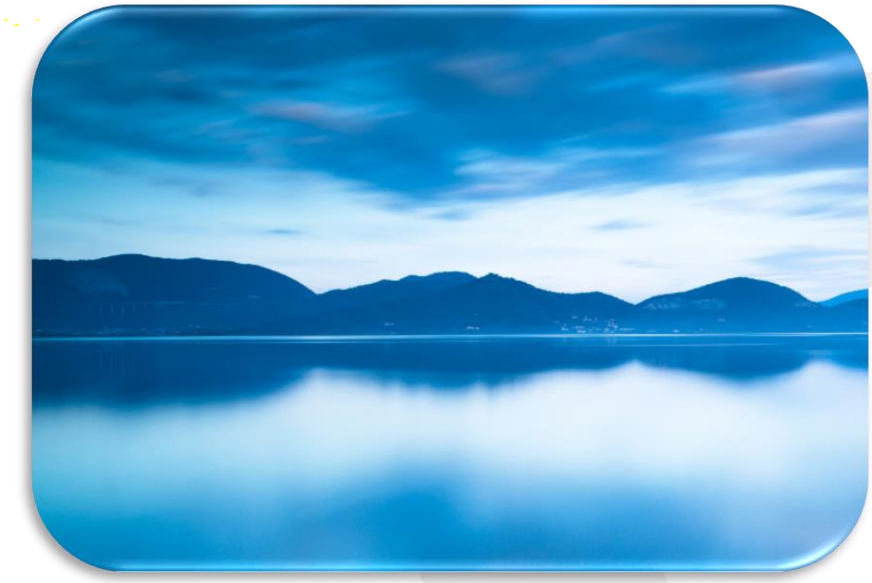
Electronic cigarettes and smoking cessation: An evidence review



Authors:

Joan Quigley

Helen Kennelly

Caitriona Lee

Doireann O'Brien

Michelle Williams

Anne McCarthy

Jean Long

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t 353 1 234 5000
f 353 1 661 2335
e hrb@hrb.ie
w www.hrb.ie

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Abbreviations

Abbreviation	Explanation
BMJ	British Medical Journal
CI	Confidence interval
CrI	credible interval
DOH	Department of Health
e-cigarette(s)	electronic cigarette(s)
e-liquid	electronic liquid
ENDS	electronic nicotine delivery systems
ENNDS	Electronic non-nicotine delivery systems
EU	European Union
FTND	Fagerström Test for Nicotine Dependence
GN-SBQ	Glover-Nilsson Smoking Behavioral Questionnaire
HIQA	Health Information and Quality Authority
HRB	Health Research Board
IQR	interquartile range
LCI	Lower confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
NHS	National Health Service
NIHR	National Institutes for Health Research
NMA	network meta-analysis
NRT	nicotine replacement therapy
Placebo EC	placebo e-cigarette without nicotine
PRESS	Peer Review of Electronic Search Strategies
RCT(s)	randomised controlled trial(s)
RoB2	Cochrane Risk of Bias (Version 2) tool
RR	relative risk
SD	standard deviation
UK	United Kingdom
UCI	Upper confidence interval
USA	United States of America
WHO	World Health Organization

Executive summary

Purpose

In 2013, the Department of Health's Tobacco Policy Review Group published the report Tobacco Free Ireland, which set a target for Ireland to reduce smoking prevalence to less than 5% by 2025. Tobacco Free Ireland was the first policy document to be launched under the Department of Health's Healthy Ireland framework, and it was endorsed by the Government. Achieving the 5% smoking prevalence target in the reduction of smoking prevalence would play a major role in realising the vision set out in Healthy Ireland. The Tobacco Free Ireland report identified tobacco-related harm reduction as a key issue for consideration. It specifically highlighted the role of electronic cigarettes (e-cigarettes) as a potential harm reduction strategy. Since the introduction of e-cigarettes in 2006, research has expanded on the potential benefits and public health harms of e-cigarettes. This systematic evidence review outlines what is known to date about e-cigarette and heat-not-burn tobacco devices' efficacy in terms of smoking cessation in randomised controlled trials (RCTs) and adverse events recorded in those trials, which will help to inform the Department of Health's policy position with respect to e-cigarettes.

Questions

- What is the efficacy and safety of e-cigarettes in helping people who smoke to achieve abstinence (smoking cessation)?
- What is the efficacy and safety of heat-not-burn tobacco products in helping people who smoke to achieve abstinence (smoking cessation)?

Methods

We used systematic review techniques to complete this review. These included a systematic search, double screening, assessment of bias, formal extraction of data and a feasibility assessment to decide if we should do meta-analysis. Searches were carried out in February 2020 in the following databases: Ovid MEDLINE, Cochrane Library, and Elsevier Embase. We searched for randomised controlled trials (RCTs) of e-cigarettes or heat-not-burn tobacco products compared with electronic non-nicotine delivery systems (ENNDS) or placebo heat-not-burn tobacco products, or any comparator treatment or combination of treatments usually given for smoking cessation. Our primary outcome of interest was smoking cessation as defined by European Medicines Agency guidance, measured at 6 months or 1 year after treatment initiation. Verified data were preferred, but self-reported data were also included. In addition, we extracted data on adverse events.

We analysed the trial data using network meta-analysis, which is a statistical technique for comparison of three or more treatments in a single analysis by combining direct and indirect evidence in a single network. We used the 'gemtc' package in R version 3.6.0 to conduct a network meta-analysis of smoking cessation at 6 months for e-cigarette trials.

Findings: e-cigarettes

Study characteristics

Nine RCTs reported in 15 publications met the inclusion criteria for efficacy (N=7) and safety (N=9) of e-cigarettes in helping people who smoke to achieve abstinence (smoking cessation). Two trials reported safety data only. The number of participants in the RCTs ranged from 30 to 2,012. Of the nine trials, two were based in Italy, three in the USA, two in the UK, and one each in South Korea and New Zealand. On average, participants in the included RCTs were males aged 40–50 years who were dependent, heavy smokers. The participants were a mix of those who were motivated to quit and those who had no intention to quit. One trial appeared to include lighter smokers, and the influence of this trial on the network meta-analysis was examined through a sensitivity analysis.

The two studies included for safety data only allowed participants to have nicotine doses of 24-48mg/mL.

Smoking cessation data reported at 24 or 26 weeks and 52 weeks were included. Self-reported data, which was then biochemically verified, was preferred over self-reported status only, and unverified data was excluded in a sensitivity analysis to test its impact on the overall network meta-analysis results.

Risk of bias

The HRB carried out a risk of bias analysis using the Cochrane Risk of Bias (Version 2) tool for randomised trials. Of the included nine RCTs, eight were at a high risk of bias. These ratings were mainly driven by missing outcome data. The numbers lost to follow-up were high in nine RCTs, and the proportions of successful cessation events were low in the RCTs, both of which introduced uncertainty to the results of this systematic review.

Smoking cessation

The network meta-analysis of smoking cessation at 24 or 26 weeks is based on seven RCTs.

Using NRT as the reference treatment, the incidences of smoking cessation at 24 or 26 weeks are very similar in both the ENDS and the NRT groups (RR: 1.17; 95% Credible Interval [CrI]: 0.61–1.99), which indicates there is no evidence for a difference in effect. Electronic non-nicotine delivery systems (ENNDS) are somewhat less effective in achieving smoking cessation than NRT (RR: 0.65; 95% CrI: 0.24–1.42), but the result is not statistically significant. NRT is more effective than no additional treatment and this result is statistically significant (RR:0.35; 95% CrI: 0.11-0.88).

