population costs (varenicline versus placebo, payer) (€):** Austria 760,243 Germany 855,133 Hungary 338,911 **Incremental population costs (varenicline**	**Incremental population QALYs (varenicline versus placebo):** Austria 144.1 Germany 145.8 Hungary 106.5 **Incremental QALYs per person (varenicline**	**Incremental cost per QALY gained (varenicline versus placebo) (€):** Payers perspective: Austria 5,278 Germany 5,867 Hungary 3,183 Societal perspective: In all countries, varenicline	Results from the deterministic sensitivity analysis showed marginal changes in ICER across all settings. The probabilistic sensitivity analysis found that in all scenarios and countries, varenicline remained cost-effective under a threshold of €12,500 per QALY gained.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Cohort of 1,000 patients with history of CVD problems **Time horizon:** Lifetime (65 years) **Study aim:** To evaluate the cost-effectiveness of varenicline plus counselling as a smoking cessation **Intervention:** Varenicline plus counselling [a] **Comparator(s):** Placebo plus counselling [a]				**Intervention cost of per person (€):** Austria Varenicline 17,730,771 Placebo 16,970,528 Germany Varenicline 32,278,318 Placebo 31,423,185 Hungary Varenicline 6,110,250 Placebo 5,771,339 **Total costs per person (€):** *CALCULATED BY YHEC* [d] Austria Varenicline 17,731 Placebo 16,971 Germany	Placebo 4,405 **QALYS per person:** *CALCULATED BY YHEC* [d]: Austria Varenicline 5.32 Placebo 5.17 Germany Varenicline 5.24 Placebo 5.10 Hungary Varenicline 4.51 Placebo 4.41 **% abstinent at 12 months:** Varenicline 19.2% Placebo 7.2%	**versus placebo, societal) (€):** Austria -1,631,857 Germany -1,517,876 Hungary -231,063 **Incremental costs per person(varenicline versus placebo, payer) (€):** *CALCULATED BY YHEC* [e] Austria 760 Germany 855 Hungary 339 **Incremental costs per person**	**versus placebo):** *CALCULATED BY YHEC* [e]: Austria 0.14 Germany 0.15 Hungary 0.11	plus counselling was cost saving with positive incremental QALYs so dominant over placebo plus counselling	

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
				Varenicline 32,278 Placebo 31,423 Hungary Varenicline 6,110 Placebo 5,771 **Currency & cost year:** EUR (€); 2010		**(varenicline versus placebo, societal) (€):** *CALCULATED BY YHEC* [e] Austria -1,632 Germany -1,518 Hungary -231			
Data sources									
Health outcomes: % Abstinence rates after 52 weeks [c] from double-blind placebo RCT **Quality-of-life weights:** Numerous published studies from both included countries and countries not included in the study. **Cost sources:** Numerous country dependent published sources used, generally from national data registries, national tariff schemes and published studies.									
Abbreviations: CHD: Chronic heart disease; CVD: Cardio-vascular disease; PVD: Peripheral vascular disease; QALY: Quality-adjusted life-year;									
(a) Counselling was 12 weekly clinic visits lasting a maximum of 10 minutes, plus a single telephone call 3 days after the quit date									
(b) Unclear whether all data is taken from the best sources									
(c) European (Austria, Germany and Hungary) setting, so care is needed when using these results in a UK setting									
(d) Calculated by total costs/QALYs over population size of 1000									
(e) Calculated by total incremental costs/QALYs over population size of 1000									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Huber, 2018 (Germany) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Current smokers in Germany **Population size:** Not reported **Time horizon:** Lifetime **Study aim:** To evaluate the cost-effectiveness of Varenicline as a smoking cessation **Intervention:** Varenicline (12 weeks) [a]	Major limitations [b]	Partly applicable [c]	None	**Total population costs (€):** Not reported **Total lifetime cost per person (€):** Not reported **Intervention cost of per person (€):** Varenicline 293 Zero investment - **Currency & cost year:** EUR (€), 2015	**Total population QALYs:** Not reported **Lifetime QALYs per person:** Not reported **Risk ratio versus usual care:** Varenicline 2.27	**Incremental costs per smoker (€):** Prospective scenario 1[d]: Zero investment - Varenicline -0.02 Prospective scenario 2[e]: Zero investment - Varenicline -0.25	**Incremental QALYs per smoker:** Prospective scenario 1[d]: Zero investment - Varenicline 0.0002 Prospective scenario 2[e]: Zero investment - Varenicline 0.0031	**Lifetime incremental cost-effectiveness ratio per QALY gained (€):** Prospective scenario 1[d]: Varenicline Dominant (-77.81) versus zero investment Prospective scenario 2[e]: Varenicline Dominant (-77.80) versus zero investment	There was no sensitivity analysis that focussed solely on varenicline. The only analysis included other, non-drug comparators like a financial incentive, with no breakdown of individual interventions.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Comparator(s): Zero investment									
Data sources									
Health outcomes: Taken from systematic review, studies with self-reported abstinence were excluded (only studies with biochemical testing were included) **Quality-of-life weights:** NR **Cost sources:** Varenicline treatment cost calculated from German pharmacy pricing. Smoking-related disease costs were not reported.									
Abbreviations: CHD: Coronary heart disease; EQUIPTMOD: European study on quantifying utility of investment in protection from tobacco model; QALY: Quality-adjusted life-year;									
(a) Dosage not reported. Treatment was made up of starter kit then maintenance.									
(b) Study setting is Germany so care is needed when using results in a UK context. The comparators are not clear.									
(c) There was no sensitivity analysis. Data sources were unclear.									
(d) In prospective scenario 1, varenicline uptake was increased by 1% causing 57,915 more quit attempts (ie a population of 57,915 analysed).									
(e) In prospective scenario 2, varenicline uptake was increased to UK levels (by 14.49%) causing 839,188 more quit attempts (ie a population of ~800.000 analysed).									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Kautiainen 2017 (Finland) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Current smoker willing to make a quit attempt	Minor limitations [b]	Partly applicable [c]	Similar model to Annemans (2012) but in a Finnish context	**Total population costs (€, millions):** 2QA varenicline 2,605 2QA bupropion 2,645	**Total population QALYs:** 2QA varenicline 1,835,400 2QA bupropion 1,831,805 2QA NRT	**Incremental costs (total population) (€, millions):** Compared with 2QA varenicline 2QA bupropion 40.1	**Incremental QALYs (total population):** Compared with 2QA varenicline 2QA bupropion -3,595 2QA NRT	**Incremental cost per QALY (€):** 2QA varenicline dominates all other interventions	Both one-way univariate analyses and probabilistic sensitivity analysis were performed. Univariate sensitivity analyses found discount rates, cost of NRT and

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Population size: 116,533 (hypothetical) **Time horizon:** Lifetime (100 years or dead) **Study aim:** To evaluate the cost-effectiveness of re-treatment with varenicline compared with other smoking cessation interventions **Intervention** [a]**:** 2QA varenicline: 1QA with varenicline followed by varenicline re-treatment in case of failure or relapse **Comparators** [a]**:** 2QA NRT: 1QA with NRT followed by NRT				2QA NRT 2,618 2QA unaided 6,660 1QA varenicline 2,633 **Total cost per person (€):** *CALUCLATED BY YHEC* [d] 2QA varenicline 22,354 2QA bupropion 22,687 2QA NRT 22,466 2QA unaided 57,151 1QA varenicline 22,594 **Currency & cost year:**	1,831,175 2QA unaided 1,823,452 1QA varenicline 1,829,742 **QALYS per person:** *CALUCLATED BY YHEC* [d] 2QA varenicline 15.8 2QA bupropion 15.7 2QA NRT 15.7 2QA unaided 15.6 1QA varenicline 15.7 **% abstinent at 12 months 1st**	2QA NRT 12.7 2QA unaided 54.9 1QA varenicline 27.6 **Incremental costs per person (€):** *CALUCLATED BY YHEC* [e] Compared with 2QA varenicline 2QA bupropion 344 2QA NRT 109 2QA unaided 471 1QA varenicline 237	-4,225 2QA unaided -11,948 1QA varenicline -5,658 **Incremental QALYs per person:** *CALUCLATED BY YHEC* [e] Compared with 2QA varenicline 2QA bupropion -3,595 2QA NRT -4,225 2QA unaided -11,948 1QA varenicline -5,658		relative risks of smoking related diseases in long term quitters were the most influential parameters. However, changes to these parameters did not affect the conclusion that 2QA varenicline dominates all other interventions. Significant uncertainty related to varenicline retreatment efficacy was investigated by varying the parameter +/- 20%. At the lower limit, 2QA varenicline vs 2QA bupropion gave an ICER of 4,550€/QALY and vs NRT it was 1,584€/QALY. Probabilistic sensitivity

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
re-treatment in case of failure or relapse 2QA bupropion: 1QA with bupropion followed by bupropion re-treatment in case of failure or relapse 2QA unaided: 1QA unaided followed by a subsequent unaided attempt in the case of failure or relapse 1QA varenicline: 1QA with varenicline followed by 1QA with placebo				EUR (€); 2013/2014	**attempt (2nd attempt):** Varenicline 21.1% (20.1%) Bupropion 15.7% (15.7%) NRT 14.9% (14.9%) Unaided 5% (5%)				analysis indicated that the conclusions are robust. Compared with 2QA NRT, 2QA varenicline is 99.9% cost-effective at a willingness to pay threshold of 5,000€ per QALY.
Data sources									
Health outcomes: First line treatment efficacies were derived from the Cochrane systematic review (Cahill et al., 2013). Second line treatment efficacy for varenicline was from a RCT. Second line treatment efficacies for NRT and bupropion conservatively used the same value as first line treatment due to lack of evidence. **Quality-of-life weights:** Utility weights for health states are from published data sources. **Cost sources:** Unit costs were taken from Kapianen at al., Finnish version of NordDRGs and pharmaceuticals pricing board (PPB)									
Abbreviations: ICER: Incremental cost-effectiveness ratio; NRT: Nicotine replacement therapy; QA: quit attempt; QALY: Quality-adjusted life year									
a) The length of treatment is not specified within the study. A 12-week treatment length is assumed in line with the cost per intervention.									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
b) The model includes all important, and relevant, costs and outcomes. It is assumed that the first and second quit attempts for NRT, bupropion and unaided cessation have equal efficacy. In addition, the varenicline re-treatment efficacy estimate is based on only one RCT.									
c) The interventions considered are relevant to the UK context, but caution is required when transferring the results of the study given the difference in prices and healthcare systems between the UK and Finland.									
d) Assumed to be total population costs/QALYS divided by population size (116,533).									
e) Assumed to be incremental costs/QALYS (total population) divided by population size (116,533).									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Knight 2012 (Belgium) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Current smokers willing to quit with pharmacological agent **Population size:** 168,239 (hypothetical) **Time horizon:** Lifetime **Study aim:**	Minor limitations [b]	Partly applicable [c]	Similar model to Athanasakis (2012) in a Belgium context	**Total population costs (millions):** Varenicline (12 + 12 weeks) plus brief counselling: €1,946 Varenicline (12 weeks) plus brief counselling: €1,941 Bupropion (12 weeks) plus brief counselling: €1,957	**Total population QALYs (millions):** Varenicline (12 + 12 weeks) plus brief counselling: 3.102 Varenicline (12 weeks) plus brief counselling: 3.097 Bupropion (12 weeks) plus brief counselling: 3.089	**Incremental costs (total population) (€):** Compared with varenicline (12 weeks) plus brief counselling Varenicline (12+12 weeks) plus brief counselling 6,000,000 Bupropion (12 weeks) plus brief counselling 16,000,000	**Incremental QALYs (total population):** Compared with varenicline (12 weeks) plus brief counselling Varenicline (12+12 weeks) plus brief counselling 5,000 Bupropion (12 weeks) plus brief counselling -8,000	**Incremental cost per QALY (€):** Varenicline (12 weeks) plus brief counselling vs. varenicline (12+12 weeks) plus brief counselling 1,101 The extended course of varenicline dominates all other interventions	Probabilistic sensitivity analysis was used to investigate the stability of the ICER when comparing the extended and non-extended course of varenicline. The extended course had an ICER below 30,000 € per QALYS 81.7% of the time. 30.9% of the time the extended course dominated the non-extended course.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
To evaluate the cost-effectiveness of an extended 12+12-week course of varenicline for smoking cessation **Intervention:** Varenicline (12+12 weeks) plus brief counselling [a] **Comparator(s):** Varenicline (12 weeks) plus brief counselling Bupropion (12 weeks) plus brief counselling Brief counselling alone				Brief counselling alone: €1,973 **Total cost per person (€):** *CALCULATED BY YHEC* [e] Varenicline (12+12 weeks) plus brief counselling 11,566 Varenicline (12 weeks) plus brief counselling 11,537 Bupropion (12 weeks) plus brief counselling 11,632 Brief counselling alone 11,727	Brief counselling alone: 3.081 **QALYS per person:** *CALCULATED BY YHEC* [e] Varenicline (12+12 weeks) plus brief counselling 3.102 18.43 Varenicline (12 weeks) plus brief counselling 18.41 Bupropion (12 weeks) plus brief counselling 18.36 Brief counselling alone 18.31 **% abstinent at 12**	Brief counselling alone 32,100,000 **Incremental costs (total population) (€):** *CALCULATED BY YHEC* [f] Compared with varenicline (12 weeks) plus brief counselling Varenicline (12+12 weeks) plus brief counselling 35.7 Bupropion (12 weeks) plus brief counselling 95.1 Brief counselling alone 190.8	Brief counselling alone -15,000 **Incremental QALYs (total population) :** *CALCULATED BY YHEC* [f] Compared with varenicline (12 weeks) plus brief counselling Varenicline (12+12 weeks) plus brief counselling 0.03 Bupropion (12 weeks) plus brief counselling -0.05 Brief counselling alone -0.09		

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
				Intervention costs per person [d]: Varenicline (12+12 weeks) plus brief counselling 547.52 Varenicline (12 weeks) plus brief counselling 382.14 Bupropion (12 weeks) plus brief counselling 288.23 Brief counselling alone 205.08 **Currency & cost year:** EUR (€); 2011	**months:** Varenicline (12+12 weeks) plus brief counselling 27.7% Varenicline (12 weeks) plus brief counselling 22.9% Bupropion (12 weeks) plus brief counselling 15.9% Brief counselling alone 9.3%				
Data sources									
Health outcomes: 1-year quit rates reported in Knight et al. (2012). **Quality-of-life weights:** Utility weights for health states are as published in Annemans et al. (2009). **Cost sources:** Publicly available costs from the national institute for health insurance (RIZIV/INAMI), published hospital costs for the appropriate All Patient Refined Diagnosis Related Group and two published studies; Annemans et al. (2009) and Muls et al. (1998). Costs were inflated to 2011 price were necessary.									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Abbreviations: BENESCO: Benefit of smoking cessation on outcomes; ICER: Incremental cost-effectiveness ratio; NRT: Nicotine replacement therapy; QALY: Quality-adjusted life year									
(a) The extended 12+12 weeks course of varenicline was only available to those who had remained abstinent after the initial 12-week period. Brief counselling consists of 12 GP visits within the first 12 weeks for each intervention. Subjects in the (12+12 weeks) intervention group received an additional 5 brief counselling GP visits in the following 12-week period.									
(b) The model includes all important, and relevant, costs and outcomes. Some parameter values are taken from previous BENESCO model(s) without detailed methodology on how these were derived. In addition, there were differences in the quantity of brief counselling with more sessions offered to the Varenicline 12+12 weeks intervention group if they remained abstinent after the initial 12 weeks.									
(c) The interventions considered are relevant to the UK context, but caution is required when transferring the results of the study given the difference in prices and healthcare systems between the UK and Belgium.									
(d) Starter pack was at quitters own expense for both varenicline and bupropion and not include in the cost. Treatment following the starter pack were included plus GP visits.									
(e) Assumed to be total population costs/QALYS divided by population size (168,239).									
(f) Assumed to be incremental costs/QALYS (total population) divided by population size (168,239).									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Linden, 2010 (UK) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Current Finnish smokers making a single quit attempt	No limitations	Partly applicable [c]	None	**Total lifetime population costs (€):** Varenicline 5,170,773,916 Bupropion 5,185,427,331 Unaided cessation 5,213,398,246	**Total lifetime population QALYs:** Varenicline 4,161,579 Bupropion 4,156,728 Unaided cessation 4,149,094	**Lifetime incremental costs (€):** Varenicline versus bupropion: Cost-saving Varenicline versus unaided cessation: Cost-saving	**Lifetime population incremental QALYs:** Varenicline versus bupropion: 4,851 Varenicline versus unaided cessation: 12,485	**Lifetime incremental cost-effectiveness ratio per QALY gained (€):** Varenicline dominates both bupropion and unaided cessation (lower total costs and	The 20-year time horizon found ICER per QALYs of €8,791 and €7,791 for varenicline versus bupropion and unaided cessation respectively. The deterministic sensitivity analysis found that even with major changes of