Three sensitivity analyses were carried out. The first excluded the RCT which appeared to include lighter smokers, the second included only those RCTs which had biochemically verified their smoking data, and the third excluded the study with a lower dose of nicotine from the ENDS arm. The results of these sensitivity analyses indicate that the main analysis is robust to assumptions relating to the smoking history of participants and inclusion of unverified data, and marginally less robust to the assumption of nicotine dose.

The HRB was unable to undertake a network meta-analysis of smoking cessation at 52 weeks due to limited data; only three RCTs reported data for this timepoint.

Findings: heat-not-burn tobacco products

There were no RCTs that met the inclusion criteria for the question on efficacy of heat-not-burn tobacco products in helping people who smoke to achieve abstinence (smoking cessation).

Two studies reported adverse event data for heat-not-burn tobacco products. The Cochrane Risk of Bias (Version 2) tool was used to assess risk of bias in these two RCTs and both were found to be at a high risk of bias. No conclusions could be reached from these data and further research is needed if these tobacco products are to be considered as a safe smoking cessation tool.

Adverse events: e-cigarettes and heat-not-burn tobacco products

This systematic review found that standardised definitions were not used to collect data on adverse events in all of nine included studies. Data on several of the adverse event categories recommended for observation by the European Medicines Agency were not captured in all the included studies. These included the cardiovascular category (where only three out of the nine studies reported adverse event findings) and the psychiatric category (where, once again, only three out of the nine studies reported findings).

Pulmonary events were consistently monitored in six of the nine trials studied. Respiratory symptoms that were collected included shortness of breath and cough. For all reported adverse events, the incidence was lower in the control arms (NRT or ENNDS) than in the e-cigarette arm, except for shortness of breath in one study and cough in one study.

No serious adverse events were designated as being related to treatment in the four studies that reported serious adverse events; however, the procedure for determining if a serious adverse event was related to the smoking cessation intervention was often unclear.

The adverse events in this study were all collected over a short period of time (≤ 12 months), and longer-term studies are therefore needed in order to fill this knowledge gap.

Level and certainty of evidence

We assigned a Level 2 evidence rating using the Centre for Evidence-Based Medicine levels of evidence guidelines, as we had seven RCTs in the network meta-analysis, but six of the seven trials had a high risk of bias. With respect to the certainty of evidence, we believe that there is low certainty of evidence that e-

cigarettes have the same levels of success in achieving smoking cessation as other medically approved (by the Health Products Regulatory Authority in Ireland or the European Medicines Agency) cessation interventions, based on the results of the network meta-analysis at 6 months, because of the high risk of bias in six of the seven trials, the low number of successful events in the trials, and the high dropout rates.

There is a very low certainty of evidence that e-cigarettes have the same levels of success in achieving smoking cessation as other medically approved cessation interventions, based on three trials, for smoking cessation at 52 weeks, and therefore results are inconclusive.

For heat-not-burn tobacco products, there is a very low (or no) certainty of evidence for using these tobacco products as a smoking cessation intervention.

Strengths and limitations

The main strength of this systematic review is that it used a comprehensive search strategy that is likely to have captured all relevant trials and that it adds five new trials to the statistical synthesis by Cochrane, leading to an updated systematic review of the topic.

The main limitation of this review is that e-cigarettes are not a standardised intervention. A variety of first- and second-generation e-cigarettes were tested, and the nicotine doses varied.

Other limitations of this review are the small sample sizes in the examined trials and the low number of participants achieving smoking cessation. Seven RCTs reported smoking cessation at 24 or 26 weeks, and only three of those also reported smoking cessation at 52 weeks. In addition, loss to follow-up was very high and exceeded 20% in at least one arm of eight of the nine included trials

During the 12-week observation period that followed the active treatment period, participants could purchase further smoking cessation therapies; these data were not recorded by most of the trials. One trial asked participants to sign a commitment not to use the non-assigned treatment for at least 4 weeks after their quit date.

The power of the comparisons between the comparator arms of the HRB's network meta-analysis would have been increased if we had widened our inclusion criteria to RCTs examining medically approved cessation therapies as well as behavioural therapies that were not compared directly to e-cigarettes. However, our brief was to examine the efficacy of e-cigarettes and their contribution to smoking cessation.

Conclusions

The systematic review and network meta-analysis of electronic nicotine delivery systems (e-cigarettes) versus therapies usually given for smoking cessation showed that there is no evidence of a difference in effect on incidences of smoking cessation. There is a low-level of certainty in these results due to low successful event rates and high rates lost to follow-up in all studies.

The systematic review of evidence for heat-not-burn tobacco products showed that there is no evidence from RCTs on efficacy for smoking cessation compared with current standard care, and insufficient evidence on the safety of heat-not-burn tobacco products from RCTs.

Identified respiratory adverse events, including shortness of breath and cough, appeared to be higher in electronic nicotine delivery systems users, but in the main, RCT evidence on adverse events is lacking. The long-term data on electronic nicotine delivery systems, in line with European Medicines Agency recommendations, are limited for both smoking cessation and adverse events, and further large-scale research using a standardised product to decrease uncertainly at the 1-year timepoint and beyond is needed.

1 Introduction

1.1 Policy background

In 2013, the Tobacco Policy Review Group published *Tobacco Free Ireland*, a report which set a target for Ireland to reduce smoking prevalence to less than 5% by 2025.[1] *Tobacco Free Ireland* was the first policy document to be launched under the Healthy Ireland framework, and it was endorsed by the Government. Achieving the target in the reduction of smoking prevalence would play a major role in realising the vision set out in Healthy Ireland.

The *Tobacco Free Ireland* report identified tobacco-related harm reduction as a key issue for consideration.[1] It specifically highlighted the role of electronic cigarettes (e-cigarettes) as a potential harm reduction strategy. Since e-cigarettes' launch in the European Union (EU) in 2006 and in the United States of America (USA) in 2007, research on their potential benefits in terms of tobacco-related harm reduction, and on the public health harms of e-cigarettes, has grown.

The DOH asked the Health Research Board (HRB) to complete a programme of research and to answer five research questions:

1. What are the public health benefits and harms of e-cigarettes?
2. What are the public health benefits and harms of heat-not-burn tobacco products?
3. What is the efficacy and safety of e-cigarettes in helping people who smoke to achieve abstinence (smoking cessation)?
4. What is the efficacy and safety of heat-not-burn tobacco products in helping people who smoke to achieve abstinence (smoking cessation)?
5. Does e-cigarette use by adolescents who are cigarette naive at baseline lead to subsequent cigarette smoking?

1.2 Research questions

We answer the following questions in this systematic review:

- What is the efficacy and safety of e-cigarettes in helping people who smoke to achieve abstinence (smoking cessation)?
- What is the efficacy and safety of heat-not-burn tobacco products in helping people who smoke to achieve abstinence (smoking cessation)?

2 Background

2.1 E-cigarette devices

It is generally accepted that e-cigarettes were launched in the EU in 2006 and in the USA in 2007. Since then, the e-cigarette industry has represented a burgeoning dynamic market with rapid product innovation. E-cigarettes encompass a wide range of battery-operated devices that vaporise or, more correctly, aerosolise nicotine and other contents for inhalation. There are currently four generations of e-cigarettes. As of 2014, more than 460 different e-cigarette brands and 7,000 unique electronic liquid (e-liquid) flavours were reported to have been for sale on English-language Internet sites.[2] These numbers are likely to have increased considerably between 2014 and 2019.

2.2 Existing research on e-cigarettes and smoking cessation

We identified two systematic reviews and a health technology assessment that investigated the effect of e-cigarette use on smoking cessation.