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Population size: (229,301) **Time horizon:** 20 years and lifetime **Study aim:** To evaluate the cost-effectiveness of Varenicline as a smoking cessation **Intervention:** Varenicline (12 weeks) plus single physician visit [a,b] **Comparator(s):** Bupropion (7 weeks) plus single physician visit [a,b] Unaided cessation				**Intervention cost of per person (€):** Varenicline 386.47 Bupropion 229.92 Unaided cessation - **Total lifetime cost per person (€):** *CALCULATED BY YHEC* [d] Varenicline 22,550 Bupropion 22,614 Unaided cessation 22,736 **Currency & cost year:** EUR (€); 2006 (apart from healthcare sub-index of	**Lifetime QALYs per person:** *CALCULATED BY YHEC* [e] Varenicline 18.15 Bupropion 18.13 Unaided cessation 18.09 **% abstinent at 12 months:** Varenicline 22.5% Bupropion 15.7% Unaided cessation 5%		**Lifetime incremental QALYs per person:** *CALCULATED BY YHEC* [f] Varenicline versus bupropion: 0.02 Varenicline versus unaided cessation: 0.05	higher total QALYs)	the input values, varenicline remained dominant below the ICER threshold of £30,000 (€33,200) over a lifetime horizon. The probabilistic sensitivity analysis found that, when the willingness-to-pay threshold was €10,000, varenicline was cost-effective compared with bupropion (unaided cessation) 65% (80%) of the time.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
				Finnish cost-of-living index, 2007)					

Abbreviations: ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life-year

(a) Dosage was not reported for either varenicline or bupropion

(b) Patients had a single physician visit at the initiation of treatment

(c) Study setting is Finland so care is needed when using results in a UK context

(d) Calculated by total cost of intervention and treatment over population of 229,301

(e) Calculated by total QALYs of intervention over population of 229,301

(f) Calculated by total incremental QALYs over population of 229,301

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Lock, 2011 (UK) **Economic analysis:** Cost-utility analysis (CUA) **Population:** Current cigarette smokers with COPD **Population size:** Not reported **Time horizon:**	Minor limitations [c]	Directly applicable	None	**Total population costs:** Not reported **Intervention cost per person (€):** Varenicline 914 Placebo 723 **Total cost per person (€):** Varenicline 14,978	**Total population QALYs:** Not reported **QALYS per person:** Varenicline 5.78 Placebo 5.62 **% abstinent at 12 months:** Varenicline 18.6%	**Incremental costs per person (varenicline versus placebo) (€):** *CALCULATED BY YHEC* [d] 740 per person	**Incremental QALYs per person (varenicline versus placebo):** *CALCULATED BY YHEC* [e] 0.16 per person	**Incremental cost-effectiveness ratio per QALY gained (€):** Varenicline versus placebo 4,478	There was limited sensitivity analysis around the UK model. At an implicit threshold of €30,000 per QALY gained, varenicline has a high probability of being cost-effective when compared with placebo.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
28 years, with mean starting age of 57 **Study aim:** To evaluate the cost-effectiveness of Varenicline as a smoking cessation **Intervention:** Varenicline (12 weeks) plus booklet and counselling [a,b] **Comparator(s):** Placebo (12 weeks) plus booklet and counselling				Placebo 14,238 **Currency & cost year:** EUR (€); 2010	Placebo 5.6%				
Data sources									
Health outcomes: % Abstinence rates after 52 weeks from a 27-centre double-blind placebo RCT [c] **Quality-of-life weights:** Estimated according to the UK EQ-5D tariff, taken from previous model of natural history and economic impact of COPD (Borg et al, 2004) **Cost sources:** Numerous cost sources used, prices inflated to 2010 levels and GDP converted to EUR at 2010 exchange rates when necessary. 'Whenever possible, state-specific costs are derived from peer-reviewed publications containing country-specific sources'.									
Abbreviations: COPD: Chronic obstructive pulmonary disease; QALY: Quality-adjusted life year;									
(a) Dosage was 1 mg by mouth twice daily for 12 weeks, though first week was 0.5mg once daily for 3 days, 0.5mg twice daily for 4 days									
(b) Persons were given an educational booklet on smoking cessation and brief (≤10 mins) counselling sessions at a weekly clinic visit. Further clinic visits and telephone calls were made during the 40-week follow-up period									
(c) Limited sensitivity analysis									
(d) Calculated by total cost for varenicline minus total cost for placebo									
(e) Calculated by total QALYs for varenicline minus total QALYs for placebo									

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Von Wartburg 2014 (Canada) **Economic analysis:** Cost utility analysis (CUA) **Population**: Adult smokers who are assumed to make a quit attempt within the next 30 days **Population size:** 1,275,481 (hypothetical) **Time horizon:** Lifetime **Study aim:** to estimate the cost-effectiveness of an extended (12+12 weeks) course of	Minor limitations [c]	Partly applicable [d]	Similar model to Knight (2012) in a Canadian context	**Lifetime costs (CAD$, millions) – Payer perspective [e]** Varenicline (12 weeks) 25,369 Varenicline (12+12 weeks) 25,426 Bupropion 25,510 NRT 25,705 Unaided cessation 25,746 **Lifetime costs (CAD$, millions) – Societal perspective [f]** Varenicline (12 weeks) 98,739	**Lifetime QALYs:** Varenicline (12 weeks) 15,398,000 Varenicline (12+12 weeks) 15,413,000 Bupropion 15,376,000 NRT 15,374,000 Unaided cessation 15,342 **1-year quit rates [d]:** Varenicline (12+12 weeks) 27.7% Varenicline (12 weeks) 22.9%	**Lifetime population costs (CAD$, millions) – Payer perspective** vs varenicline 12 weeks Varenicline (12+12 weeks) 56 Bupropion 140 NRT 336 Unaided cessation 376 **Lifetime population costs (CAD$) – Societal perspective**	**Incremental population QALYs:** vs varenicline (12+12 weeks) Varenicline (12 weeks) -15,000 Bupropion -37,000 NRT -39,000 Unaided cessation -71,000 **Incremental QALYs per person vs varenicline (12+12 weeks)** *CALCULATED BY YHEC* [i] Varenicline	**Incremental cost per QALY (CAD$) - Payer perspective [h]** Varenicline (12 + 12 weeks) vs varenicline (12 weeks): 3,758 Varenicline (12 + 12 weeks) dominated all the other interventions. **Incremental cost per QALY - Societal perspective** Varenicline (12 + 12 weeks) was dominant compared with all the other options.	Probabilistic sensitivity analysis (PSA) showed that varenicline (12+12 weeks) had a 95% probability of being cost-effective at a willingness to pay threshold of CAD$30,000 per QALY compared with varenicline (12 weeks) and 100% compared with the other interventions (from the payer perspective).

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
varenicline using the Benefits of Smoking Cessation on Outcomes (BENESCO) model **Intervention:** Varenicline [a] (12 + 12 weeks) Smoking cessation for 12 weeks plus additional 12 weeks of Varenicline maintenance for quitters **Comparator** [b]: Varenicline (12 weeks) for smoking cessation plus 12 weeks placebo maintenance for quitters Bupropion (12 weeks) for				Varenicline (12+12 weeks 98,902 Bupropion 99,902 NRT 100,177 Unaided cessation 101,730 **Currency & cost year:** CAD ($); 2009	Bupropion 15.9% NRT 15.4% Unaided cessation 5%	**(vs varenicline 12+12 weeks)** Varenicline (12 weeks) 645 Bupropion 1,807 NRT 2,082 Unaided cessation 3,635 **Lifetime costs per person (CAD$) – Payer perspective (vs varenicline 12 weeks)** *CALCULATED BY YHEC* [i] Varenicline (12+12 weeks) 43.9	(12 weeks) -0.012 Bupropion -0.029 NRT -0.031 Unaided cessation -0.056		

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
smoking cessation Nicotine replacement therapy (NRT) (12 weeks) for smoking cessation Unaided cessation: no further description was provided						Bupropion 109.8 NRT 263.43 Unaided cessation 294.8 **Lifetime costs per person (CAD$, millions) – Societal perspective (vs varenicline 12+12 weeks)** *CALCULATED BY YHEC* [i] Varenicline (12 weeks) 505.7 Bupropion 1,416.7 NRT 1632.3			

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
						Unaided cessation 2849.9			

Data sources

Health outcomes: 1-year quit rates were derived from a mixed treatment comparison of 3 RCTs (Knight 2010) and for NRT were taken from a meta-analysis by Silagy, 2004. **Quality-of-life weights:** These were taken from published literature but no further details were given. **Cost sources:** Costs associated with smoking-related morbidities were taken from published literature but were not described. Costs of interventions were taken from Pharmastat, Public Claim Data for Québec

Abbreviations: CUA: Cost-utility analysis; NRT: Nicotine replacement therapy; PSA: Probabilistic sensitivity analysis; QALY: Quality-adjusted life year; RCT: Randomised controlled trial

a) All Varenicline cessation and maintenance doses were 1mg taken twice daily.
b) Details on the dose of bupropion was not provided. NRT comprised of chewing gum, transdermal patches, nasal spray, inhalers and tablets, doses were not provided.
c) The study was based on multiple RCTs. When required, conservative assumptions were made.
d) The interventions considered appear relevant to the UK context, but caution is required in transferring the results of this study given the differences in prices between Canada and the UK.
e) Cost components of the payer perspective included intervention costs (drug costs and a single GP visit) and healthcare resources to treat smoking related comorbidities (lung cancer, stroke, coronary heart disease, chronic obstructive pulmonary disease and asthma)
f) The cost components for the wider societal perspective included all those for the payer perspective and the following indirect costs: productivity benefits from improved health & reduced absenteeism, reduced tax from tobaccos sales, cost savings from reduced second-hand smoker and smoke related fires.
g) 1-year quit rates for Varenicline (12+12 weeks), Varenicline (12 weeks) and Bupropion were derived from a mixed treatment comparison of 3 RCTs which established abstinence through self-reported non-smoking and exhaled CO readings < 10 parts per million; the 1-year quit rates for NRT was obtained from a meta-analysis which confirmed abstinence through a combination of self-reported non-smoking and CO readings.
h) Cost-effectiveness driven by efficacy rates which result in a higher ratio of non-smoker to smokers and fewer smoking related comorbidities/deaths.
i) Calculated by total incremental costs/QALYs over population size of 1,275,841

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Wilson, 2012 (Europe) **Economic analysis:**	Minor limitations [b]	Partly applicable [c]	Similar population and interventions to Hettle,	**Total population costs (€):** Belgium	**Total population QALYs (millions):** Belgium	**Incremental population costs (varenicline versus**	**Incremental QALYs (varenicline versus placebo):**	**Incremental cost-effectiveness ratio per QALY gained**	The one-way sensitivity analysis determined that assumptions on

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Cost-utility analysis (CUA) **Population:** Three groups: patients with CHD, patients with a history of stroke, patients with PVD **Population size:** Cohort of 1,000 patients with history of CVD problems **Time horizon:** Lifetime (65 years) **Study aim:** To evaluate the cost-effectiveness of Varenicline plus counselling as a smoking cessation **Intervention:** Varenicline plus counselling [a]			2012 but in four different countries	Varenicline 34,812,609 Placebo 33,828,993 Spain Varenicline 25,984,405 Placebo 25,239,643 Portugal Varenicline 28,201,146 Placebo 27,451,663 Italy Varenicline 26,581,362 Placebo 25,706,868 **Total costs per person (€):** *CALCULATED BY YHEC* [d] Belgium Varenicline 34,813 Placebo 33,829 Spain	Varenicline 5311 Placebo 5150 Spain Varenicline 5154 Placebo 5010 Portugal Varenicline 5231 Placebo 5091 Italy Varenicline 5296 Placebo 5135 **QALYs per person:** *CALCULATED BY YHEC* [d] Belgium Varenicline 5.31 Placebo 5.15 Spain	**placebo, payer) (€):** Belgium 983,615 Spain 744,762 Portugal 749,483 Italy 874,494 **Incremental population costs (varenicline versus placebo, societal) (€):** Belgium -1,434,061 Spain -1,017,494 Portugal -1,493,532 Italy -1,210,496 **Incremental costs per**	Belgium 160.7 Spain 144.6 Portugal 139.9 Italy 161.0 **Incremental QALYs (varenicline versus placebo):** *CALCULATED BY YHEC* [e] Belgium 0.16 Spain 0.14 Portugal 0.14 Italy 0.16	**(varenicline versus placebo) (€):** Payer's perspective: Belgium 6,120 Spain 5,151 Portugal 5,357 Italy 5,433 Societal perspective: In all countries, varenicline plus counselling was cost saving with positive incremental QALYs, so dominant	cost parameters did not exhibit a strong influence on outcomes. It also found time horizon had no significant influence. The probabilistic sensitivity analysis found that all countries had an ICER between willingness to pay thresholds of €4,000 and €10,000 per QALY gained (ie. at a threshold of €10,000, there is 100% probability that varenicline is cost effective when compared with placebo in all countries).

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Comparator(s): Placebo plus counselling [a]				Varenicline 25,984 Placebo 25,240 Portugal Varenicline 28,201 Placebo 27,452 Italy Varenicline 26,581 Placebo 25,707 **Intervention cost of per person (€):** Belgium Varenicline 519 Placebo 272 Spain Varenicline 682 Placebo 321 Portugal	Varenicline 5.15 Placebo 5.01 Portugal Varenicline 5.23 Placebo 5.09 Italy Varenicline 5.30 Placebo 5.14 **% abstinent at 12 months:**[e] Varenicline 19.2% Placebo 7.2%	**person (varenicline versus placebo, payer) (€):** *CALCULATED BY YHEC* [f] Belgium 984 Spain 745 Portugal 749 Italy 874 **Incremental costs per person (varenicline versus placebo, societal) (€):** *CALCULATED BY YHEC* [f] Belgium -1,434 Spain -1,017			

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
				Varenicline 665 Placebo 372 Italy Varenicline 575 Placebo 225 **Currency & cost year:** EUR (€), 2010		Portugal -1,494 Italy -1,210			
Data sources									
Health outcomes: % Abstinence rates after 52 weeks [c] from a single double-blind placebo RCT. **Quality-of-life weights:** Numerous country dependent published sources used, generally published studies. **Cost sources:** Numerous country dependent published sources used, generally published studies.									
Abbreviations: CHD: Coronary heart disease; CVD: Cardio-vascular disease; ICER: Incremental cost-effectiveness ratio; PVD: Peripheral vascular disease; QALY: Quality-adjusted life-year;									
(a) Counselling was 12 weekly clinic visits, plus a single telephone call 3 days after the quit date									
(b) Unclear whether all data is taken from the best sources									
(c) European (Spain, Italy, Portugal and Belgium) setting, so care is needed when using these results in a UK setting									
(d) Calculated by total population cost/QALYs over population size of 1,000									
(e) Abstinence data taken from a multi-centre, randomised, double-blind, placebo-controlled trial, and the same data is used for each country.									
(f) Calculated by total incremental costs/QALYs over population size of 1000									

E-cigarette interventions

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Li 2019 (UK) **Economic analysis:** Cost-effectiveness analysis (CEA) **Population:** Adult smokers who sought help to quit **Sample size (RCT):** 886 **Cohort size (lifetime model):** 1000 **Time horizon:**	Minor limitations [b]	Directly applicable	A randomised control trial (RCT) was conducted with 12-month costs and effectiveness reported as the primary analysis. Following this, a Markov model was used to project lifetime cost-effectiveness.	**Total population costs:** Not reported **Total cost per participant (SE) (£) [c]:** **12-Month** EC 1174 (147) NRT 1116 (163) **Lifetime** EC 3184 (169)	**Total population QALYs:** Not reported **QALYS per participant (SE):** **12-Month** EC 0.886 (0.008) NRT 0.882 (0.009) **Lifetime** EC 24.14 (0.31)	**Estimated incremental costs (£) [f]:** **12-Month** 11 **Lifetime** 9	**Estimated incremental QALYs [f]:** **12-Month** 0.010 **Lifetime** 0.14	**Estimated incremental cost per QALY(£) [f]:** EC compared with NRT **12-Month** 1,100 per QALY gained **Lifetime** 65 per QALY gained	Cost-effectiveness acceptability curves estimated the probability of EC being cost-effective in comparison with NRT to be: **12-month** 87% at £20,00/QALY and 90% at £30,00/QALY **Lifetime [g]** 85% at both 20,000/QALY and 30,000/QALY thresholds.

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
12-month and lifetime **Study aim:** To evaluate the cost-effectiveness of e-cigarettes as a smoking cessation aid used in routine stop smoking services **Intervention:** E-cigarette (EC) + behavioural support [a] **Comparator:** Nicotine replacement therapy (NRT) + behavioural support [a]				NRT 3175 (161) **Currency & cost year:** GBP (£); 2015/16	NRT 24.28 (0.31) **% abstinent at 12 months [d, e]:** EC 18.0% NRT 9.9%				

Study	Limitations	Applicability	Other comments	Costs	Effects	Incremental cost	Incremental effects	Economic analyses outcomes	Uncertainty
Data sources									
Health outcomes: 1-year quit rates were used directly from RCT. **Quality-of-life weights**: EQ-5D utility values were based on a study of Health Survey for England data, with a sample size of 13,241. **Cost sources**: Costs were source from the NHS, NICE, PSSRU and government publications.									
Abbreviations: EC: E-cigarette; ICER: Incremental cost-effectiveness ratio; NRT: Nicotine replacement therapy; QALY: Quality-adjusted life year; RCT: Randomised control trial; SE: Standard error									
a) All participants were offered six weekly behavioural support sessions at their local stop smoking services (SSS) as per standard practice, with the second session on the target quit date.									
b) The lifetime model did not take into consideration the possible long-term effects of using EC on health and personal finance due to lack of evidence. The RCT had a 35% missing data level which make cost-effectiveness less certain. The 6-month recall period for self-reported health-care services use could potentially cause recall bias. QALYs were derived based on smoking status, and were not disease specific.									
c) Total costs include treatment costs, smoking cessation costs and health-care costs. Treatment costs consist of training and delivery costs. For NRT, supplies were provided for up to 3 months, as per usual practice. For EC, the 'One Kit' device and a 30-ml bottle of e-liquid was provided. Participants were instructed to obtain further e-liquid themselves although one additional 10-ml bottle of e-liquid could be requested if requires.									
d) Carbon monoxide (CO)-validated.									
e) 1-year quit rates were applied to the first cycle of the lifetime model. An annual relapse rate of 10% was applied for the following 10 years and abstinence was subsequently assumed to be permanent.									
f) Incremental costs and incremental QALYs were estimated using regression adjusting for baseline covariates and their respective baseline values. A generalized linear regression model controlled for utility value at baseline, age, gender, study site, entitlement of free prescriptions and FTCD at baseline.									
g) While the ICERs are lower over a lifetime horizon, uncertainty analysis shows a lower chance of being cost-effective. The author does not explain the reasoning. However, it is assumed that this is due to the use of wider confidence intervals for the long-term data.									

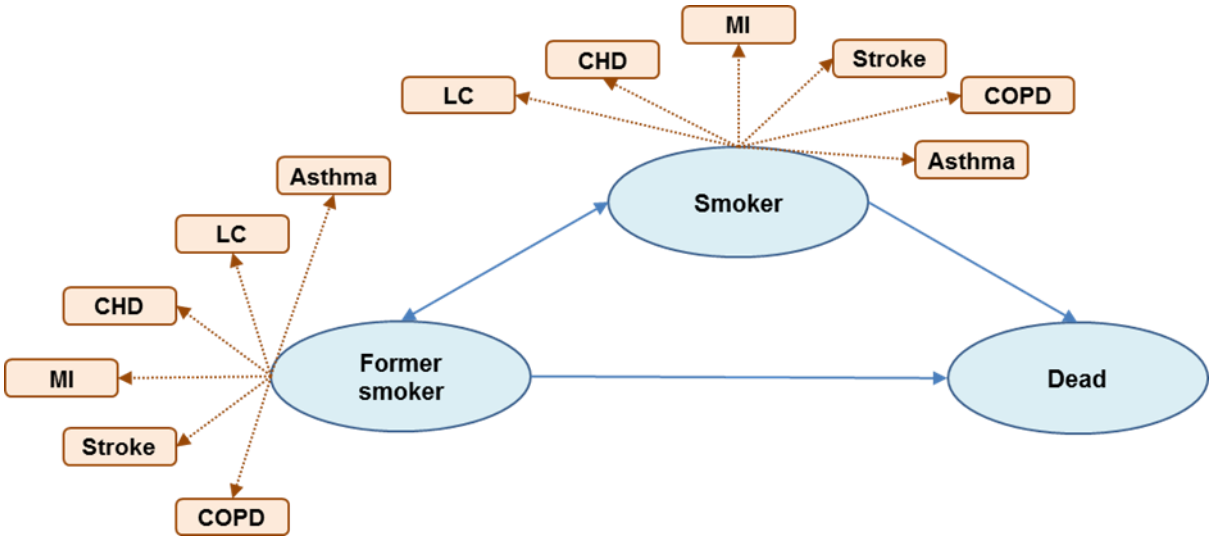
Economic model

The economic model used to assess the cost-effectiveness of smoking cessation interventions was an adapted version of the model previously used to inform NICE guidelines on smoking cessation [NG92

Model Structure

t uses the same structure as was developed in the original NG92 model (8), considering long-term epidemiological data in order to capture the lifetime complications associated with six long-term smoking-related illnesses (Figure 1). A similar model structure has been used in past cost-effectiveness models for smoking interventions (PHG10, PHG45).

Figure 1: Model structure



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

The Markov model includes annual cycles where smokers have a probability of quitting (and becoming 'former smokers') and former smokers have a probability of relapsing. People from either the 'smoker' or 'former smoker' health state can move to the 'dead' health state. The model doesn't include benefits for tobacco harm reduction.

The model includes six smoking related comorbidities: lung cancer (LC), coronary heart disease (CHD), myocardial infarction (MI), stroke, chronic obstructive pulmonary disease (COPD), and asthma. It uses published literature sources to establish the prevalence of LC, CHD, MI, stroke and COPD, and incidence of asthma, for smokers and non-smokers by age and gender. Each comorbidity has an associated NHS treatment cost and disutility. These costs and disutilities are applied based on prevalence and incidence rates for each cycle and summed to estimate lifetime costs and QALYs across all cycles.

The model calculates the average lifetime costs, lifetime QALYs, and subsequent cost-effectiveness across all populations between the ages of 12 and 100. Age 12 was selected as this was assumed to be the earliest age that someone would take up smoking.

Model inputs

This section outlines the model inputs that have been used to populate the economic model and also highlights any area in which there are data gaps. Where required targeted searches were carried out to identify new data to update parameter values in the existing NG92 model.

Numerous parameters remained the same as in the original model, since either the same source was found, or no better or more recent source was found.

Effectiveness estimates

Intervention effectiveness (relative risks of smoking abstinence at 6 months) was sourced from NICE evidence review K (5).

The PHAC were interested in comparing the cost-effectiveness of each intervention versus one another and versus a comparator, and therefore the incremental economic analysis included placebo as an intervention option.

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

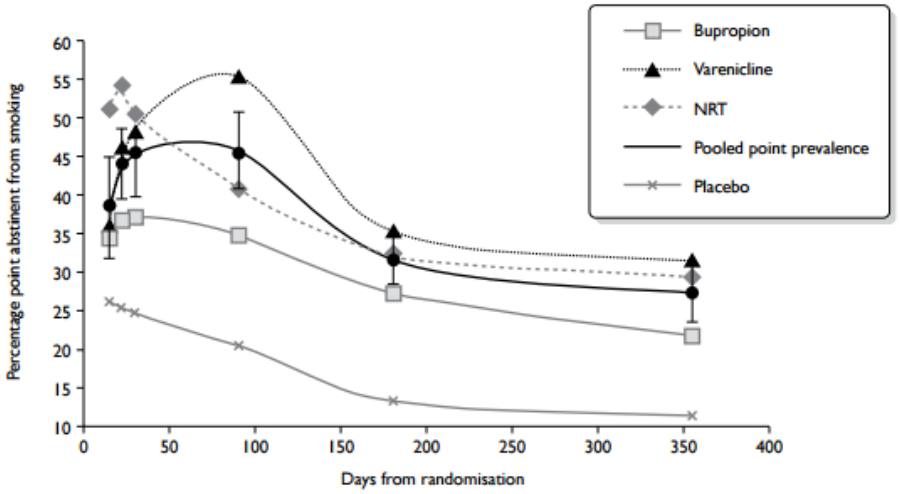
To be consistent with the annual cycle lengths included in the economic model, probabilities of smoking cessation at 6-months were converted to probabilities of smoking cessation at 12-months, accounting for smoking relapse between these two time points. Long term relapse curves were used to adjust probabilities providing quit rate at one year (Figure 2). Relapse after 12 months was included as part of the natural rate of smoking cessation that was applied in the model. The rate was set equal to 2%, and incorporates both the expected number of people who quit smoking and relapse from smoking annually.

All RRs were obtained from the NMA results in Table 20 of NICE evidence review K. The RRs and absolute probabilities of quitting at 6-months and 12-months are outlined in Table 7.

Table 7: Intervention effectiveness

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

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



Intervention costs

The cost of behavioural support (£82.96) was applied equally to both the placebo arms and each intervention arm. This was because the majority of studies informing the NICE NMA included some form of behavioural support in both the intervention and placebo arms.

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

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

The total cost of each of the included interventions, the components used to calculate the costs and the sources are summarised in Table 8.

Table 8 Intervention costs (NHS/PSS)

Intervention	Total cost	Components	Unit Costs (per dose)	Source
Behavioural support (applies to placebo *and* all other interventions)	£82.96	Total of 5.35 behavioural support sessions through LSSS. Sessions 1-2 assumed to last 30 minutes, with all subsequent sessions lasting 20 minutes. Total session number derived as a weighted mean trial arm.	N/A	Li et al (2020) (15)
NRT l/s*	£48.88	Weighted average: NRT patch (23.5%), NRT Lozenge (17.74%), NRT gum (31.48%), NRT Spray (10.15%), NRT Inhalator (17.27%)	NRT patch=£54.84 NRT lozenge=£26.93 NRT gum=£47.89 NRT spray=£50.63 NRT inhalator=£63.71	Weightings: Prescription Cost Analysis (2018) (16) Unit costs: Table 2
NRT l&s*	£104.17	100% receive long acting NRT patch plus a weighted average cost across short acting NRT. Weightings for short acting NRT= gum (25.45%),	NRT patch=£54.84 NRT gum=£47.89	Weightings: Updated NICE NMA (5)

		spray (50.72%), any (18.09%), inhalator (5.74%).	NRT spray=£50.63 NRT inhalator=£63.71 NRT any short acting=£43.56	Unit costs: Table 2
Varenicline	£160.88	500 micrograms take once daily for 3 days, 500 micrograms twice daily for 4 days, and 1mg twice daily for 11 weeks.	£0.98 [for both 500 microgram & 1mg]	Drug costs and dosage (BNF online 2020) (7)
Bupropion	£44.10	150mg daily for 1 week, then 150mg twice daily for 8 weeks	£0.70	(BNF online 2020) (7)
E-cigarettes	£0.00	E-cigarettes are not currently licenced by the NHS and therefore all costs are assumed to be incurred OTC for the base case analysis.		
Bupropion & NRT l/s*	£92.98	Cost of bupropion plus cost of NRT l/s.		
Bupropion & NRT l&s*	£148.27	Cost of bupropion plus cost of NRT l&s.		
Varenicline & NRT l/s*	£209.76	Cost of varenicline plus cost of NRT l/s.		
Varenicline & Bupropion	£204.98	Cost of varenicline plus cost of bupropion.		
E-cigarettes & NRT l/s*	£48.88	Cost of e-cigarettes plus cost of NRT l/s.		

Private costs

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

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

The private costs of NRT included costs for the 52% of NRT products purchased OTC, the % being informed by the study by Hajek et al. (2019). As there was no information on dose and type of NRT purchased OTC, it was assumed prescribed and private unit costs would be equivalent. Therefore, all costing was as described previously for each NRT intervention classification in Table 8. The private costs for each intervention are reported in Table 9

Table 9: Private costs (OTC)

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

Bupropion & NRT l&s	£112.85
Varenicline & NRT l/s	£52.96
Varenicline & Bupropion	£0.00
E-cigarettes & NRT l/s	£169.10

Comorbidity costs

The comorbidity costs were sourced from the same publications as were used in the original NG92 model. A pragmatic literature search in online databases was conducted which combined key terms and synonyms relating to each comorbidity combined with common search terms for healthcare costs and/or economic studies (for example, costs, healthcare costs, NHS costs, burden of illness, economic evaluation). The searches did not identify any relevant evidence from more recent publications. Each annual cost was inflated to 2019 prices from the original source using the PSSRU H&CHS inflation indices[d]. It was not possible to report overall costs for social care separately and, therefore, results are reported for NHS and personal social services as a whole.

The costs associated with each co-morbidity reflect on-going annual costs and are multiplied by the number of people with each co-morbidity each cycle. As the model estimates costs using a prevalence-based approach i.e. establishing the total proportion of smokers/ex-smokers in the population with a comorbidity at a certain time, the comorbidity costs represent an "average" cost per year for people with the comorbidity (see Table 10).

Table 10: On-going annual comorbidity costs (NHS/PSS)

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

[d] Personal Social Services Research Unit (PSSRU). Unit Costs of Health & Social Care 2015. Canterbury: University of Kent2015.

Asthma exacerbation	£1,433	Leaviss *et al.* (2014) (25) Inflated from 2010/11 to 2018/19 prices using PSSRU (2019) H&CHS indices (20)

Productivity costs

The base case model was for a health and social care perspective. Productivity costs for smokers and non-smokers were included in the model as part of a scenario analysis which expanded the perspective to include wider societal costs. Full details of this can be found in Report Q.

Utilities

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

It is possible to experience more than one comorbidity. When patients experience multiple comorbidities at one time, it is not clear how this affects their quality of life. If each disease is associated with a decrement in quality of life, would a person with two diseases experience the sum of both decrements, only the decrement associated with the most severe comorbidity or somewhere in between. The base analysis applies the disutility associated with each comorbidity. Deterministic scenario analyses are used to explore the impact of applying only the disutility associated with the most severe comorbidity. The utility inputs included in the model are shown in Table 11.

Table 11: Utility values

Parameter	Utility value	Source
Stroke	0.48	Tengs and Wallace (28)
Lung cancer	0.61	Bolin *et al.* (2009) (29)
MI	0.80	Tengs and Wallace (28)
CHD	0.76	Stevanovic (30)
COPD	0.73	Rutten-van Molken *et al.* 2006 (31)
Asthma exacerbation*	0.729	For one week. Briggs et al.(2006) (32)
Smoker	0.8486	Vogl *et al.* (2012) (33)
Former smoker	0.8669	Vogl *et al.* (2012) (33)

*Assumed that disutility is incurred for 1 week

Comorbidity epidemiology

The model generates average (or 'expected') outcomes for specific baseline characteristics (i.e. the outcomes are calculated for a person of a pre-specified age, gender and smoking status). However, results are calculated for every possible baseline characteristic, and the

model then produces a 'weighted average' output, based on the known demographics of the assessed group. The specific parameters that varied by age group were smoking status, comorbidity prevalence and mortality risk. We were not able to identify age specific variables within the published sources so all other factors within the model were assumed to stay constant by age. The inputs required to inform the calculations of the prevalence of comorbidities by age, gender and smoking status are summarised in this section. Table 12 summarises the sources used for the prevalence of each comorbidity.

Table 12: Sources for prevalence of comorbidities

Prevalence	Source/notes
Stroke	Bhatnagar *et al.* (2015) (34)*
Lung cancer	Maddams *et al.* (2009) (35)*
MI	Health Survey for England (2017), Table 1: Prevalence of ever having any doctor-diagnosed MI by age and sex. (34)*
CHD	Townsend et al. (2012) (36). Assumed that 12 to 15-year olds had 0% prevalence. This assumption was made based on (i) the prevalence for the 16 to 24 age group was 0.1% (females) and 0.1% (males) and (ii) the younger age group (12 to 15) would have a lower risk for CHD than those aged 16 to 25. The youngest age group that data was available for was in people aged 16 to 24 years (0.1%)
COPD	Public Health England data set (not reported by gender). Assumed 12 to 15-year olds had 0.1% prevalence (given that the prevalence for the 16 to 24 age group 1.28% and the risk reduces with age). Data were only reported for ages as low as 16 to 24 years (1.28%)

Table 13 summarises the sources used for the relative risks by smoker, never-smoker and former smoker by gender. The pragmatic searches identified a new relevant source for the MI RR's, therefore Millet et al. (2018) was used as the source for this parameter in the updated model. All other RR values were retained from the original NG92 model. The between group differences in the intervention and comparator arms for the comorbidities are determined by smoking status based on the RR values. Each RR was obtained from a source in the published literature which applied an appropriate statistical technique to adjust for confounding factors which could also explain differences in comorbidity prevalence rates including age, sex, and disease risk factors.

Table 13: Sources for relative risks (RR) of comorbidities

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

Asthma Exacerbation Inputs

The incidence of asthma exacerbations for smokers, short term (<=4 years) and long term quitters (> 4 years) follows the methods in the HTA report by Leaviss et al 2014 where mortality associated with asthma exacerbation was assumed to equal all-cause mortality (i.e.

asthma exacerbations did not result in death). In addition, it was assumed that asthma exacerbations were transient in nature and resolved within one year.