2.2.1 Systematic reviews

Using a systematic review approach, Hartmann-Boyce *et al.* evaluated the safety and effect of using e-cigarettes to help people who smoke to achieve 'long-term smoking abstinence'.[3] They included people defined as current smokers at the time of their enrolment into the studies, where participants could be motivated or unmotivated to quit.[3] The authors included randomised controlled trials (RCTs) in which smokers were randomised to e-cigarettes or to a control intervention, which measured abstinence rates at 6 months or longer in order to determine the efficacy of e-cigarettes as an aid to smoking cessation. For adverse events and biomarkers, the authors included randomised crossover trials and cohort follow-up studies with a follow-up of greater than 1 week. They compared nicotine e-cigarettes to non-nicotine or placebo e-cigarettes; e-cigarettes to alternative smoking cessation aids, including nicotine replacement therapy (NRT) or no intervention; and e-cigarettes used in combination with standard smoking cessation treatment (behavioural or pharmacological or both) to standard treatment alone. They measured cessation at the longest follow-up point, which was at least 6 months from the start of the intervention, and "using the strictest definition of abstinence".[3(p8)] The authors only identified two completed RCTs[4,5] that contributed data on cessation at 6 months or longer.

Hartmann-Boyce *et al*. concluded that a limited number of RCTs had been reported; hence, certainty about the effects of e-cigarettes on smoking cessation was low. They noted that more data are needed in order to "strengthen confidence in the estimates",[3(p23)] and there was evidence from the pooled results of two trials that e-cigarettes with nicotine, compared with placebo e-cigarettes, helped smokers to stop smoking long term. They added that there was evidence from one trial that e-cigarettes may lead to 6-month quit rates similar to those achieved with NRT, but that the confidence interval (CI) was wide. They also acknowledged that "e-cigarettes are an evolving technology and the effects of newer devices with better nicotine delivery are unknown".[3(p. 23)]

El Dib *et al.* also conducted a systematic review focusing on e-cigarettes and smoking cessation, and they reported similar findings to Hartmann-Boyce *et al*.[6] Using pooled data from two RCTs with a combined total of 481 participants, they concluded that there was evidence for a possible increase in tobacco smoking cessation success rates when e-cigarettes were used in comparison with electronic non-nicotine delivery systems – that is, a placebo e-cigarette without nicotine.[6] However, the authors point out that the 95% CI of the relative risk crossed 1.0, and therefore the evidence was of low certainty.

2.2.2 Health technology assessment

The Health Information and Quality Authority (HIQA) carried out a health technology assessment of smoking cessation interventions in Ireland. The assessment aimed to examine the clinical effectiveness, safety, and cost-effectiveness of smoking cessation interventions, in addition to the organisational, societal, and ethical implications of "potential changes to the mix of treatments that people use to help them stop smoking".[7(p10)] Two trials were pooled, and neither of the trials reported a statistically significant benefit. Both trials had absolute quit rates in the control and intervention arms that were low compared with average absolute quit rates in trials of NRT. The report concluded that due to the limited number of RCTs and the rapidly evolving range of e-cigarette products, there is a high level of uncertainty regarding the clinical effectiveness and cost-effectiveness of e-cigarettes. It also noted that the long-term health effects of e-cigarettes are unclear, and

highlighted concerns that “their widespread promotion by health professionals could normalise nicotine consumption or act as a gateway to using tobacco for new generations of people who have never previously smoked”.[7(p28)]

3 Methods

This systematic review is part of a wider project assessing the public health harms and benefits of e-cigarettes and heat-not-burn tobacco products; a single standard systematic search approach was used for the five questions outlined in Section 1.1. The methods in this section refer to question 3 and 4 only.

3.1 Information searches

Literature searches were carried on the 26 and 27 February 2020. The databases used were Ovid MEDLINE, Elsevier Embase (www.embase.com) and the John Wiley & Sons Cochrane Library, including Cochrane CENTRAL. The full search strategies for these searches are available from Appendix A. The concepts included in the search were e-cigarettes/heat-not-burn tobacco products, and randomised controlled trials (RCTs). For the MEDLINE search, the Cochrane highly-sensitive RCT filter was used.[8] Search results (n=1,880; of which Ovid MEDLINE n=344, Embase n= 827, Cochrane (trials only) n=709) were combined and deduplicated in Endnote X9.1. When duplicates were removed the number was reduced to 1,396. These results were dual screened by the researcher (JQ) and the information specialist (CL).

3.2 Eligibility criteria

The eligibility criteria used in this systematic review is given in Table 1.

The European Medicines Agency recommends continuous smoking abstinence (smoking cessation) as the primary endpoint in trials of medicinal products.[9] The European Medicines Agency concedes that while different terms may be used for the smoking cessation outcome in trials, its definition should reflect continuous abstinence rate without slips or episodes of relapse to smoking throughout the follow-up period and this is the definition which the HRB used in this systematic review. This guidance also recommends a 12-month endpoint for analysis. However, many trials only report up to the 6-month timepoint, and so we have included both 6-month (24 or 26-week) and 12-month (52-week) timepoints.

Table 1 Eligibility criteria

Element	Inclusion	Exclusion
Population	Current regular smokers	Non-smokers Subgroups of smokers; pregnant women and those with mental health illness Dual users
Intervention	**E-cigarette** (electronic device containing nicotine) ± usual care (i.e. smoking cessation counselling), or **heat-not-burn tobacco products** ± usual care (i.e. smoking cessation counselling) **Time on treatment ≥6 weeks**	E-cigarettes in combination with other active treatments such as NRT or pharmacological interventions
Control	Placebo e-cigarette (without nicotine) or any comparator treatment or combination of treatments usually given for smoking cessation	Regular cigarettes Denicotinized cigarettes
Outcomes	Smoking cessation: Continuous abstinence measured at 6 months or 1 year after treatment initiation Adverse events	
Study design	RCTs	Crossover design Conference abstracts
Language	Studies published in English	

In order to undertake a statistical analysis as described in section 3.6, one treatment must be specified as a reference treatment against which all other treatments will be compared. For this analysis, we have selected NRT as the reference treatment because it is currently recommended for use in Ireland,[7,10] and because it was a common control treatment in the RCTs identified.

3.3 Screening

Studies were compared against the inclusion criteria in Section 3.2 in order to determine inclusion. Abstracts (JQ and CL) and full-text articles (JQ, JL and CL. JL and CL split one round of screening) were screened independently by two researchers, and disagreements were resolved by discussion until a consensus was reached.

3.4 Data extraction

Data were extracted into a bespoke data extraction form by a single reviewer (HK), and data were verified by a second reviewer (JQ). The following data were extracted:

- Date and place of publication
- Study design
- RCT inclusion and exclusion criteria
- Study participant characteristics
- Summary of intervention and control conditions
- Number of participants in each arm
- Smoking cessation outcomes
- Biochemical validation
- Adverse events, and
- Assessment timepoints.

3.4.1 Adverse events

Adverse events are undesirable symptoms which occur during a trial and may or may not be related to the treatment given. As well as referring readers to specific guidance for safety assessments in clinical trials, the European Medicines Agency lists specific adverse events of interest:[9]

1. Interactions
2. Vital signs
3. Psychiatric adverse events
4. Cardiovascular and pulmonary compromised patients
5. Nicotine-conjugate antigens, and
6. Rebound and withdrawal and addiction potential.