Mortality epidemiology

The mortality rates were obtained from Doll et al. (1994) which is an observational study with 40-year follow up using data the British doctors survey. The authors of the study have published a more recent paper which provides 50-year follow-up (45). However, the 40-year follow up data was used because it provided annual mortality by smoking habits at age of death, which was not available in the 50-year follow up. The mortality rates from Doll et al. (1994) were adjusted to reflect the general population mortality rates.

Sensitivity analyses

Deterministic sensitivity analysis (DSA)
Univariate deterministic sensitivity analyses were conducted for several key parameters in the economic model. These included: intervention effectiveness (RR), the probability of cessation at 12-months for placebo; the time horizon; intervention costs; the annual rate of cessation and relapse; the discount rate for costs and QALYs; comorbidity costs; comorbidity disutilities, and applying NHS intervention costs for e-cigarettes.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was carried out to explore the impact of changing the value of parameter inputs on the results produced by the model. In the base case model, a weighted average of incremental costs and QALYs is obtained for one year age ranges i.e. age 12, age 13, age 14…100. Incremental costs and QALYs across all population ages are calculated as a weighted mean across all individual ages with weighting based on the proportion of the UK population at each age individual.

To reduce the computational burden of the PSA, age categories were condensed from yearly increments i.e. age 12, 13, 14, 15, … , 100, to every ten years. To ensure the results of the PSA were in alignment with the base case analysis, the youngest population age was set equal to 12 (youngest age for the base case model) plus the midpoint of the age increment. This meant the PSA calculated weighted averages for populations aged 17, 27, 37, ., 97. The final results for the PSA were then calculated as a weighted average across results for people aged 17, 27, 37, …, 97 using a corresponding age weighting based on ONS population estimates (13).

The parameters used in the PSA were intervention effectiveness, smoking status (by age and gender), mortality, comorbidities, utilities, intervention costs and comorbidity costs.

Scenario analysis

In addition, several scenario analyses were carried out to explore the following:

1. the impact of comparing all interventions to NRT l/s rather than placebo,
2. the impact of including an additional study e-cigarette study (Hajek et al 2019) in the NMA (see Review K appendices for further information and results),
3. the impact of allocating the cost of e-cigarettes to the NHS

Subgroup analysis

The cost effectiveness of pharmacotherapies for smoking cessation specifically for a population with mental health problems. The characteristics of the mental health subgroup

was informed by the populations included in the updated NMA by Thomas et al. (2020) (6) in NICE evidence review K. This included people with depression, psychiatric disorder, bipolar, schizophrenia and post-traumatic stress disorder. For full details of changes to parameters relevant to mental health populations see full model report.

Exploratory analysis

To address the committee's concerns about possible health harms associated with use of e-cigarettes and the potential for e-cigarettes to promote uptake of smoking in non-smoking populations two analyses were carried out to explore the following:

1. the total amount of QALYs/costs worth of adverse events per person that would make e-cigarettes not cost-effective vs usual care,
2. the trade-off between lifetime costs and QALYs gained in populations who quit smoking due to e-cigarettes and those lost in populations who take up smoking due to e-cigarettes.

Model results

Basecase - full incremental analysis

The full incremental analysis compares the cost-effectiveness of each of the smoking cessation interventions with one-another and to placebo in the general population. All results are obtained as weighted averages of results for populations aged 12 to 100, this representing everybody who could feasibly have been classified as smokers when entering the model.

The base case results for the fully incremental analysis are displayed in Table 14. Bupropion + NRT l&s was the most cost-effective strategy and was dominant versus each of the other interventions having the lowest total healthcare costs (£10,802) and highest lifetime QALYs (15.37) per person, and subsequently the highest net monetary benefit vs. placebo, equal to £5,928 per person.

Table 14: Cost-effectiveness results (per person)

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

NRT l&s	2.71 (4)	267	£11,035	15.29	£4,035	3
E-cigarettes + NRT l/s	2.93 (2)	288	£10,903	15.31	£4,623	2
Bupropion + NRT l&s	3.51 (1)	345	£10,802	15.37	£5,928	1

RR= relative risk versus placebo
CE = cost-effectiveness

Basecase – pairwise analyses vs placebo

As well as establishing the most cost-effective treatment option, the committee requested that the economic analysis identified the cost-effectiveness of each intervention versus placebo. A full breakdown of the pairwise comparisons is provided in Table 15.

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

Table 15: Incremental cost-effectiveness results (per person): Pairwise results vs. placebo

Intervention	RR vs. placebo	Incremental outcomes vs. placebo			ICER
		Quitters @ 12 months (per 1,000)	Lifetime costs	Lifetime QALYs	
Bupropion	1.73	72	-£209	0.07	Dominant
NRT l/s	1.83	82	-£238	0.08	Dominant
Bupropion + NRT l/s	1.93	92	-£229	0.09	Dominant
Varenicline	2.27	125	-£279	0.13	Dominant
E-cigarettes	2.25	123	-£433	0.13	Dominant
Varenicline + NRT l/s	2.58	156	-£337	0.16	Dominant
Varenicline + bupropion	2.75	173	-£401	0.18	Dominant
NRT l&s	2.71	169	-£488	0.18	Dominant
E-cigarettes + NRT l/s	2.93	190	-£620	0.20	Dominant
Bupropion + NRT l&s	3.51	247	-£721	0.26	Dominant

Deterministic sensitivity analysis

Univariate deterministic sensitivity analyses were conducted for several key parameters in the economic model. These included: intervention effectiveness (RR), the probability of cessation at 12-months for placebo; the time horizon; intervention costs; the annual rate of cessation and relapse; the discount rate for costs and QALYs; comorbidity costs; comorbidity disutilities, and applying NHS intervention costs for e-cigarettes.

Applying the lower 95% CI RR values did not affect the pairwise results as each intervention remained cost-effective and dominant (decreased lifetime costs, increased QALYs) versus placebo. However, the DSA affected the fully incremental analysis and there were also substantial changes to the cost-effectiveness ranks. The full results, including those for several additional DSAs are available in the modelling report.

Probabilistic Sensitivity Analysis (PSA)

The results of the PSA, conducted at a cost-effectiveness threshold of £20,000 per QALY are displayed in Table 16. All interventions were highly cost-effective in the pairwise comparison, with each intervention being cost-effective in above 99% of the 3,000 PSA iterations versus placebo.

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

Table 16: PSA results for the base case, cost effectiveness threshold = £20,000

Intervention	Probability cost-effective	
	Pairwise analysis (Vs. placebo)	Fully incremental analysis (Vs. all other interventions)
Placebo	N/A	0%
Bupropion	100%	0%
NRT l/s	100%	0%
Bupropion + NRT l/s	100%	0%
Varenicline	100%	0%
E-cigarettes	99.97%	3.13%
Varenicline + NRT l/s	100%	4.53%
Varenicline + bupropion	100%	10.67%
NRT l&s	100%	4.50%
E-cigarettes + NRT l/s	99.90%	22.87%
Bupropion + NRT l&s	99.93%	54.30%

The results of one of the pairwise comparison (for e-cigarettes versus placebo) is displayed in Figure 3. The figure plots PSA results on a cost-effectiveness plane, each point (in red)

represents one PSA iteration. Interventions are cost-effective if their incremental costs and QALYs fall to the south-east of the cost-effectiveness threshold, equal to £20,000 per QALY.

Figure 3: Cost effectiveness plane e-cigarettes versus placebo

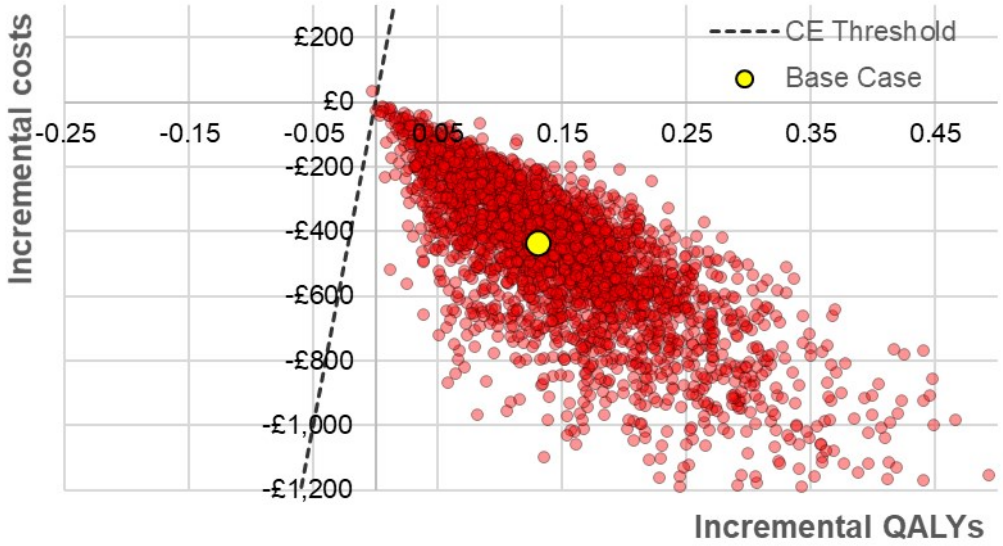
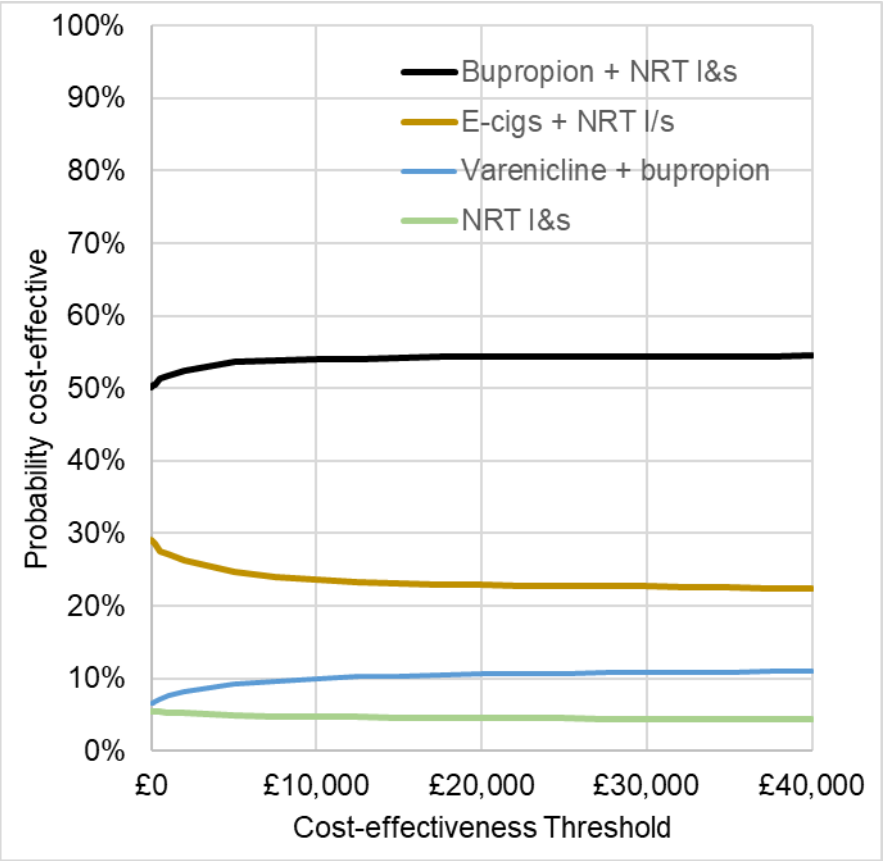


Figure 4 displays the results of the fully incremental PSA in a cost-effectiveness acceptability curve (CEAC) for the four interventions with the largest probability of being cost-effective. The CEAC is a graph summarising the impact of uncertainty on the result of an economic evaluation, frequently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

Figure 4: Cost effectiveness acceptability curves, fully incremental analysis*



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

Scenario analyses

Full incremental analysis excluding placebo

In the scenario analysis placebo was removed and all ten interventions were compared with one-another with NRT l/s acting as the reference category. As with the basecase which included placebo, Bupropion + NRT l&s was the most cost-effective strategy in the scenario analysis. The DSA did not result in any changes to the base case cost-effectiveness results, as bupropion + NRT l&s remained the dominant strategy. Furthermore, each intervention retained the same CE ranking when ordered by NMB.

Applying costs of e-cigarettes to NHS

In the scenario analysis a cost of £55.75 was applied to the NHS. This assumed 48% of costs would be incurred via prescriptions and 52% would be purchased privately OTC. The basecase assumed the cost of e-cigarettes was incurred privately. When including costs for usual care the total costs of: e-cigarettes increased from £82.96 in the base case to £138.71 in the scenario analysis; and e-cigarettes + NRT l/s increased from £131.84 in the base case to £187.59 in the scenario analysis.

The results of the scenario analysis were very similar to the base case analysis. Bupropion + NRT l&s remained the cost-effective strategy. There was a minor change in the results for the e-cigarettes intervention, which became the seventh ranking cost-effective strategy as

opposed to the sixth ranking strategy in the base case analysis (trading positions with varenicline). All other strategies had an identical NMB rank.

Mental health subgroup analysis

Full incremental analysis

The fully incremental analysis identified Bupropion + NRT l/s as the most cost-effective and dominant strategy versus each of the other interventions. This differed from results in the general population where bupropion + NRT l&s was the most cost-effective strategy. Bupropion + NRT l/s had the lowest total healthcare costs (£18,728) and highest lifetime QALYs (12.06) per person, and subsequently the highest net monetary benefit vs. placebo, equal to £6,797 per person. As with the base case analysis, cost-effectiveness was driven by the effectiveness parameters. The RR rank for each intervention directly corresponded with the net monetary benefit rank in the cost-effectiveness analysis (see Table 17). The major difference between the mental health subgroup and the base case analysis were related to the values of lifetime total costs, which substantially increased, and lifetime total QALYs, which substantially decreased.

Table 17 Cost effectiveness results (per person): full incremental analysis for mental health subgroup

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

RR= relative risk versus placebo
CE= cost-effectiveness

Pairwise results vs placebo

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

Deterministic sensitivity analysis (RR values)

In the DSA for the mental health subgroup the effectiveness rates were set equal to the lower and upper 95% CI RR values. Applying the lower value impacted the cost effectiveness of some interventions and rank order of all interventions included in the analysis. For example, bupropion + NRT l&s became the most cost-effective strategy and bupropion + NRT l/s moved from being most cost-effective to being less effective and cost-effective than placebo. In contrast, applying the upper 95% CI values for the RR parameters resulted in all interventions being highly cost-effective versus placebo. The full results are available in the modelling report.

Probabilistic sensitivity analysis

The results of the PSA for the mental health subgroup are shown in Table 18: all interventions were highly cost effective in the pairwise comparison versus placebo. With the exception of NRT l&s, all other interventions had a probability of over 90% of being cost effective at a threshold of £20,000 per QALY.

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

Table 18: PSA results for mental health subgroup, cost effectiveness threshold = £20,000

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

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

Figure 5: Cost-effectiveness acceptability curves, mental health subgroup, fully incremental analysis*

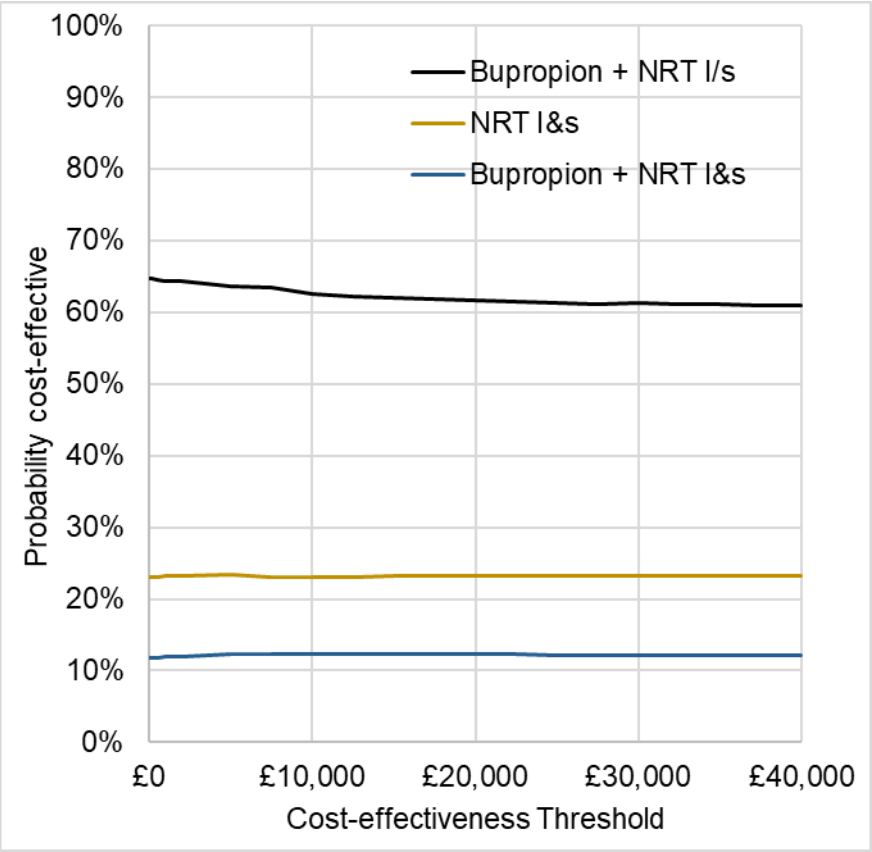


*Figure plots the CEACs for the three interventions with the highest probability of cost-effectiveness. Bupropion, NRT l/s, and varenicline were not included in the graph as the associated probability of cost-effectiveness was insubstantial (i.e. below 2.5%).