As this study focused on RCTs only, we did not extract data on interactions; interactions tend to be the focus of non-RCTs conducted earlier in the medicinal product development cycle. We also did not extract data on nicotine-conjugate antigens, as vaccinations against nicotine were not interventions or comparators of interest. Therefore, we extracted data for the remaining four adverse events categories (splitting cardiovascular and pulmonary adverse events into two categories). In addition, we included a category for serious adverse events, as serious adverse events should be routinely reported by clinical trials. The European Medicines Agency guidelines also suggest that measures should, at a minimum, be taken at baseline, during active treatment, immediately after the end of treatment, and at 6- or 12-month follow-up.[9]

3.5 Quality assessment

JQ, HK and JL assessed the risk of bias for the included RCTs using Version 2 of the Cochrane risk-of-bias tool for randomised trials – 'RoB 2'.[11] This tool uses five groups of items to assess the level of bias in the design, conduct, and analysis of RCTs. The five groups of items are: randomisation process, deviations from intended intervention(s), missing outcome data, measurement of the outcome, and selection of the reported results.

Each RCT was independently assessed by the researchers, with any disagreements resolved by consensus. We did not use our assessment of bias results to exclude studies from the main analysis, but the assessment was used to describe the main strengths and limitations of the studies.

3.6 Data analysis: network meta-analysis

Network meta-analysis (NMA) is a statistical technique for comparison of three or more treatments in a single analysis by combining direct and indirect evidence in a single network.[12] We applied this technique to evidence collected by the systematic review methods. Before the analysis was undertaken, a feasibility assessment was conducted to assess the feasibility and appropriateness of undertaking an NMA, and this is described in Section 6.7.

3.6.1 Evidence networks

Evidence networks were drawn for endpoints that were reported in three or more trials, and the geometry of the networks was analysed. This geometric analysis determined whether NMA would be feasible.

Indirect treatment comparisons, based on the Bucher method, were considered for endpoints which could not be analysed through NMA.[13] Indirect treatment comparisons were only conducted if the analysis could strengthen the comparison of electronic nicotine delivery systems (ENDS) with the reference treatment, NRT.

Network plots are presented against the results of those analyses that were deemed feasible in Section 7 of this report. The lines in the network plot are proportional to the strength of the evidence, i.e. the number of studies informing that comparison.

3.6.2 Model for analysis

Analysis was conducted in a Bayesian framework in R version 3.6.0[14] using the 'gemtc' package.[15] Neupane *et al.* reviewed the packages that were available for conducting NMA in R,[16] and based on the results presented in the review and the advice of peer-reviewers, the 'gemtc' package was deemed to be most suitable, as it allows for arm-based data to be analysed and the package can summarise the comparative treatments effects as relative risks. Using an arm-based approach can help to avoid some of the difficulties which arise from including multi-arm trials in an NMA.[17]

The HRB specified the following parameters: 250,000 'burn-in' iterations to be discarded, 500,000 iterations for the analysis, and three separate chains. Diagnostic tests were run to check model convergence. Thinning of the chains was specified to reduce the risk of autocorrelation. Default priors as specified by the 'gemtc' package were used.

3.6.3 Endpoints and methods to handle missing data

As outlined in Section 3.2, we followed the European Medicines Agency definition of abstinence. The European Medicines Agency also recommended that self-reported smoking status should be verified by biomarkers such as carbon monoxide; therefore, we extracted verified self-reported data as the preference, but we used self-reported data when verified data was not available.

For the 6-month timepoint data, we considered data published at both 24 weeks and 26 weeks, as both of these timepoints were used by the identified RCTs.

Relative risks for the efficacy endpoints were computed for individual studies for comparison purposes if these were not reported for the RCT in the original paper. These were not used in the NMA. However, binary counts were entered instead, as this was the requirement of the analytical programme.

3.6.4 Heterogeneity

Heterogeneity between studies was examined qualitatively by examining the study eligibility criteria and baseline characteristics of participants in the trials. Sensitivity analyses were conducted to assess the impact of

identified heterogeneity. Heterogeneity was quantitatively estimated using tau and is presented alongside the full results of each analysis in Appendix E.

Meta-regression was considered as an approach to assess the impact of heterogeneity, for example including nicotine dose as a covariate, however, there were an insufficient number of studies identified to reliably carry out a meta-regression.

The results of random effects models only are presented because of identified points of heterogeneity between studies; random effects models allow for more conservative estimates of effect where there is heterogeneity.[18]

3.6.5 Inconsistency assessment

A key assumption of NMA is that of evidence consistency. The requirement is that in every trial in the network, regardless of the actual treatments that were compared, the true effect of treatment Y relative to treatment X is exchangeable between trials.[19] This exchangeability assumption can be tested in an inconsistency assessment. The HRB intended to carry out an inconsistency assessment using the Bucher method, as this is the simplest method and therefore preferred for transparency reasons.[13,17-19] All loops in the network were identified and considered for this assessment. However, on close examination of the data, we were unable to use this method due to the presence of muti-arms trials which affected the independence of the loops. Where independent tests cannot be constructed, Dias *et al.* suggested that the standard consistency model be compared with an inconsistency model.[19] To check whether the consistency assumption as assumed in the NMA is reasonable for a dataset, Dias et al. suggested that we can compare that NMA model with a model where no such consistency is assumed. By looking at model fit statistics (deviance information criterion) we can assess whether eliminating the assumption of consistency for all contrasts has resulted in a better fitting model. We have compared the main model (consistency model) against an inconsistency model that assumes unrelated mean (relative) effects using a function of the 'gemtc' package.[15]

We also compared the direct head to head meta-analysis results versus the NMA outputs to check for potential inconsistency. Meta-analyses for the direct comparisons were run using the 'Metagen' package for the R programming language.[20,21] This package uses the inverse variance method for weighting of studies.[20,21]

3.6.6 Presentation of results

In order to undertake an NMA, one treatment in the network must be specified as a reference treatment against which all other treatments will be compared. For this analysis, we have selected NRT as the reference treatment because it is currently recommended for use in Ireland,[7,10] and because it was a common control treatment in the RCTs identified.

Results of the analysis are presented as median relative risks (RRs) with associated 95% credible intervals (95% CrI) which compares incidences of smoking cessation in ENDS users compared with the reference treatment, NRT.

4 Search results

From an initial 1,396 studies, 11 RCTs reported in 19 publications met the inclusion criteria for this systematic review.

An overview of the number of studies included and excluded at each stage of screening is given in Figure 1. A list of the included studies, giving their primary and secondary publications, is presented in Table 2. We have assigned each of the studies an identification code (ID), which is based on the trial name or the first author's name and date if no trial name was reported, and we will use this ID throughout the report. Studies excluded at full-text screening are tabulated alongside the reason for exclusion, and are presented in Appendix B.

There were no RCTs that met the inclusion criteria for the question on efficacy of heat-not-burn tobacco products in helping people who smoke to achieve abstinence (smoking cessation) but two studies reported on adverse events.[22,23]

Of the 11 trials, four were two-arm trials,[24-27] five were three-arm trials,[4,5,22,23,28], one was a four-arm trial,[29] and one was a five-arm trial.[30]

Haziza 2019, Ludicke 2018 and Hatsukami 2019 all contained conventional cigarette arms which were excluded and the fourth arm of the Hatsukami trial which assigned users to dual use was excluded.[22,23,29] The five-arm Halpern *et al.* 2018 trial comprised three arms that did not meet the systematic review inclusion criteria, and therefore only two of that trial's study arms are included in this report.

The number of participants in the RCTs ranged from 30[26] to 2,012.[30] Of the 11 trials, two were based in Italy,[5,28], four in the USA[26,29-31], two in the UK[24,27] and one each was based in South Korea,[25] Japan,[23] and New Zealand.[4] Table 2 also gives the comparators from each of the trials. Heat-not-burn tobacco products or ENDS was the intervention in all trials, and it was compared against NRT single or combination treatments, placebo e-cigarettes (Electronic non-nicotine delivery systems, ENNDS), and no additional treatment. The comparisons from the trials indicated that network meta-analysis was possible; however, before any analysis was undertaken, it was necessary to conduct a feasibility assessment.

Table 2 Overview of included studies

Study ID	Primary publication	Secondary publication	Participants (N)	Country	Comparator 1	Comparator 2
Heat-not-burn tobacco product studies						
Haziza 2019	Haziza *et al.* (2019 part 1)[31]	Haziza *et al.* (2019 part 2)[22]	119	USA	No additional treatment	
Ludicke 2018	Ludicke *et al.* (2018 part 1)[32]	Ludicke *et al.* (2018 part 2)[23]	118	Japan	No additional treatment	
ENDS studies						
ASCEND	Bullen *et al.* (2013)[4]	-	657	New Zealand	NRT patches	Placebo e-cigarette
ECLAT	Caponnetto *et al.* (2013)[5]	Campagna *et al.* 2016[33], Cibella *et al.* (2016)[34], Farsalinos *et al.* (2016)[35], Russo *et al.* (2016)[36]	300	Italy	Placebo e-cigarette	-
TEC	Hajek *et al.* (2019a)[24]	Hajek *et al.* (2019b)[37]	886	UK	NRT: participants' choice, including product combinations	-

Study ID	Primary publication	Secondary publication	Participants (N)	Country	Comparator 1	Comparator 2
Halpern 2018	Halpern *et al*. (2018)[30]	-	2,012[a]	USA	No additional treatment	-
Lee 2019	Lee *et al.* (2019)[25]	-	150	South Korea	NRT gum	-
BETOFREE	Masiero *et al*. (2019)[28]	Lucchiari *et al*. (2020)[38]	210	Italy	Placebo e-cigarette	No additional treatment
Holliday 2019	Holliday 2019[27]	-	80	UK	No additional treatment	-
Hatsukami 2019	Hatsukami 2019[29]	-	152	USA	NRT gum	-
Lee 2018	Lee 2018[26]	-	30	USA	NRT patches	-

[a]There were 6,006 participants in the five arms of the trial, but 2,012 in the two arms included in this review.

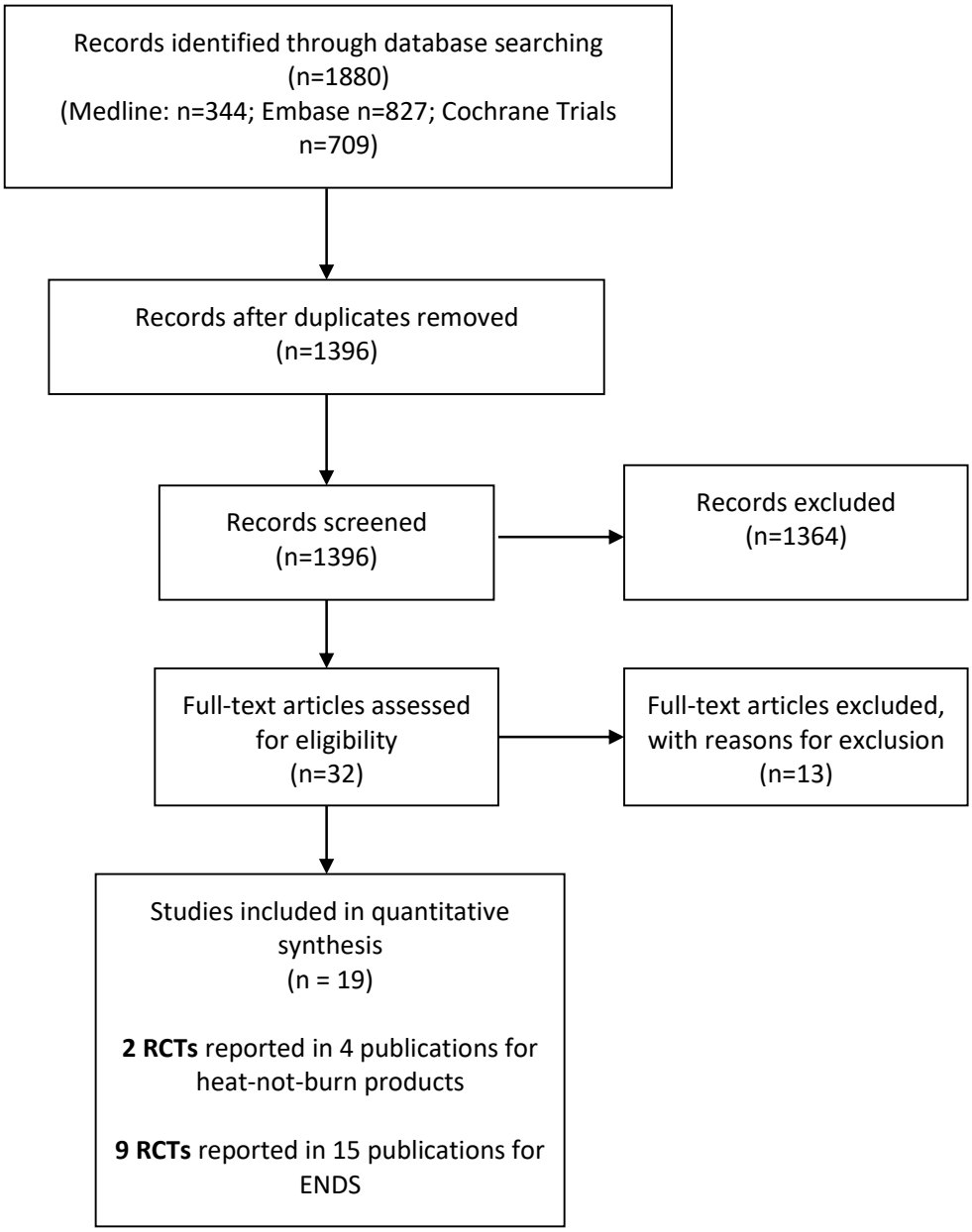

Figure 1 PRISMA flow chart

5 Results of systematic review for heat-not-burn tobacco products

As outlined in section 4, two studies reporting data for heat-not-burn tobacco products were identified.[22,32] The Ludicke 2018 trial was carried out in Japan and the Haziza 2019 trial was carried out in the USA. Both studies reported safety data only.

In Ludicke 2018, participants were randomised to one of three arms; the menthol Tobacco Heating System 2.2, continuing smoking and smoking abstinence only.[32] Only the Tobacco Heating System 2.2 and the smoking abstinence arms are relevant to this systematic review. Participants were monitored for five days in confinement and 85 days in an ambulatory setting giving a three-month trial period. In this RCT, 78 participants were randomised to the Tobacco Health System 2.2 and 40 to smoking abstinence. The mean age of participants was 37.2 years and 57.5% of participants were male.

Haziza 2019 followed the same trial design as Ludicke 2018 but was conducted in the USA. In this study 80 participants were randomised to the Tobacco Heating System 2.2 arm and 39 were assigned to smoking abstinence. The mean age of participants was 37.7 years and 60% of participants were male.

5.1 Risk of bias

We assessed studies for a risk of bias using the Cochrane RoB 2 tool.[11] The overall risk of bias in the two heat-not-burn tobacco product RCTs was high as shown in Figure 2. A full explanation of the assignment of the risk of bias criteria is given in Appendix C. A breakdown of missing data in the RCTs is given in

Table 3; there was a very high number of participants with missing data in Haziza 2019.