Exploratory analyses

E-cigarette health harms

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

Figure 1: E-cigarettes health harms

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

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

E-cigarette uptake

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

The analysis involved two calculations, firstly the total population benefit of e-cigarettes if used for tobacco cessation in current smokers in the UK is approximated. Secondly, the total harm from e-cigarettes in the UK population due to non-smokers taking up smoking due to e-cigarettes is approximated. These values are then summed summed these values to identify the net impact of e-cigarettes in the UK population.

The net impact of e-cigarettes is shown in Figure 7. For example, the results indicate that e-cigarettes would still likely have a positive budget impact if: 1.5% or fewer non-smokers (never smokers and ex-smokers) take up e-cigarettes and 20% of this population become regular tobacco smokers due to e-cigarette use; or alternatively, if 5% or fewer non-smokers (never smokers and ex-smokers) took up e-cigarettes and 5% or of this population become regular tobacco smokers due to e-cigarette use.

Figure 7: E-cigarettes uptake analysis

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

Summary of the evidence

Relative effectiveness at 6 month follow-up

Table 19: Evidence summary for relative effectiveness NMA (cessation at 6 months)

Full results for the relative effectiveness of various treatments for cessation can be found in Appendix J. The below table summarises the results from the mileage chart for the full NMA. Results have been reversed where necessary (where A is shown as better than B in the mileage chart, it has also been reversed to show that B is worse than A in this table).

Cessation at 6 months	Treatments									
	NRT long/short acting	**NRT long & short acting**	**Bupropion**	**Varenicline**	**E-cigarette**	**Bupropion + NRT long/short acting**	**Bupropion + NRT long & short acting**	**Varenicline + NRT long/short acting**	**Varenicline + bupropion**	**E-cigarette + NRT long/short acting**
Treatment* is significantly more effective than:	• Placebo • No drug treatment • Usual care	• Placebo • No drug treatment • Waitlist • Usual care • NRT long/short • Bupropion	• Placebo • No drug treatment • Usual care	• Placebo • No drug treatment • Waitlist • Usual care • NRT long/short • Bupropion	• Placebo • Usual care	• Placebo • No drug treatment • Usual care	• Placebo • No drug treatment • Waitlist • Usual care • Bupropion	• Placebo • No drug treatment • Waitlist • Usual care	• Placebo • No drug treatment • Waitlist • Usual care	• Placebo • No drug treatment • Usual care
Treatment* is significantly less effective than:	• NRT long & short • Varenicline	-	• NRT long & short • Varenicline • Bupropion + NRT long & short	-	-	-	-	-	-	-
An effect was not detected of the treatment* compared with:	• Waitlist • Bupropion • E-cigarette • Bupropion + NRT long/short • Bupropion + NRT	• Varenicline • E-cigarette • Bupropion + NRT long/short • Bupropion + NRT	• Waitlist • NRT long/short • E-cigarette • Bupropion + NRT long/short	• NRT long & short • E-cigarette • Bupropion + NRT long/short • Bupropion + NRT	• No drug treatment • Waitlist • Bupropion • NRT long/short • NRT long & short	• Waitlist • NRT long/short • NRT long & short • Bupropion • Varenicline • E-cigarette	• NRT long/short • NRT long & short • Varenicline • E-cigarette	• NRT long/short • NRT long & short • Bupropion • Varenicline • E-cigarette	• NRT long/short • NRT long & short • Bupropion • Varenicline • E-cigarette	• Waitlist • NRT long/short • NRT long & short • Bupropion • Varenicline • E-cigarette

Cessation at 6 months	Treatments									
	NRT long/short acting	**NRT long & short acting**	**Bupropion**	**Varenicline**	**E-cigarette**	**Bupropion + NRT long/short acting**	**Bupropion + NRT long & short acting**	**Varenicline + NRT long/short acting**	**Varenicline + bupropion**	**E-cigarette + NRT long/short acting**
	long & short • Varenicline + NRT long/short • Varenicline + bupropion • E-cigarette + NRT long/short	long & short • Varenicline + NRT long/short • Varenicline + bupropion • E-cigarette + NRT long/short	• Varenicline + NRT long/short • Varenicline + bupropion • E-cigarette + NRT long/short	long & short • Varenicline + NRT long/short • Varenicline + bupropion • E-cigarette + NRT long/short	• Varenicline • Bupropion + NRT long/short • Bupropion + NRT long & short • Varenicline + NRT long/short • Varenicline + bupropion • E-cigarette + NRT long/short	• Bupropion + NRT long & short • Varenicline + NRT long/short • Varenicline + bupropion • E-cigarette + NRT long/short	• Bupropion + NRT long/short • Varenicline + NRT long/short • Varenicline + bupropion • E-cigarette + NRT long/short	• Bupropion + NRT long/short • Bupropion + NRT long & short • Varenicline + bupropion • E-cigarette + NRT long/short	• Bupropion + NRT long/short • Bupropion + NRT long & short • Varenicline + NRT long/short • E-cigarette + NRT long/short	• Bupropion + NRT long/short • Bupropion + NRT long & short • Varenicline + NRT long / short • Varenicline + bupropion

* This refers to the treatment at the head of each column.

Mental health subgroup

Table 8: Evidence summary for relative effectiveness NMA, mental health subgroup (cessation at 6 months)

Full results for the relative effectiveness of various treatments in those with mental health conditions for cessation can be found in Appendix J. The below table summarises the results from the mileage chart for the NMA of studies conducted in populations with mental health conditions. Results have been reversed where necessary (where A is shown as better than B in the mileage chart, it has also been reversed to show that B is worse than A in this table).

Cessation at 6 months		Treatments				
	NRT long/short acting	**NRT long & short acting**	**Bupropion**	**Varenicline**	**Bupropion + NRT long &short acting**	**Bupropion + NRT long / short acting**
Treatment* is significantly	• Placebo	-	-	• Placebo	-	• Placebo • Usual care

Cessation at 6 months		Treatments				
	NRT long/short acting	NRT long & short acting	Bupropion	Varenicline	Bupropion + NRT long &short acting	Bupropion + NRT long / short acting
more effective than:						• Bupropion
Treatment* is significantly less effective than:	-	-	• Bupropion + NRT long/short	-	-	-
An effect was not detected of the treatment* compared with:	• No drug treatment • Usual care • Bupropion • Varenicline • Bupropion + NRT long/short • Bupropion + NRT long & short	• Placebo • No drug treatment • Usual care • NRT long/short • NRT long & short • Varenicline • Bupropion + NRT long/short • Bupropion + NRT long & short	• Placebo • No drug treatment • Usual care • NRT long/short • NRT long & short • Varenicline • Bupropion + NRT long/short • Bupropion + NRT long & short	• No drug treatment • Usual care • NRT long/short • NRT long & short • Bupropion • Bupropion + NRT long/short • Bupropion + NRT long & short	• Placebo • No drug treatment • Usual care • NRT long/short • NRT long & short • Bupropion • Varenicline • Bupropion + NRT long & short	• No drug treatment • NRT long/short • NRT long & short • Varenicline • Bupropion + NRT long/short

* This refers to the treatment at the head of each column.

Adverse events

This table is an overview of the results presented in GRADE tables 47 to 49. The GRADE tables contain more information about confidence in the evidence and limitations (Appendix F).

Table 9: Evidence summary for adverse events

Comparison	Summary	Confidence	GRADE profile
E-cigarette vs no drug treatment	The results suggested a clinically important increase in irritability in the e-cigarette group compared with the no drug treatment group. The results suggest a clinically important increase in abnormal dreams, anxiety, dry mouth, fatigue, insomnia, nausea, serious adverse events, skin rash and sleep disorders in the e-cigarette group compared with the no drug treatment group, with high uncertainty. The results suggest no clinically important difference in arrhythmia, headache or withdrawal from the study due to adverse events in the e-cigarette group compared with the no drug treatment group, with high uncertainty. The results suggest no clinically important increase in death (all causes) in the e-cigarette group compared with the no drug treatment group.	Moderate to very low	47
E-cigarette vs NRT	The results suggest a clinically important increase in abnormal dreams, depression, non-fatal MI, non-fatal stroke, pruritus and suicidal ideation in the e-cigarette group compared with the NRT group, with high uncertainty. The results suggest a clinically important decrease in anxiety, headache, insomnia, skin rash, palpitations and transient ischaemic attack in the e-cigarette group compared with the NRT group, with high uncertainty. The results suggest a clinically important increase in serious adverse events and hospital admissions in the e-cigarette group compared with the NRT group, with some uncertainty. The results suggest no clinically important difference in fatigue in the e-cigarette group compared with the NRT group, with high uncertainty. The results suggest no clinically important difference in nausea in the e-cigarette group compared with the NRT group, with some uncertainty.	High to very low	48

Comparison	Summary	Confidence	GRADE profile
	The results suggest no clinically important increase in death (all causes) or cardiovascular death in the e-cigarette group compared with the NRT group.		
E-cigarette vs placebo e-cigarette	The results suggest a clinically important increase in fatigue, insomnia and nausea in the e-cigarette group compared with the placebo e-cigarette group, with high uncertainty. The results suggest a clinically important decrease in non-fatal MI in the e-cigarette group compared with the placebo e-cigarette group, with high uncertainty. The results suggest a clinically important increase in abnormal dreams in the e-cigarette group compared with the placebo e-cigarette group, with some uncertainty. The results suggest no clinically important difference in headache, hospitalisation, non-fatal stroke, palpitations or serious adverse events in the e-cigarette group compared with the placebo e-cigarette group, with high uncertainty. The results suggest no clinically important decrease in death (all causes) or cardiovascular death in the e-cigarette group compared with the placebo e-cigarette group.	Moderate to Low (4 studies in this area)	49

Relative effectiveness at short follow-up

This table is an overview of the results presented in GRADE tables 50 to 52. The GRADE tables contain more information about confidence in the evidence and limitations (Appendix F).

Table 10: Evidence summary for short term follow-up (outcome is smoking cessation)

Comparison	Summary	Confidence	GRADE profile
E-cigarette vs placebo e-cigarette	The results suggest no clinically important difference in smoking cessation in the e-cigarette group compared with the placebo e-cigarette group at either 1-3 months or at 3-6 months.	1-3 months: Low (2 studies) 3-6 months: Moderate (2 studies)	50
E-cigarette vs NRT	The results suggest a clinically important increase in smoking cessation in the e-cigarette group compared with the NRT group at 1-3 months.	1-3 months: Moderate (3 studies) 3-6 months: Low (1 study)	51

Comparison	Summary	Confidence	GRADE profile
	The results suggest no clinically important difference in smoking cessation in the e-cigarette group compared with the NRT group at 3-6 months.		
E-cigarette vs no / minimal intervention	The results suggest no clinically important difference in smoking cessation in the e-cigarette group compared with the no / minimal intervention group at 1-3 months. The results suggest a clinically important increase in smoking cessation in the e-cigarette group compared with the no / minimal intervention group at 3-6 months.	1-3 months: Very Low (1 study) 3-6 months: Low (2 studies)	52

In all cases, 1-3 months indicates follow-up of more than or equal to one month but less than three months, and 3-6 months indicates follow-up of more than or equal to 3 months but less than 24 weeks. Follow-up of 24 weeks or more is included in the NMA instead of in the short follow-up analysis.

Economic evidence statements

Annemans (2015) found that re-treatment with varenicline for a smoking cessation was cost-effective compared with re-treatment with bupropion, re-treatment with NRT, re-treatment with placebo and treatment with varenicline followed by re-treatment with placebo. The economic evaluation showed that two quit attempts (2QA) with varenicline dominated all other interventions. Both deterministic sensitivity analyses (DSA) and probabilistic sensitivity analysis (PSA) indicated that the conclusions are robust. For every treatment comparison, the PSA results confirmed that 2QA varenicline was significantly dominated comparators. Due to lack of evidence, it was assumed that NRT and bupropion cessations have equal efficacy for first and second quit attempts. In addition, the author commented that the analysis did not take into account productivity-related costs, likely leading to an underestimation of the economic benefit of 2QA varenicline. The analysis was assessed as partly applicable to the review question, with minor limitations.

One cost-effectiveness analysis (Athanasakis, 2012) found that a 12-week course of varenicline is cost-effective compared with bupropion (12 weeks), NRT (12 weeks) or unaided cessation. The economic evaluation showed that varenicline (12 weeks) dominated all other interventions. The cost per additional quitter for varenicline, considering only the cost of the smoking cessation strategy, was €2,659 (€1,015) for a lifetime horizon compared with bupropion (NRT). When direct costs were incorporated into the analysis, varenicline was cost saving. The analysis was based on a BENESCO (Markov) model. Probabilistic sensitivity analysis suggests, for an implicit €30,000 threshold, varenicline was cost-effective for 82.3%, 86.6% and 85.2% of the Monte-Carlo iterations vs. bupropion, NRT and unaided cessation, respectively. The author comments that the present analysis would be more favourable if a wider perspective of calculation had been taken into account. The analysis was assessed as partly applicable to the review question, with minor limitations.

Coward (2014) found that varenicline (12 weeks) was cost-effective compared with NRT with counselling, NRT alone, counselling alone and no program for smoking cessation in patients with Crohn's disease (CD). The economic evaluation showed that varenicline (12 weeks) dominated all other interventions. The cost savings of varenicline (12 weeks) compared with

no program was 16,116,169 CAD$ over a five year time horizon. Varenicline (12 weeks) remained the most cost-effective strategy until its effectiveness was reduced below 17.7%. Although the model includes health states relating CD, the long-term effects of smoking-related morbidities were not considered. In addition, effectiveness data was taken from multiple sources without the use of meta-analysis. The analysis was assessed as partly applicable to the review question, with major limitations.

One cost-effectiveness analysis (Hagen, 2010) found that varenicline was cost-effective compared with NRT, bupropion and placebo. Results were most sensitive to changes in age, the price of varenicline, average healthcare expenses per person per year and choice of discount rate. However, changes to these parameters did not bring the ICER above the willingness to pay per life year of NOK 500,000. Probabilistic sensitivity analysis showed varenicline was the optimal choice when willingness to pay per life year was above NOK 116,000. Smoking-related morbidities were not included in the model. In addition, annual healthcare cost were assumed the same between smokers and non-smokers. The analysis was assessed as partly applicable to the review question, with minor limitations.

One cost-utility analysis (Hettle, 2012) found that a 12-week treatment of varenicline plus 12 counselling sessions was cost-effective compared with 12 weeks of placebo plus 12 counselling sessions. Three Markov models (BENESCO) were populated using 52-week abstinence rates obtained from a double-blind placebo RCT and cost and utility data from Austria, Germany and Hungary respectively. This analysis was similar to Wilson (2012). The analysis found that from a payer perspective varenicline had an incremental cost-effectiveness ratio per QALY gained of €5,278, €5,867 and €3,183 for Austria, Germany and Hungary respectively. From a societal perspective, varenicline was dominant in all countries. The probabilistic sensitivity analysis found that in all scenarios and countries, varenicline remained cost-effective under a threshold of €12,500 per QALY gained. A minor limitation was that it was unclear if the cost and utility data came from the best sources. The analysis was assessed as partly applicable to the review question since it was set in multiple European countries, but not the UK.

Huber (2018) evaluate the costs, effects and cost-effectiveness of increased reach for smoking cessation interventions in Germany. Current investment interventions included behavioural support, varenicline, bupropion, NRT, and financial incentives. A Markov model (EQUIPTMOD) was populated with efficacy, utility and cost data from Germany. The model established cost-effectiveness for different uptake scenarios where the reach of current investments increased due to an increased number of quit attempts in the population. For scenario 1 uptake attempts were increased by 1% (57,915 total); for scenario 2 intervention uptake was changed to match levels observed in England. Both scenarios were dominant (decreased costs and increased QALYs) vs. current uptake levels in Germany. Secondary outcomes included: returns through reduction in smoking-related health-care costs vs. no intervention for the financial incentive programme (€2.71 per €1 invested), group-based behavioural support (€1.63 per €1 invested) and Varenicline (€1.02 per €1 invested); and ICERs which were dominant for financial incentives, group based behavioural support and varenicline (all vs. no investment). The study was determined to be partly applicable and had major limitations as no uncertainty analysis was conducted around results for the individual interventions.