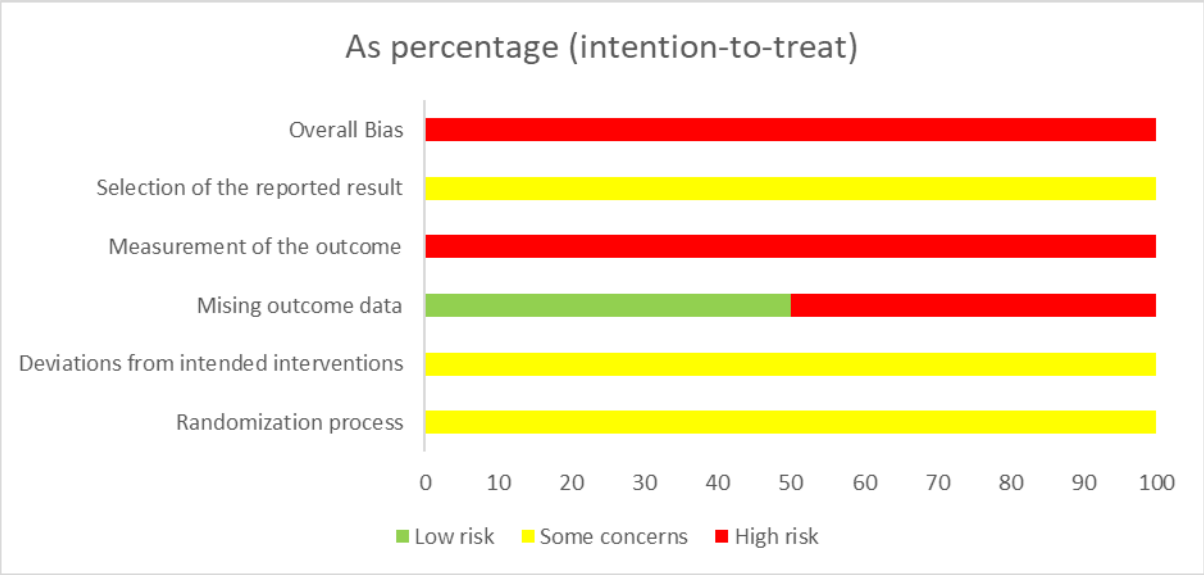

Figure 2 Risk of bias in the heat-not-burn tobacco product RCTs

Table 3 Missing data in heat-not-burn tobacco product RCTs

	Total allocated to arm N	Misrandomised	Protocol violation	Non-compliant	Discontinued	Total missing
Haziza 2019						
Tobacco Heating system	80	4	2	25	2	33
Smoking abstinence	39	5	3	21	6	34
Ludicke 2018						
Tobacco Heating system	78	-	-	-	2	2
Smoking abstinence	40	-	-	-	2	2

5.2 Adverse events

The adverse events of interest in the Haziza 2019 trial which were reported by more than one participant following randomisation are reported in Table 4.

Table 4 adverse events of interest in Haziza 2019

Adverse event	Tobacco Heating System	Smoking abstinence
Participants with any adverse events	52 (65.0)	23 (59.0)
Infections and infestations	5 (6.3)	1 (2.6)
Upper respiratory tract infection	3 (3.8)	1 (2.6)
Respiratory, thoracic, and mediastinal disorders	9 (11.3)	3 (7.7)
Cough	3 (3.8)	0
Nasal congestion	3 (3.8)	0
Oropharyngeal pain	2 (2.5)	1 (2.6)
Sinus congestion	1 (1.3)	1 (2.6)

The adverse events of interest that were observed in at least 5% of participants in the Ludicke RCT are reported in Table 5.

Table 5 Adverse events of interest in Ludicke 2018

Adverse event	Tobacco Heating System	Smoking abstinence
Participants with any adverse events	32 (41.0%)	14 (35.0%)
Infections and Infestations	6 (7.7%)	3 (7.5%)
Nasopharyngitis	3 (3.8%)	2 (5.0%)
Hordeolum	1 (1.3%)	0
Pharyngitis	1 (1.3%)	0
Psychiatric disorders	0	1 (2.5%)
Insomnia	0	1 (2.5%)

A summary of the adverse events that were reported in the studies overall is given in Table 6. The Minnesota Nicotine Withdrawal Scale was used in both studies.

Table 6 Studies documenting adverse events as recommended by the European Medicines Agency

Study ID	Vital signs	Psychiatric	Cardiovascular	Pulmonary	Rebound and withdrawal and addiction potential	Serious adverse events
Ludicke 2018	Y	Y	N	Y*	Y	N
Haziza 2019	Y	Y	N	Y	Y	Y

*Pulmonary related infections

6 Results of the systematic review for e-cigarettes

6.1 Eligibility criteria of RCTs

Data on eligibility criteria related to smoking history were extracted from the included RCTs and are given in Table 7. Five trials required participants to be smoking at least 10 cigarettes per day.[4,5,25,27,28] The criteria for the length of time participants had been smoking ranged from at least 1 year[4,29] to at least 10 years.[28] The inclusion criteria for the ECLAT trial differed in that it did not want to recruit those currently attempting to quit smoking or wishing to do so in the next 30 days. However, the same trial placed advertisements in a local newspaper inviting participants to try e-cigarettes to reduce the risk of tobacco smoking.[5] Hatsukami 2019 also excluded people if they were planning to quit smoking in the next three months.[29] The criteria on prior use of smoking cessation aids were variable; however, most trials excluded participants who were currently using cessation treatments or had recently used them (see Table 7).

Table 7 Eligibility criteria regarding smoking history from included RCTs

Study ID	N (cigarettes smoked per day)	Length of time smoking	Intention to quit smoking	Prior use of smoking cessation aids
ASCEND[4]	≥10	At least 1 year	Those who wanted to stop smoking	Excluding those using cessation drugs
ECLAT[5]	≥10	At least 5 years	Those not currently attempting to quit smoking or wishing to do so in the next 30 days	Use of smokeless tobacco or NRT (no time frame given)
TEC[24]	–	–	–	No strong preference to use or not to use NRT or e-cigarettes, and were currently not using either type of product
Halpern 2018[30]	–	–	–	–
Lee 2019[25]	≥10	At least 3 years	Those who were motivated to stop smoking entirely or to reduce their cigarette consumption	Excluded those who had attempted to stop smoking in the past 12 months by using other NRTs
BETOFREE[28]	≥10	At least 10 years	Those with a high motivation to stop smoking	Excluded any use of NRTs or e-cigarettes
Holliday 2019[27]	≥10	-	Intention to quit was not an inclusion criterion for this study	Included those not currently using an e-cigarette, or not having used one for more than 2 days in the last 30 days
Hatsukami 2019[29]	≥5	At least 1 year	Excluded if planning to quit smoking in the next 3 months	Excluded those currently using NRT or cessation medication
Lee 2018[26]	>2	-	-	Excluded those who were currently using smoking cessation pharmacotherapy or currently used e-cigarettes daily.

6.2 Baseline characteristics

The sociodemographic characteristics of participants are given in Table 8. Five studies recruited participants aged 40–50 years.[4,5,24,25,27,29,30] The BETOFREE trial and Lee 2018 involved slightly older patients.[28] The majority of participants were male.

The smoking characteristics of the RCT participants were also extracted (see Table 9). Most participants began smoking in their teens. Generally, the RCTs included heavy and dependent smokers, with the exception of Halpern 2018, who appeared to include lighter smokers.[30]

Table 8 Sociodemographic characteristics of participants in the six RCTs

Characteristic	ASCEND[4]	ECLAT[5]	TEC[24]	Halpern 2018[30]	Lee 2019[25]	BETOFREE[28]	Holliday 2019[27]	Lee 2018[26]	Hatsukami 2019[29]
Age in years									
Median (IQR)	-	-	41 (33–52)	44 (34.4–54)	-	-	-	-	47 (-)
Mean (SD)	42.4 (12.7)	44 (12.5)	-	-	42.3 (8.3)	62.8 (4.58)	44.3 (10.7)	53.5 (-)	-
Gender (male)	38%	63%	52%	49%	100%	63%		90%	50.8%
Ethnicity	33% Māori	-	-	-	-	-	6.3% Asian or Asian British	6% Latino	37.9% black, 8.7% other non-white
Education (second level or lower)	49%	31%	-	30%	61%	-	-	-	41.7%
Employed	-	-	70%	100%	100%	-	75%	-	90%
Entitled to free prescriptions	-	-	40.7%	-		-	-	-	-
Married	-	-	-	-	90%	-	-	-	-

IQR: Interquartile range

SD: Standard deviation

Table 9 Smoking characteristics of the RCT participants

Characteristic	ASCEND[4]	ECLAT[5]	TEC[24]	Halpern 2018[30]	Lee 2019[25]	BETOFREE[28]	Holliday 2019[27]	Lee 2018[26]	Hatsukami 2019[29]
Age started smoking (years)									
Mean (SD)	15.5 (4.5)	16.8 (3.9)	-	-	-	17.4 (3.7)	15.7 (3.0)	-	-
Median (IQR)	-	-	16 (14–18)	-	-	-	-	-	-
Number of years smoking continuously									
Mean (SD)	24.7* (-)	-	-	-	22 (8.8)	-	-	32 (-)	-
Median (IQR)	-	-	-	18 (10–29)	-	-	-		-
Number of cigarettes smoked per day									
Mean (SD)	17.9 (6.3)	-	-	-	20* (-)	19.4 (7.8)	17.4 (6.6)	13 (-)	
Median (IQR)		20 (15–25)	15 (10–20)	10 (5–15)	-	-	-		15
Lives with other smokers	54%	-	-	-	-	-	-	-	-
At least one quit attempt (%)	55% tried in last year	51% ever tried	-	-	90% ever tried	-	-	-	-
Mean self-efficacy to quit	3.7 of 5-point scale	-	-	-	6 out of 10 confidence about quitting	-	-	-	-
Mean FTND score (SD)	5.5 (2.0)	5.8 (2.2)	4.6 (2.4)	-	4.1 (2.2)	4.3 (1.9)	5.0 (2.1)	3.1	3(median)
FTND score >5 (%)	55%	-	-	-	-	-	-	-	-
Mean GN-SBQ score (SD)	20 (8.3)	20.0 (7.2)	-	-	-	-	-	-	-
E-cigarette use	-	-	41.5%	34%	-	-	-	-	-
Past NRT use	-	-	74.9%	-	-	-	-	-	-

*Calculated
IQR: Interquartile range
FTND: Fagerström Test for Nicotine Dependence
GN-SBQ: Glover-Nilsson Smoking Behavioral Questionnaire
SD: Standard deviation

6.3 Interventions

The main intervention tested was e-cigarettes with nicotine (ENDS). An overview of the intervention and comparators from each of the nine RCTs is presented in Table 10. The mg of nicotine in the intervention e-cigarettes varied from 0.01 mg/mL to 48 mg/mL. A mix of comparators was reported: nicotine replacement therapies, ENNDS (no nicotine), and no additional treatment. For this systematic review the two e-cigarette arms of the ECLAT trial have been pooled (see Section 6.7.2 for further explanation of treatment pooling).[5]

Two of the trials had a 1-week lead-in period before the agreed quit date,[4,28] and one had a 2-week lead-in period.[29] Five trials had a 12-week treatment period[4,5,24,25,28], one had a 6-week treatment period,[26], one had an 8-week treatment period,[29], one had a 24-week treatment period,[30] and one had a treatment period up to 26-weeks.[27]

However, it should be noted that in all of the studies, participants were free to purchase further treatments after the trial treatment period had ended. One trial asked participants to sign a commitment not to use the non-assigned treatment for at least 4 weeks after their quit date.[24]

Concomitant treatments are also presented in *For the purposes of this systematic review and NMA these treatment doses have been pooled

**In this study participants were able to select their preferred nicotine strength from 0mg/mL to 18mg/mL, however, none of the participants opted for the lowest concentration option. The most frequently selected nicotine strengths were 12 mg/ml and 18 mg/ml, selected by over half of participants.

*For the purposes of this systematic review and NMA these treatment doses have been pooled

**In this study participants were able to select their preferred nicotine strength from 0mg/mL to 18mg/mL, however, none of the participants opted for the lowest concentration option. The most frequently selected nicotine strengths were 12 mg/ml and 18 mg/ml, selected by over half of participants.

Table 11; apart from one trial,[5] smoking cessation counselling was provided with both the intervention and comparator(s).

The cost of treatment to participants is presented in Table 12. In the Holliday 2019 trial, the trial authors reported that participants were happy to source and purchase their own supplies of e-liquid after the initial 2-week period.[27]

Table 10 Interventions and comparators

Study ID	E-cigarette description	E-cigarette nicotine dose	Treatment 2 description	Treatment 2 dose	Treatment 3 description	Treatment 3 dose
ASCEND [4]	Elusion brand e-cigarette	10–16 mg/mL	NRT patches	21 mg/24 hours	ENNDS	–
ECLAT[5]	Categoria brand e-cigarette	5.4-7.2 mg/mL*	E-cigarette (Categoria brand of e-cigarettes (model 401) with disposable cartridges)	7.2 mg nicotine for 6 weeks, followed by 5.4 mg nicotine for another 6 weeks*	ENNDS	0 mg nicotine
TEC[24]	E-cigarette starter pack: One Kit (Aspire)	18 mg/mL	Nicotine replacement products of participants' choice, including product combinations	No dosages specified	–	–
Halpern 2018[30]	NJOY e-cigarettes	10-15 mg/mL	No additional treatment	–	–	–
Lee 2019[25]	eGO-C Ovale (Janty-Korea Co.)	0.01 mg/mL	NRT gum (Nicoman brand)	2 mg nicotine per tablet	–	–
BETOFREE[28]	VP5 electronic cigarettes kit	8mg/mL	ENNDS	No nicotine	No additional treatment	–
Holliday 2019[27]	Vype eTank	6mg-18mg/mL**	No additional treatment	-	-	-
Hatsukami 2019[29]	Vuse Solo e-cigarettes	48mg/mL	NRT gum	4mg but down-titrated to 2mg if side-effects	-	-
Lee 2018[26]	NJOY e-cigarettes	24-45mg/mL	NRT patches (Nicoderm)	14-21mg	-	-

*For the purposes of this systematic review and NMA these treatment doses have been pooled

**In this study participants were able to select their preferred nicotine strength from 0mg/mL to 18mg/mL, however, none of the participants opted for the lowest concentration option. The most frequently selected nicotine strengths were 12 mg/ml and 18 mg/ml, selected by over half of participants.