Kautiainen (2017) found that re-treatment with varenicline for a smoking cessation was cost-effective compared with re-treatment with bupropion, re-treatment with NRT, unaided re-treatment and treatment with varenicline followed by re-treatment with placebo. The economic evaluation showed that two quit attempts (2QA) with varenicline dominated all other interventions. This model was similar to Annemans (2012) but in a Finnish context. Both deterministic sensitivity analyses (DSA) and probabilistic sensitivity analysis (PSA) indicated that the conclusions are robust. Compared with 2QA NRT, 2QA varenicline is

99.9% cost-effective at a willingness to pay threshold of 5,000€ per QALY. It is assumed that the first and second quit attempts for NRT, bupropion and unaided cessation have equal efficacy and that the efficacy estimate for varenicline re-treatment is based on only one RCT. Varenicline retreatment efficacy was investigated in sensitivity analysis. At the lower limit (-20% of base case), 2QA varenicline vs 2QA bupropion gave an ICER of 4,550€/QALY and vs NRT it was 1,584€/QALY with all other comparators dominated. The analysis was assessed as partly applicable to the review question, with minor limitations.

Knight (2012) found that an extended course of varenicline (12 weeks + an additional 12 weeks for those who had remained abstinent), alongside brief counselling, is highly cost-effective compared with 12 weeks of varenicline or bupropion, both with brief counselling, or with brief counselling alone. The economic evaluation showed varenicline (12+12 weeks) compared with varenicline (12 weeks) had an ICER of €1101 per QALY gained over a subject's lifetime. All other interventions were dominated. The analysis was based on a BENESCO (Markov) model. Probabilistic sensitivity analysis suggested an 81.7% likelihood that Varenicline (12+12 weeks) is cost-effective at a willingness to pay of €30,000 per QALY. The author comments that NRT is not considered in the analysis, as it is only available at full cost to the patient. Additionally, the model ignores societal cost that may further improve the cost-effectiveness of the more effective interventions. The analysis was assessed as partially applicable to the review question, with minor limitations.

Li (2019) found that the use of e-cigarettes (EC) to aid smoking cessations was cost-effective compared with nicotine replacement therapy (NRT). The primary analysis was the 12-month cost-effectiveness informed by a self-conducted randomised control trial (RCT) with the secondary analysis a Markov model used to project long-term cost-effectiveness. The economic evaluation of EC compared with NRT gave an incremental cost-effectiveness ratio (ICER) of £1,100 per QALY gained at 12-months and £65 per QALY gained over a lifetime. Probabilistic sensitivity analysis (PSA) estimated an 87% and 85% probability that EC was cost-effective at a £20,000/QALY threshold for 12-months and lifetime horizons, respectively. The lifetime model did not consider the possible long-term effects of using EC on health and personal finance. The author highlights a 35% missing data level from the RCT which makes the analysis less certain. The analysis was assessed as directly applicable to the research question, with minor limitations.

One cost-utility analysis (Linden, 2010) found that a 12-week treatment of varenicline was cost-effective versus both a 7-week treatment of bupropion and unaided cessation. A Markov model was populated using 52-week abstinence rates obtained from numerous studies (including two head to head RCTs of identical study design) and cost and utility data from the Finland. The analysis found that from a Finnish societal perspective varenicline had total cost savings and higher total QALYs than bupropion and unaided cessation, so was dominant. Deterministic sensitivity analysis found that even with major changes of the input values, varenicline remained dominant below the ICER threshold of £30,000 (€33,200) over a lifetime horizon. Probabilistic sensitivity analysis found that, when the willingness-to-pay threshold was €10,000, varenicline was cost-effective compared with bupropion (unaided cessation) 65% (80%) of the time. The study was determined to be partly applicable to the research question since it was set in Finland and had no limitations.

One cost-utility analysis (Lock, 2011) found that a 12-week treatment of varenicline plus weekly counselling sessions and a booklet, was cost-effective versus 12 weeks of placebo with the same co-therapies. A Markov model was populated using 52-week abstinence rates obtained from a double-blind placebo RCT and cost and utility data from the UK. The analysis found that from the NHS's perspective varenicline had an incremental cost-effectiveness ratio per QALY gained of €4478. Probabilistic sensitivity analysis found that at an implicit threshold of €30,000 per QALY gained, varenicline had a high probability of being

cost-effective when compared with placebo. The study was determined to be partly applicable to the research question as the population focused on COPD patients, It had minor limitations since it is unclear whether some of the cost and utility data came from the best sources.

Von Wartburg (2014) found that 12 weeks of varenicline followed by a further 12-week course for successful quitters (varenicline 12+12 weeks) was highly cost-effective compared with standard varenicline treatment (12 weeks only). Both varenicline (12+12 weeks) and varenicline (12 weeks) dominated alternative smoking cessation interventions (NRT and bupropion). The analysis was based on the lifetime BENESCO model using the same quit rates as Knight (2010) and applying costs for a Canadian setting. From the payer perspective varenicline (12+12 weeks) led to an incremental cost per QALY of CAD$3,758 compared with standard varenicline treatment. For a societal perspective, which included indirect health and productivity costs, varenicline (12 + 12 weeks) was dominant compared with all alternatives. Cost-effectiveness was driven by increased quit rates reducing the number of smoking related comorbidities and smoking related deaths across model's lifetime time horizon. Probabilistic sensitivity analysis (PSA) showed that varenicline (12+12 weeks) had a 95% probability of being cost-effective at a willingness to pay threshold of CAD$30,000 per QALY compared with varenicline (12 weeks) and 100% compared with the other interventions (from the payer perspective).The analysis was assessed as partly applicable to the review question with minor limitations.

One cost-utility analysis (Wilson, 2012) found that a 12-week treatment of varenicline plus 12 counselling sessions was cost-effective versus 12 weeks of placebo plus 12 counselling sessions. Four Markov models (BENESCO) were populated using 52-week abstinence rates obtained from a double-blind placebo RCT and cost and utility data from Belgium, Spain, Portugal and Italy respectively. This analysis is similar to Hettle (2012). The analysis found that from a payer perspective varenicline had an incremental cost-effectiveness ratio per QALY gained of €6,120, €5,151, €5,357 and €5,433 for Belgium, Spain, Portugal and Italy respectively. From a societal perspective, varenicline was dominant in all countries. The one-way sensitivity analysis determined that assumptions on cost parameters did not exhibit a strong influence on outcomes. It also found time horizon had no significant influence. The probabilistic sensitivity analysis found that all countries had an ICER between willingness to pay thresholds of €4,000 and €10,000 per QALY gained. There were minor limitations: it is unclear if the efficacy, cost and utility data came from the best sources available and whether the efficacy data (UK adapted from a US study) was suitable. The analysis was assessed as partly applicable to the review question since it was set in multiple European countries, but not the UK.

One directly applicable cost-utility analysis with minor limitations found that multiple pharmacotherapies (NRT l/s, NRT l&s, bupropion and varenicline) combined with behaviour support and e-cigarettes combined with behaviour support were dominant (i.e. less costly and more effective than the comparator). The base case results for the fully incremental analysis indicated Bupropion + NRT l&s was the most cost-effective strategy and was dominant versus each of the other interventions having the lowest total healthcare costs (£10,802) and highest lifetime QALYs (15.37) per person, and subsequently the highest net monetary benefit vs. placebo, equal to £5,928 per person. In addition to a series of DSAs and PSAs, several scenario analyses were carried out as well as a subgroup analysis of people with mental health problems. The latter found that all interventions assessed were highly cost effective versus placebo.

Harm reduction treatments

Review question

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

Introduction

Electronic cigarettes (e-cigarettes) are a relatively new technology. Their effectiveness for harm reduction in relation to commonly used pharmacotherapies is not certain.

The only commonly used treatment for harm reduction in England is NRT. The effectiveness of e-cigarettes, and their relative effectiveness compared with NRT (categorised as either "long- or short-acting NRT" or "long- and short-acting NRT"), is uncertain and may affect patient choice. This review aims to establish whether e-cigarettes are effective and cost effective for harm reduction.

PICO table

The following table summarises the protocol for this review.

Table 11: PICO inclusion criteria

Criteria	Detail
Population	Anyone aged 18 and over who smokes and wants to reduce their harm from smoking without stopping completely. **Excluded**: People who do not smoke Pregnant and breastfeeding women People aged 17 and under People who want to stop using smokeless tobacco but not smoking.
Interventions	E-cigarettes containing nicotine **Excluded**: Therapies not licensed in the UK. Alternative and complementary therapies. Psychotherapies (unless included as co-treatment with an included smoking therapy). Therapies that are either smoked or contain tobacco.
Comparator	NRT (either single- or multi-mode) No intervention or usual care E-cigarettes without nicotine ('placebo e-cigarette')
Outcomes	**Critical outcomes** Harm reduction status at longest available follow-up (minimum 6 months). Measured as reduction in validated biochemical measures: • Carbon monoxide in expired air or blood sample • Urinary cotinine • Anabasine and anatabine in urine. Cessation: Smoking status at longest available follow-up (minimum 6 months). Measured as abstinence from smoking (relative risk).

Criteria	Detail
	Where continued abstinence is presented, this is preferred over point-prevalence abstinence. Point prevalence measures will only be used where no continuous measure is reported. Where biochemically validated measures are available (i.e. saliva cotinine / carbon monoxide validation), these will be preferred to self-reported measures. Self-reported measures will only be used where no validated measure is reported. **Important outcomes** • Reduction in smoking-related symptoms: ○ Cough ○ Phlegm ○ Shortness of breath ○ Wheezing • Adverse or unintended (positive or negative) effects of e-cigarettes when used for cessation or harm reduction at any time point, including: ○ Adverse effects such as headaches, nausea, throat irritation or dry mouth. Health-related quality of life of using e-cigarettes for cessation or harm reduction (using validated patient-report measures, for example EQ-5D).

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and in the methods chapter.

This review addresses an intervention question. Randomised evidence was assessed using the Cochrane Risk of Bias 2.0 tool, according to the NICE Manual. All GRADE ratings start at 'high' and are downgraded as appropriate. See appendix F for full GRADE tables.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Protocol deviation

The divide between cessation and harm reduction according to the protocol was intention of the participants: cessation studies had participants intending to quit; harm reduction studies had participants not intending to quit, but to reduce harm. The NMA produced by Thomas (2020) for the cessation part of this review used slightly different inclusion criteria, and so included some studies where participants did not intend to quit, but the study was clearly measuring cessation as an outcome. Therefore, *smoking cessation* and *adverse events* from those studies were reported in the cessation part of this review, where they met the other inclusion criteria. It was not anticipated that adverse events for e-cigarettes would be meaningfully different in people intending to stop smoking compared with those intending to reduce their harm, supporting the argument for combining them.

Only one study (Caponnetto 2013) reported other harm reduction outcomes of e-cigarettes (reduction in smoking-related symptoms and expired CO). Not enough data was extractable (for example, ranges) to be useful for making recommendations, and therefore this paper was also excluded from the review.

Minimal Important Differences (MIDs)

The following MIDs were applied to the outcomes in this review.

Table 12: Minimal Important Differences (MIDs) agreed

Outcome	Importance	MID
Smoking cessation	Critical	Statistical significance
Reduction in validated biochemical measures (CO, cotinine etc.)	Critical	Default (RR 0.8-1.25)
Reduction in smoking-related symptoms (cough, phlegm, shortness of breath, wheezing)	Important	Default (RR 0.8-1.25)
Adverse events	Important	Default MIDs
Health-related quality of life (HRQoL) measures	Important	Published MIDs if available for individual measure, otherwise default.

Identification of public health evidence

Included studies

A single search was used to identify relevant studies for this part of the review. No date limit was applied to the search and studies published in any year were eligible, as this is a new review question. The systematic search was undertaken in July 2019 for studies published in the English language. Website searches were not conducted for this review. Further details on the search strategy are available in appendix B.

After removal of duplicates, 1,233 unique database results were identified. 30 articles were ordered for full-text review. No studies were included in this review. The same search was rerun in November 2019. Ninety-four items were identified. One was requested for full-paper assessment, and none met the inclusion criteria.

A study identified in the surveillance review was already included from the database search. No additional studies from the surveillance reviews were included.

Excluded studies

See Appendix G for a full list of excluded studies and the reasons for exclusion.

Summary of public health studies included in the evidence review

No studies were included in this review.

Economic evidence

A systematic search was carried out to cover the questions in this evidence review (i.e. RQ 6.1a for cessation & RQ6.1b for harm reduction). The search returned 3576 records. Of these records 3409 records were excluded based on information in the title and abstract for both RQ 6.1a and RQ6.1b. Both reviewers assessed all of the records. The level of agreement between the two reviewers was 100%.

The full-text papers of 167 documents were retrieved and assessed.13 studies were assessed as meeting the eligibility criteria for RQ 6.1a and no studies were assessed as meeting the eligibility criteria for RQ 6.1b. Both reviewers assessed all of the full texts. The level of agreement between the two reviewers was 100%. The excluded references are listed with their reasons for exclusion are listed in Appendix G – Excluded studies. The selection process is shown in Appendix G.

Economic model

In the absence of effectiveness evidence no economic modelling was undertaken for the review question on tobacco harm reduction (RQ6.1b).

Summary of the evidence

No evidence was identified.

The committee's discussion of the evidence

Review questions

Note: Expert testimony has been drawn on throughout this discussion section (see Appendix K for full proformas), indicated by *(ETX).* For example (ET1) refers to Expert Testimony 1.

Interpreting the evidence

The outcomes that matter most

1a.: The critical outcome was biochemically validated cessation at 6 months follow-up. Self-reported measures were not accepted. The same outcome was used for assessing effectiveness of e-cigarettes between 1 and 6 months follow-up. Adverse effects and health related quality of life related to use of e-cigarettes were important outcomes. The adverse effects of the other interventions in the review, which have been licensed for use for cessation, are known and have been previously evaluated. The committee agreed that effectiveness of e-cigarettes should be taken account of alongside adverse events, and the benefits and harms considered. Cessation outcomes reported in studies where the aim was harm reduction rather than cessation were included in 1a. rather than 1b. (see *Methods and process* for more information).

1b.: Critical outcomes were a reduction in biochemically validated measures of smoking (exhaled CO, urinary cotinine or other commonly used measures) at 6 months. A meaningful reduction in these markers of smoking was interpreted by the committee as indicating a potential reduction in harm sustained from smoking.

Important outcomes included a reduction in smoking-related symptoms, which was considered to be an important but less reliable marker of a reduction in harm from smoking. Adverse events and health related quality of life related to e-cigarettes were also important outcomes.

The quality of the evidence

Harm reduction

No data was identified on harm reduction. The committee agreed with the approach taken for the NMA (1a.), which included both people who intended to quit and people who intended only to reduce their harm from smoking (see *Methods and process*). The committee also discussed that the link between harm reduction (temporary abstinence or cutting down numbers of cigarettes per day) and health benefits is still uncertain. Based on this, the committee decided that smoking cessation rather than dual use should be the focus of recommendations, and did not make recommendations about the potential use of e-cigarettes for harm reduction.

Short follow-up

The committee had low confidence in the results for the effectiveness of e-cigarettes at less than 6 month follow-up when compared with placebo e-cigarettes, NRT or no / minimal intervention. A variety of factors contributed to this, as explained below.

There was only a small amount of data: six studies were identified with 3,835 participants in total. A maximum of three studies were able to be combined in any single meta-analysis, due to different comparators or follow-up times. This meta-analysis had wide confidence intervals, often including the line of no effect (the MID for this outcome).

The data did not appear to be coherent. It is accepted that NRT is effective for cessation. Despite this, e-cigarettes appeared to be more effective than NRT (at 1-3 months) but no better than placebo e-cigarettes at the same time period. This pattern is not observed at later follow-up points, so could be a result of small numbers of participants. It could also be an indicator of the importance of the behavioural element of e-cigarette use (which is present in both nicotine-containing and nicotine-free e-cigarettes).

The studies were somewhat heterogeneous: although the committee decided that the studies should be statistically combined, they acknowledged the variations in the studies. One study (Lee 2018) investigated cessation in pre-operative patients who, the committee discussed, might have an increased motivation to quit compared with the those in the other studies. Another study (Halpern 2018) took place in a workplace, and despite having the largest sample size, had very low uptake of any intervention, this may be due to the included participants not having actively chosen to take part in the study. Type of e-cigarette device used may also introduce heterogeneity: studies did not always clearly report e-cigarette generation, but the committee agreed that Bullen (2013) and Lee (2018) would have used first generation e-cigarettes and that these may be less effective due to generally containing lower levels of nicotine and potentially providing a less satisfying experience (see *review L: barriers and facilitators to using e-cigarettes*).

The committee agreed that although short term cessation outcomes may indicate longer term cessation outcomes, there was not enough good quality evidence at this stage to draw any robust conclusions. They discussed the frequency of relapse to smoking in the initial stages of cessation. Therefore, they decided to consider and make recommendations based on the evidence for cessation at 6 months.

NMA – cessation

Behavioural interventions

The committee discussed the fact that a large majority of the studies included in the NMA investigated the drug intervention as an adjunct to a behavioural intervention which was present in both intervention and control arms. The results should therefore be interpreted as the effect of the intervention in combination with behavioural support. They also noted that the behavioural element of the included studies varied widely from minimal contact (brief advice or short telephone calls) to intensive courses of behavioural counselling.

Using an NMA assumes that the included studies are similar in terms of factors that may interact with the intervention effects, this is the same assumption that is made when undertaking a pairwise meta-analysis. For the majority of the studies in this review the intervention included a pharmacotherapy or e-cigarette and a behavioural aspect to the intervention and the control arm included the same behavioural aspect. The nodes have therefore been categorised by the pharmacotherapy or e-cigarette intervention as the behavioural aspect was in all arms. The committee acknowledged that in a minority of studies included in the NMA, there was an imbalance in how intense the behavioural intervention was between arms. In most of these cases the arm receiving the intervention under investigation (pharmacotherapy or e-cigarettes) also received a more intensive

behavioural intervention than the comparator arm, but the inverse also occurred. For this small number of studies this could result in an overestimation of the intervention effect in assuming that all of any effect seen was due to the pharmacotherapy or e-cigarette aspect of the intervention, while a more intensive behavioural intervention in this arm may have interacted causing the resultant effect. This is a limitation of the NMA, as the NMA attributed the effect of *intervention under investigation plus behavioural elements* to *intervention under investigation* alone (see Appendix I and J and table 16 for full explanation). The committee discussed and agreed that they did not consider that this affected any particular interventions more than other interventions in a way which was likely to impact the results of the NMA, the studies would remain as part of the NMA. There were also inconsistency checks completed as part of the quality assurance on the NMA, further details on these can be found in Appendix J.

Characteristics of included studies

The committee considered the characteristics of the included studies. The committee noted that a large number of studies (59/192) were considered to be at high risk of bias, which resulted in serious risk of bias for the full NMA in GRADE. They noted that this was often due to studies not blinding participants or personnel to the allocated treatments. They discussed that although blinding reduces bias, it may be very difficult to achieve in these studies, and therefore took this into account when interpreting the results.

The committee discussed the overall number of participants in the NMA. They noted that they may have expected to see a larger number of participants (n = 92,067) bearing in mind the accepted critical importance of the smoking cessation, and the length of time it has been researched. This implied the relative paucity of studies investigating bioverified outcomes to 6 months.

The committee discussed that the results for interventions investigated by fewer studies should be interpreted with some caution as they rely on few sources of data. Some interventions were included in a large number of studies (for example NRT long/short acting [n = 116]). where others – mainly combinations of treatments – appeared infrequently (for example bupropion + NRT long & short acting [n = 2], varenicline + bupropion [n = 2] and e-cigarette + NRT long/short acting [n = 2]). This concern is somewhat reduced in the NMA, where estimates are less sensitive to any one source of data, however the committee agreed that the evidence was not certain enough to recommend specific combinations of treatments.

Confidence in the NMA was reduced by the risk of bias and by inconsistency indicated by the better fit of a random effects model for between studies. The committee agreed that although the overall the confidence in the results of the full NMA was low, recommendations could be made due to the large amount of data for this cessation outcome and strong association between the outcome at 6 months and a longer-term behavioural change.

Mental health subgroup NMA

This subgroup included studies taking place in populations with mental illness. Mental illness includes both common mental disorders (CMD), for example anxiety and depression, and severe mental illness (SMI) for example schizophrenia. Most of the included studies took place in people with SMI. The subgroup NMA was small, with only 13 studies included. This may be in part attributable to many studies in groups with mental illness tailoring the intervention to the needs and context of the individuals, resulting in not being able to classify studies in a way that allowed their inclusion in the NMA. This smaller NMA had wider confidence intervals and was not able to differentiate effectiveness of active treatments from each other. The NMA was judged to have serious imprecision in GRADE. There was very serious risk of bias in the NMA, due to 6/13 studies having high risk of bias. The NMA was also downgraded for inconsistency (for the same reasons as the full NMA, above). This resulted in very low confidence in the results of the network.

The committee discussed these limitations, and whether they would expect the treatments to act differently for a population with mental illness compared with the general population. They noted that there has historically been a focus on groups with mental illness as different from the general population; either requiring different approaches or the view that the mental illness should be addressed or treated before – or instead of – their smoking. The committee agreed that this is not an appropriate approach due to the severity of the impact smoking has on people with mental health conditions. People with SMI in particular may have a life expectancy 20 years lower than that in the general population, part of which is attributable to smoking. The committee further noted that although smoking rates have substantially decreased in the general population, for those with mental health conditions rates have remained stagnant, indicating an increasing health inequality which needs addressing. The committee also discussed that beliefs that have been held in the past (such as that people with mental health conditions often do not want to quit, or that quitting will be detrimental to their mental health) are increasingly being challenged by new research and should not form the basis for decisions about offering cessation treatment (ET4).

The committee agreed that there should be a considerable focus on stopping smoking for those with mental health conditions. They agreed that interventions that work for the general population are also likely to work, and should be provided in the same way, and equitably, for people with mental illness. Therefore, the committee did not use this subgroup NMA to make recommendations. Instead, they combined their experience of smoking cessation in people with mental illness with the results of the full NMA, an analysis in which there were fewer concerns about quality and generally higher confidence in the findings.

Adverse events

Of the 9 studies which reported on adverse events of e-cigarettes, 5 were at high risk of bias. The main concern was a lack of blinding of participants and personnel, where comparators were noticeably different from each other. The committee discussed that where the comparator arm was an active intervention like NRT – in which case blinding was often not carried out – participants might reasonably expect adverse events from either intervention. However, lack of blinding of personnel could be more problematic and could bias results in favour of the new treatment under investigation.

The committee also noted that one study (Cravo 2016) was funded by Fontem ventures, a tobacco organisation (see NICE's statement on engagement with tobacco industry organisations). The study was included in line with NICE's methods for dealing with data from tobacco organisations. This study provided the only data for most outcomes comparing e-cigarettes to no drug treatment (continued smoking), with the exception of nausea which was also contributed to by Carpenter (2017). Results from Cravo (2016) were similar to results from the other studies, which had very low precision meaning there was no clinically important difference in most adverse events between e-cigarette and the comparator.

The committee discussed the fact that the low event rates and widespread imprecision seen in the adverse events outcomes may be attributed to studies not being powered for these outcomes (primary outcomes were effectiveness). Although adverse event outcomes were difficult to draw conclusions from, the committee did further discuss them when making recommendations about e-cigarettes – see benefits and harms section below for detail.

Benefits and harms

Effect sizes

The committee discussed the effect sizes seen in the evidence, noting that the absolute cessation rates in many of the studies appear to be quite low, though this was something that tallied with their experience. The committee discussed that even a small increase in cessation has a public health impact. They discussed the complex nature of tobacco

addiction, noting that addiction to smoking includes both physical as well as behavioural and psychological aspects and can therefore be very strong.

Technical discussion of NMA results

The committee discussed the four comparator treatments (placebo, no drug treatment, waitlist, usual care), and how to interpret effects in relation to these. They noted that the placebo node was comprised of placebo versions of all included treatments. This means that the estimate for *treatment vs placebo* is not comparing the treatment to only the placebo version of itself, but to all placebos. The usual care arm was discussed, and the committee noted that this is likely to include a wide range of interventions due to the varied settings and countries that the studies took place in, they discussed that usual care in the UK may be very different to the usual care in non-UK based studies. In both cases, they agreed that this did not reduce their certainty in the usefulness of those estimates but was borne in mind for their interpretation.

The committee discussed that NMA results may be different from pairwise results of the same comparison. The NMA used a random effects model, this averages the heterogeneity from all the results and applies that average. If the result has higher heterogeneity in the NMA, the NMA result will have wider credible intervals, potentially changing the conclusion about whether an intervention is effective against a given comparator. Where a result has lower heterogeneity in the NMA, the credible intervals will narrow. Credible intervals are also narrowed where the addition of indirect evidence increases precision of the effect estimate.

Choosing a treatment for cessation

The committee had agreed that there was no plausible reason for any of the active interventions to act differently for a population with mental health conditions. Expert testimony (ET4) highlighted that the same issues, both in terms of addiction to smoking and attitudes towards the various treatments, are likely to be present for both the general population and for people with mental health conditions, and that persistent beliefs that people with mental illness are not interested in quitting or that quitting interferes with recovery are false. The remainder of this discussion draws on the full NMA and applies to both the general population and those with mental illness unless otherwise specified.

The committee agreed that the evidence supported doing something over doing nothing. They strongly agreed that people interested in stopping smoking should be given a choice of treatments, and that the relative effectiveness presented in this review should not be a reason to narrow or restrict the range of cessation treatments available through stop smoking support. They agreed that the provision of information on the potential benefits and harms of each option was crucial to facilitate discussion and ensure informed choice. The same treatment may work differently for different people depending on the nature of their addiction, their previous experience of products, previous cessation attempts, what they value about smoking and other lifestyle factors. The committee decided that these factors should all be taken into account alongside effectiveness, and that all recommendations about cessation treatments should be centred around making sure individuals have the information to feel empowered to make their own choice. This includes information on any cost that the individual might incur; how the product works, how best to use the products, what is currently known about adverse events and long-term harms of each intervention; and information on the difference between the continued use of nicotine and continuing to smoke.

The committee did not consider it appropriate to rank each individual treatment in the recommendations – individual factors and preferences are likely to play a large role which may supersede small differences in effectiveness. The committee discussed their experience of individuals wanting to incorporate research evidence or the practitioner's expertise into their decision-making, and for this reason the committee decided to use the NMA results to identify what interventions were likely to be most and least effective.

They also discussed that as many of the included studies are unblinded, whether there may have been some impact on the effectiveness of participants knowing that they were receiving a combination treatment. As discussed previously the committee noted that many initial and subsequent attempts to stop smoking are often not successful. They discussed the importance of providing different options to encourage a further quit attempt.

The committee discussed the combination treatments and noted that many of these are not currently used in practice. This is because in their experience, there are concerns over adherence to multiple interventions given that it is difficult for people who want to quit smoking to adhere to a single intervention. The committee were also concerned that there may be difficulty in obtaining prescriptions for multiple products. Also the committee commented that, based on the NMA and their experience, the effectiveness of the combinations appears to be attributable to the NRT component.

The committee agreed that while the combination of bupropion + NRT long / short acting was the most cost-effective option, this combination was not significantly better than NRT alone in the effectiveness analyses. The committee also acknowledged that this combination has been used in the past but this is no longer common practice in many stop smoking services.

For the combination of e-cigarette + NRT long/short the committee discussed the limited evidence available (2 studies) and noted that this is a combination of a medicinally licensed and unlicensed products. They further discussed the similarities of how they are used by those seeking to stop smoking. Thus they agreed that they would not recommend this combination treatment.

The committee expressed caution regarding the use of combination varenicline + bupropion, they noted that this is not used in practice and that there may be uncertainties about the combined side effects or interactions. There were only 2 studies that investigated this combination (compared with varenicline) and the committee agreed that they would not recommend this combination treatment.

The combination of different forms of NRT (short acting and long acting) and different methods of delivery was shown to be effective and so the committee recommended these as an option for smoking cessation.

Overall, as the other combinations showed similar effectiveness to the individual interventions alone, the committee recommended the use of individual treatment options and this specific combination of short and long acting NRT options.

The committee discussed and agreed that varenicline and NRT long and short acting were likely to be the most effective pharmacotherapies which are licensed for cessation, and bupropion and long acting *or* short acting NRT may also be helpful for achieving cessation from smoking but may be less effective treatments. The committee noted that bupropion is not often used in practice, despite being investigated by 44 included studies.

The committee further discussed and agreed that e-cigarettes may be similarly effective to varenicline or NRT long and short acting, however they are not medicinally-licensed and no long-term health effects data are available, specifically in relation to harms. Some committee members suggested that e-cigarettes can be thought of as a type of short acting NRT in terms of how they deliver nicotine, but not medicinally-licensed for smoking cessation. The committee discussed and agreed that although there was more uncertainty around the effect of e-cigarettes, possibly due to the small number of studies,, they were still effective. They further noted that as there are ongoing e-cigarette studies and that future additional evidence

in this area may alter the findings of the NMA. There were many more studies for the other cessation interventions. They also discussed that it is not clear in some of the studies which generation of e-cigarettes was being used noting that the older generations of e-cigarettes may have been less helpful for smoking cessation as the nicotine levels in these were lower. The increasing evidence being published can be seen during the reruns searching during the development of this guideline which identified a further four studies for inclusion in relation to the use of e-cigarettes for smoking cessation. The committee noted that there was a recent UK based e-cigarette study that did not meet the inclusion criteria as these criteria specified biochemically validated cessation at 6 months follow up. This study considered e-cigarettes and behavioural intervention compared with NRT long/short acting and behavioural intervention in 886 participants. The cessation outcomes were bioverfied at 3 and 12 months, the outcomes at 6 months were self-report. A sensitivity analysis was undertaken that included this additional UK e-cigarette study (Hajek, 2019). This involved the running of an NMA that included the Hajek (2019) study to consider whether additional studies on e-cigarettes have the potential to further impact on the findings of this analysis. findings of this sensitivity analysis (see Appendix J) did show differences in the NMA outcomes, further supporting the view that e-cigarettes are an effective option for smoking cessation. Therefore, it is important that further research is undertaken regarding the use of e-cigarettes for smoking cessation.

Based on committee expertise and evidence from the qualitative review of barriers and facilitators to e-cigarettes (review [L]), the committee discussed the fact that many people who choose to quit smoking using NRT or e-cigarettes are concerned about the continued use of nicotine. The committee agreed that it was important for people to understand the importance of stopping smoking, and to be reassured that nicotine is not the major cause of damage to people's health from smoking. The committee noted that for NRT to be effective for cessation, people must use it in a way that ensures they get enough nicotine. Nicotine-containing e-cigarettes may present more of a challenge in terms of knowing how to match the level of nicotine, particularly as different types or generations may facilitate differing intake, and e-liquid is available in many different nicotine strengths. Seeking advice from a health practitioner may help as they may be able to obtain up to date information from PHE, or from the NCSCT training materials on e-cigarettes.

The committee were aware of concerns about the use of varenicline by people with mental illness. They agreed it was important that practitioners were aware that there appears to be no increased risk of neuropsychiatric effects in people who use varenicline (see the Summary of Product Characteristics for CHAMPIX [emc, 2019] and the Royal College of Psychiatrists' position statement [2018] for more information). Expert testimony (ET4) highlighted that people with mental health conditions are disproportionately burdened by smoking and the resulting adverse health effects. The committee emphasised the importance, supported by expert testimony (ET4), of addressing smoking in this group by making all effective interventions available for use (while acknowledging that bupropion is an antidepressant which needs consideration when prescribed to certain subgroups). They agreed that varenicline should be available for those with mental illness in the same way as for the general population. Expert testimony (ET4) put forward that smoking cessation support should be a core part of mental health care provision rather than an optional element. Committee agreed the importance of supporting smoking cessation in this group. They considered that this should be explored alongside other support provided and discussed a possible role for dedicated stop smoking advisers as part of the mental health service.

Cost effectiveness and resource use

The committee considered evidence from 13 published cost effectiveness analyses. They noted 12 were assessed as partly applicable and 1 as directly applicable, 11 had minor limitations and 2 had potentially serious limitations. They observed that 12 studies assessed varenicline and 1 study assessed e-cigarettes.

One study (Lock 2011), which included a UK population, found 12-weeks of varenicline plus weekly counselling sessions and a booklet was cost-effective vs. 12 weeks of placebo with same co-therapies in a population with COPD. The remaining 11 non-UK studies of varenicline differed by course length. Seven studies established cost-effectiveness for a standard length course of varenicline vs. comparators including bupropion, NRT, placebo. Two studies established cost-effectives of varenicline for multiple quit attempts vs. varenicline for single quit attempt (& bupropion & NRT for multiple quit) and 2 studies established cost-effectiveness for an extended course of (12 weeks + 12 weeks for quitters) vs. standard 12 weeks course of varenicline, bupropion and NRT.

The committee agreed the evidence was comprehensive and robust in showing varenicline is cost-effective vs. bupropion, NRT, placebo and unaided cessation. However, they were mindful that four studies were informed by efficacy data from a single RCT.

The committee noted the results were consistent across multiple countries and considered it reasonable to assume non-UK results are applicable. They also noted multiple and extended courses of varenicline are likely to be cost-effective vs. shorter varenicline courses including for multiple quit attempts and extended courses to prevent relapse.

One UK study (Li 2019) found e-cigarettes were cost effective compared with nicotine replacement therapy. The finding was associated with a high level of certainty at 12 months (87%) and across a lifetime horizon (85%) using a cost effectiveness threshold of £20,000/QALY. Whilst the committee accepted the results of the study they were mindful the model did not consider the possible long-term effects of using e-cigarettes on health and personal finance and noted the high level of missing data (35%) from the RCT.

The committee discussed whether the main drivers were cost of treatment, effectiveness and difference in health care costs of the lifetime. They agreed the evidence pointed to intervention effectiveness as the main driver and as opposed to the cost of the intervention. The committee agreed that unless there are very small differences in effect sizes or very large differences in intervention in general economic models will identify most effective interventions as cost effective because the long term benefits of stopping smoking are so pronounced.

Economic model

General population

The committee discussed the results from the de novo economic model which assessed ten pharmaceutical interventions using evidence from the network meta analysis reported in this review (Evidence review K). In the basecase analysis which included the cost of the interventions to the NHS, the committee observed that bupropion, NRT l/s and l&s, varenicline, bupropion + NRT l/s, varenicline + NRT l/s, varenicline + bupropion and bupropion + NRT l&s were all dominant meaning they were more effective and less costly than the comparator.

The committee noted e-cigarettes only or combined with NRT l/s were dominant (more effective and less costly than the comparator) and this finding applied irrespective of whether the costs were assumed to be incurred over the counter (i.e. £0.00 cost to the NHS) or by the NHS (scenario analysis). They also noted that including an additional study of e-cigarettes (Hajek et al 2019) in the network meta-analysis impacted the results of the economic analysis such that E-cigarettes + NRT l/s became the most cost-effective strategy. The inclusion also impacted the NMB rankings with e-cigarettes moving from rank six in the base case analysis to the third rank in the scenario analysis (see Appendix J for results). As indicated above, the committee were mindful that the evidence base on this topic is still emerging and that future studies may change the conclusions. However, based on the evidence available to date the committee agreed e-cigarettes should be included in the list of cost-effective interventions recommended for smoking cessation.

The committee observed across all base case and deterministic scenarios, that when any intervention was more effective than placebo, it was also cost-effective. They also observed the PSA identified very low levels of uncertainty regarding the cost-effectiveness of each intervention versus placebo.

The committee noted the results assume pharmacological interventions are delivered alongside behaviour support because the estimates of effectiveness are from studies which included behaviour support in the intervention and comparator arms. They discussed the timing of the benefits and agreed that whilst some of these can take 10 to 15 years to accrue others may accrue in a relatively short timescale such as myocardial infarction which showed a decline in incidence just 1 year after the smoking ban was introduced.

The committee considered the findings of the full incremental analyses which showed bupropion + NRT l&s was the most cost-effective intervention strategy having the lowest healthcare costs and highest lifetime QALYs per person. When ordered by NMB they observed the cost effectiveness ranking of each intervention remained the same with or without the inclusion of the placebo. They also noted the incremental findings were associated with high levels of uncertainty. For example, in the PSA bupropion + NRT l&s was cost-effective in 54% of PSA iterations but was not the most cost-effective strategy in the remaining 46% of iterations. Given the uncertainty and limited number of studies for some of the interventions the committee agreed there was no convincing evidence to sequence the recommendations for interventions based on their individual rankings.

The committee agreed the economic model is likely to have underestimated the benefits of smoking cessation as many other outcomes were not included such as impact on other smoking related diseases, co-morbidities and associated costs, benefits to local authorities and public sector more widely as well as benefits to employers through reduced sickness absence and increase productivity and financial benefits to individuals who quit smoking.

Mental health subgroup

The economic model was also used to assess the cost effectiveness of six pharmacotherapies for the sub-population with mental health problems. Using evidence from the network meta-analysis the basecase analysis for this subgroup showed that NRT (l/s and l&s), bupropion, varenicline, and bupropion + NRT (l/s and l&s) were all cost effective versus the comparator. As with the basecase for the general population all interventions for the mental health subgroup were dominant resulting in more QALYs than the comparator and healthcare savings.

The committee noted that in the DSA when the effectiveness rates were set to equal the lower 95% CI three interventions - NRT l&s, bupropion + NRT l/s and bupropion - moved from being cost effective to being less effective and more costly than the comparator. The other interventions remained cost effective. However, in the PSA which considers the uncertainty in the value of multiple parameters in the model, five of the interventions had a probability of >90% of being cost effective versus the comparator at a threshold of £20,000/QALY. Only NRT l&s had a lower probability (79%) which the committee considered sufficient evidence to support including it among the interventions recommended for the subgroup with mental health problems.

E-cigarette health harms and uptake

The committee had concerns regarding the cost effectiveness of e-cigarettes as there is currently no evidence to indicate whether they are safe over the long term. To address their concerns an exploratory threshold analysis was carried out to determine the level of adverse events at which e-cigarettes would not be cost effective compared with usual care. The committee noted the analysis suggested e-cigarettes would need to cause a very high number of adverse outcomes before they were considered not to be cost-effective versus placebo. For example, e-cigarettes would not be cost effective if more than 10% of people

who used them experienced an adverse event, and the net cost per adverse event was equal to £25,000 which is similar to the 5-year treatment costs for stroke (NICE CG92).

The committee were also concerned that e-cigarettes might promote smoking uptake by acting as a gateway to tobacco smoking in non-smoking populations. The results of the exploratory analysis indicated that e-cigarettes would have a net positive impact on health and healthcare resources if acting as a gateway to tobacco smoking in up to 0.25% on the non-smoking UK population. This value is equivalent to 2.5% of non-smokers taking up e-cigarettes and up to 10% of this population subsequently taking up tobacco smoking. Based on the evidence seen by the committee, some members agreed it would be useful to include research recommendation on whether the use of e-cigarettes increases the chance of a non-smoker taking up cigarettes.

Overall discussion of evidence across multiple reviews

Gaps in the evidence

The committee noted that smoking prevalence is not distributed equally throughout society. A range of inequalities were identified in the Equality Impact Assessment (EIA), including inequalities by socioeconomic status, sexual orientation, and mental illness. Published evidence to address these inequalities was limited, and the committee concluded that there was not enough evidence to make recommendations for specific groups. They highlighted this as a gap in the evidence that could be addressed with expert testimony. Expert testimony provided to the committee on these inequalities is relevant to multiple reviews and is detailed in full in this review (Appendix K). It is referenced throughout the committee discussion where it has been drawn on in decision-making.

The Medicines and Healthcare products Regulatory Agency (MHRA) provided expert testimony on e-cigarettes and the Yellow Card Scheme, including current information on adverse events and monitoring.

Implications of recommending e-cigarettes

This section on the implications of recommending e-cigarettes covers discussion that the committee had in relation to a number of e-cigarette reviews:

- Reviews F and G: e-cigarettes and young people
- Review K: cessation and harm reduction treatments
- Review L: barriers and facilitators to using e-cigarettes for cessation or harm reduction
- Review M: long-term health effects of e-cigarettes.

The committee have made recommendations that all e-cigarette use (including both nicotine-containing e-cigarettes and e-cigarettes without nicotine) should be discouraged in children, young people and young adults who do not smoke, and that the products should be clearly differentiated from tobacco products. It is also recommended that nicotine-containing e-cigarettes are discussed with people interested in stopping smoking. To support this the committee has made recommendations about the advice that people providing stop smoking support should give people about e-cigarettes, in order that people can make informed decisions The committee have also recommended that nicotine-containing products are included as options for sale in secondary care settings (for example in hospital shops).

Use by young people

Evidence on e-cigarette use by children, young people and young adults is presented in reviews F and G.

The committee discussed the implications of making recommendations about e-cigarettes as an effective intervention for smoking cessation. The committee were aware of the wider

international discussions about the use of e-cigarettes by children, young people and young adults who do not smoke (see *reviews F and G: e-cigarettes and young people* for a full discussion of the identified evidence). The included studies showed an association between use of e-cigarettes and ever smoking in the future. The committee noted that a small proportion of children, young people and young adults who have never smoked use e-cigarettes, and therefore might be exposed to this increased risk of trying smoking in the future. The committee discussed that the size of the risk of taking up smoking following e-cigarette use is somewhat uncertain as many of the studies have considerable limitations. They also discussed that it is possible that people moving from e-cigarettes to smoking might have been at higher risk for smoking for other reasons (for example, peer or family smoking).

There is no benefit to never-smokers using e-cigarettes and because the harm of smoking is so great, the committee agreed there was justification to strongly discourage use of e-cigarettes in these groups. The current review indicates that e-cigarettes are likely to be effective for cessation, and so the committee agreed that children, young people and young adults should not be told that e-cigarettes are to be avoided by all people at all times, and that e-cigarettes should be clearly differentiated from tobacco products. They agreed that the emphasis should be placed on discouraging use of e-cigarettes among never smokers.

Long-term health effects and safety of e-cigarettes

Evidence on long-term health effects of e-cigarettes is presented in review M.

A very small amount of evidence which was at high risk of bias was identified from database searches, and no new evidence was identified through the call for evidence process (see *review M: long-term health effects of e-cigarettes* for the full discussion on the evidence). The committee were concerned about the lack of evidence about harms in comparison with licensed treatments and recommended that research should be conducted. They noted that possible long-term outcomes may take decades to emerge and will require carefully planned studies to reliably identify them.

The committee agreed that the severity of smoking harms was so high that it was important to discuss e-cigarettes further as an option despite the lack of evidence on any long-term health effects. They noted the importance of weighing up harms and benefits of using e-cigarettes in relation to the alternatives:

- Cessation using licensed treatments: The committee heard expert testimony (ET1) that gave the view that for some e-cigarettes have become the preferred smoking cessation aid, exceeding licensed products. While the committee emphasised that licensed products offer much greater certainty about side effects and harms, they recognised evidence (see *review L: barriers and facilitators to e-cigarettes*) that many people found using e-cigarettes convenient and a more satisfying experience compared with NRT. These factors may contribute to their effectiveness and may be particularly important for people who have attempted to stop smoking unsuccessfully using licensed products in the past.
- Continued smoking: For many people who smoke, the alternative to using e-cigarettes might be continued smoking. The extensive harms of smoking are well known, and it is considered unlikely that use of e-cigarettes could cause similar levels of harm. The committee noted and discussed the evidence reviews produced annually by PHE, the most recent of which states that “vaping regulated nicotine products has a small fraction of the risks of smoking, but this does not mean it is safe” (PHE 2020, p.10). Evidence from studies to support this was not found for review M, but the committee drew on their knowledge of the components of e-cigarettes compared with tobacco cigarettes to agree that vaping is likely to be less harmful than smoking.

The committee also discussed the development of events around e-cigarettes in the US reported on by the CDC (2019) and others, and the UK response to these. They noted that the latest findings suggest that the events (which included lung injury and death) have been linked to vaping tetrahydrocannabinol (THC) and vitamin E acetate oil. These compounds are not permitted in e-cigarettes in the UK. E-cigarettes are more tightly regulated in the UK

than in the US, and nicotine-containing e-cigarettes are regulated through the Tobacco and Related Products Regulations 2016 (TRPR). Although the MHRA has received reports of 4 deaths which were suspected as being related to vaping through its Yellow Card Scheme, 2 of the deaths happened before the implementation of TRPR and PHE states that in all the deaths the connection with nicotine-containing e-cigarettes has not yet been established (PHE 2020).

In order to address the potential risk posed by using e-cigarettes which contain harmful compounds not permitted in the UK, the committee noted that e-cigarettes should not be customised by adding components or mixing e-liquids. The committee agreed the importance of providing those thinking about using e-cigarettes to stop smoking with clear and up-to-date information, This recommendation is also supported by evidence from *review L: barriers and facilitators to using e-cigarettes*, which found that people had concerns about how to use e-cigarettes safely and whether contents were properly regulated.

The committee heard expert testimony directly from the MHRA about the monitoring of e-cigarettes through the Yellow Card Scheme (ET5). Signalling evidence collected through the Scheme is preliminary and, although it has not raised any particular concerns relating to e-cigarettes, it relies on voluntary reporting. The committee chose to recommend that health professionals ask those using e-cigarettes about any possible adverse effects or safety concerns with their use, and report these using the Yellow Card Scheme to support the growing evidence base. This supports advice from the MHRA on how healthcare professionals can be vigilant for suspected adverse reactions associated with the use of e-cigarettes (MHRA 2020). The committee also heard about the need to work with trading standards to ensure that only e-cigarette devices which have been notified to the MHRA are in circulation.

The committee recognised that while most of the other recommended treatments are usually used for a defined period, and stopped within a number of months, people using e-cigarettes to stop smoking may be more likely to use them for longer. A view from an Expert testimony (ET1) highlighted that some groups tending to use e-cigarettes for longer periods after cessation had been more dependent on tobacco, and so longer use of the devices after a quit may have been necessary to prevent relapse. The committee discussed that e-cigarettes may need to be used for as long as is necessary to prevent relapse. They emphasised that this practice made it especially important to give people up to date information on long-term harms, which are currently not known (see review M: long-term health effects of e-cigarettes for more details about evidence on long-term harms, and about the call for evidence NICE conducted in this area).

The committee discussed that the size of the population that could benefit from using the devices – and the size of the benefit that could be delivered – warranted recommending e-cigarettes as an option for cessation, alongside continued monitoring and evidence gathering. The committee noted that the recommendations take place in a context in which e-cigarettes and related advertising are tightly regulated, and suspected adverse reactions are being monitored.

Adverse events of e-cigarettes

The committee agreed that considering adverse events of e-cigarettes was important (the adverse effects of the other treatments in this review, which have been licensed for use for cessation, are well-known). Possible adverse events of all treatments should be communicated to people looking to quit. The committee highlighted that adverse events should be discussed with emphasis on the very considerable health benefits of stopping smoking. They agreed that many of the adverse event outcomes recorded for e-cigarettes may be linked with stopping smoking, and so may occur as a result of cessation regardless of the method used. The committee considered this as likely to be the case in the single significant result for adverse events: significantly increased irritability in those using e-cigarettes compared with no drug treatment (continued smoking) (see *Summary of the*

evidence). They added that this was feasible even when nicotine containing therapies were used for cessation, as many people do not match their previous levels of nicotine consumption.

The committee discussed serious adverse events (SAE) in detail. This outcome was reported for e-cigarettes when compared with no drug treatment, NRT and placebo e-cigarettes. None of these comparisons showed e-cigarettes to result in significantly more events. In addition, the committee noted the diverse range of events included in this outcome, including hospitalisation and knee surgery. Based on this information and that the studies were not powered to detect adverse event outcomes, the committee were not confident that the outcomes could be attributed to the intervention. They considered most of the adverse events to be outweighed by the significant and well documented benefits of stopping smoking.

See also section in the economic discussion around adverse events and cost effectiveness.

Making e-cigarettes accessible

The committee discussed the method of provision for e-cigarettes. They recognised that e-cigarettes are categorised as appliances rather than medicines. This means that they can only be prescribed if they are listed in part IX of the NHS Electronic Drug Tariff. E-cigarettes are not currently listed in the tariff. This means that e-cigarettes must be provided by other means. The committee chose to recommend that commissioners and providers of stop smoking support make e-cigarettes accessible along with the other evidence-based interventions. Expert testimony (ET4) identified that the cost of e-cigarette devices may be prohibitive for some groups, particularly disadvantaged groups or those with mental health conditions. The committee discussed that there are various ways that e-cigarettes could be made more accessible, and that schemes already exist in some local areas that are trialing these. For example, stop smoking support could focus on being 'e-cigarette friendly' by ensuring that support (for example, behavioural support) is still provided to people using e-cigarettes as part of a quit attempt and providing evidence-based advice about e-cigarettes; e-cigarettes could be offered for sale in some health settings, or the devices and / or e-liquid could be offered free of charge or through a voucher scheme for a set period of time.

The reviews in this guideline did not look at evidence about the most effective ways of making e-cigarettes accessible for cessation. The committee agreed that decisions about how to make e-cigarettes accessible should be made at a local level dependent on how stop smoking services and other relevant settings are set up and link together. They discussed the fact that this area may develop over the lifetime of this guideline.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.12.1 to 1.12.6, 1.12.13 to 1.12.17, 1.14.19, 1.22.1 to 1.22.2, 1.22.14, and the research recommendations on health effects of e-cigarettes, stop-smoking interventions for under-served groups, support for people with mental health conditions to stop smoking, e-cigarettes for harm reduction, use of e-cigarettes (amount and frequency), and e-cigarette flavours. Other evidence supporting these recommendations can be found in the evidence reviews on barriers and facilitators to e-cigarettes (review L), long-term health effects of e cigarettes (review M), smoking relapse prevention (review N) and tailored interventions for those with mental health conditions (review O).

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