Table 11 Time on treatment, and concomitant treatment

Study ID	Prior to quit date	Post quit date	Concomitant treatment
ASCEND[4]	1 week	12 weeks	Phone or text-based support
ECLAT[5]	–	12 weeks	None
TEC[24]	–	12 weeks	Weekly behavioural support for at least 4 weeks
Halpern 2018[30]	–	24 weeks	Access to information regarding the benefits of smoking cessation and to a motivational text messaging service
Lee 2019[25]	–	12 weeks	50-minute education sessions on smoking cessation and the use of smoking cessation aids. The participants were asked to visit the medical office every 4 weeks for evaluation and counselling by an independent health practitioner.
BETOFREE[28]	1 week	11 weeks	Low-intensity telephone counselling at weeks 1, 4, 8, and 12
Holliday 2019[27]	-	Up to 26 weeks	Advice from dentist and option for referral to the 'Newcastle Stop Smoking' services
Hatsukami 2019[29]	2 weeks	8 weeks	Brief counselling on how to avoid smoking cigarettes
Lee 2018[26]	-	6 weeks	All participants received brief counselling by the research team, a brochure produced by the American Society of Anaesthesiologists explaining the benefits of preoperative smoking cessation, and a referral to the California Smokers' Helpline.

Table 12 Cost of intervention to participants

Study ID	Cost to participants
ASCEND[4]	The e-cigarettes were couriered to participants, and those allocated to the patch arm of the study were mailed a voucher to exchange for NRT at a pharmacy, and received a separate voucher to cover the dispensing costs.
ECLAT[5]	None
TEC[24]	In the e-cigarette group, participants were asked to purchase their future e-liquid online or from local vape shops and to buy a different e-cigarette device if the one supplied did not meet their needs. Initially, participants were given only one 30 mL bottle of e-liquid. They were encouraged to experiment with e-liquids of different strengths and flavours. Those who were unable to obtain their own supply were provided with one additional 10 mL bottle, but this was not offered proactively.
Halpern 2018[30]	In relevant groups, e-cigarettes and NRT (patches, gum, and lozenges) could be ordered directly through the trial website at no cost. Costs of prescription medicines obtained through a physician were reimbursable through the trial website. Use of all products was free until 6 months after the quit date.
Lee 2019[25]	None
BETOFREE[28]	None
Holliday 2019[27]	Participants in the ENDS group were provided with an approximately 2-week supply of e-liquid (with a choice of flavour and nicotine strength) and information on where to buy more.
Hatsukami 2019[29]	None
Lee 2018[26]	None

6.4 Efficacy of intervention

6.4.1 Smoking cessation at 24 or 26 weeks

Seven included trials reported smoking cessation results at 24 or 26 weeks and the trial-level results are presented in Table 13.

Three studies compared ENDS with NRT,[4,24,25] and only one of these RCTs found a statistically significant difference in smoking cessation incidence for ENDS versus NRT.[24]

Three studies compared ENDS with a ENNDS (no nicotine).[4,5,28] None of these trials found a statistically significant difference between ENDS and ENNDSs for smoking cessation at 24 or 26 weeks.

Three studies compared ENDS with no additional treatment,[27,28,30] and one of these studies found a statistically significant difference in favour of ENDS.[30]

Absolute quit rates were ranged greatly across the studies from 0%[30] to 35%. [24]

Table 13 RCT results with smoking cessation at 24 or 26 weeks

Study ID	Treatment	N=cessation events	N=arm total	Quit rate	Verified	Comparison	RR	LCI	UCI	*p*-value
ASCEND[4]	ENDS	21	289	7%	Yes	–	1	–	–	–
ASCEND[4]	NRT	17	295	6%	Yes	ENDS vs NRT	1.26	0.68	2.34	0.46
ASCEND[4]	ENNDS	3	73	4%	Yes	ENDS vs ENNDS	1.77	0.54	5.77	0.44
ECLAT[5]	ENDS	22	200	11%	Yes	–	1	–	–	–
ECLAT[5]	ENNDS	5	100	5%	Yes	ENDS vs ENNDS	2.20	0.86	5.64	0.10
TEC[24]	ENDS	155	438	35%	No*	–	1	–	–	–
TEC[24]	NRT	112	446	25%	No*	ENDS vs NRT	1.40	1.14	1.72	–
Halpern 2018[30]	ENDS	12	1,199	1%	Yes	–	1	–	–	–
Halpern 2018[30]	No additional treatment	1	813	0%	Yes	ENDS vs no additional treatment	8.14	1.06	62.46	0.04**
Lee 2019[25]	ENDS	16	75	21%	Yes	–	1	–	–	–
Lee 2019[25]	NRT	21	75	28%	Yes	ENDS vs NRT	0.76	0.43	1.34	0.34
BETOFREE[28]	ENDS	13	70	19%	Yes	–	1	–	–	–
BETOFREE[28]	ENNDS	11	70	16%	Yes	ENDS vs ENNDS	1.18	0.57	2.46	0.65
BETOFREE[28]	No additional treatment	7	70	10%	Yes	ENDS vs no additional treatment	1.86	0.79	4.38	0.16
Holliday 2019[27]	ENDS	6	40	15%	Yes	-	-	-	-	-
Holliday 2019[27]	No additional treatment	2	40	5%	Yes	ENDS vs no additional treatment	3.00	0.64	13..98	0.16

*Not verified at this timepoint

**This study intended to use the Holm method to determine significance, however, we report the unadjusted difference here as this is what is extracted for all studies. Using the Holm method, this comparison was not considered significantly different.

RR: Relative risk; LCI: Lower confidence interval; UCI: Upper confidence interval

6.4.2 Smoking cessation at 52 weeks

Only three RCTs reported data collected at this timepoint. Each study compared e-cigarettes to a different control, and the results are presented in Table 14. One study with 300 participants found that ENDS appear more effective than ENNDS (no nicotine) for smoking cessation (RR: 2.75; 95% CI: 0.97–7.76), but the difference is not statistically significant.[5] One study (N=2,012) shows that ENDS appear more effective than no additional treatment (RR: 6.11; 95% CI: 0.33–113.24), but again this difference is not statistically significant.[30] One trial (N=886 participants) shows that ENDS are more effective than NRT (RR: 1.83; 95% CI: 1.30–2.58), and this difference is statistically significant.[24]

Table 14 RCT results with smoking cessation at 52 weeks

Study ID	Treatment	N=cessation events	N=arm total	Verified	Comparison	RR	LCI	UCI	*p*-value
ECLAT[5]	ENDS	22	200	Yes	–	1	–	–	–
ECLAT[5]	ENNDS	4	100	Yes	ENDS vs ENNDS	2.75	0.97	7.76	0.06
TEC[24]	ENDS	79	439	Yes	–	1	–	–	–
TEC[24]	NRT	44	447	Yes	ENDS vs NRT	1.83	1.30	2.58	<0.001
Halpern 2018[30]	ENDS	4	1,199	Yes	–	1	–	–	–
Halpern 2018[30]	No additional treatment	0	813	Yes	ENDS vs no additional treatment	6.11	0.33	113.24	0.22

RR: Relative risk
LCI: Lower confidence interval
UCI: Upper confidence interval

6.5 Adverse events

6.5.1 Study definitions of an adverse event

Only two studies used standardised definitions for the coding of adverse events, and only one of these specified the coding guidelines that were followed. The TEC trial defined an adverse event according to the Medical Dictionary for Regulatory Activities (MedDRA) coding guidelines.[24] The standard terms listed by MedDRA are used to classify adverse event data from clinical trials and ad hoc reporting. While the ASCEND trial state that adverse events were defined according to international guidelines, they do not state which guidelines were used, simply describing that this was in line with the CONsolidated Standards of Reporting Trials (CONSORT) 2010 Statement.[4]

6.5.2 Adverse events by type

Studies were checked for reporting of adverse events under the categories recommended by the European Medicines Agency, as outlined in Section 3.4.1. All studies except Halpern 2018[30] describe adverse events, and provide data at timepoints of 8 weeks,[26,29] 12 weeks,[25] 6 months,[4,27,28], or 52 weeks.[5,24]

The types of adverse events documented during the RCTs studied are indicated in Table 15, whereby 'Y' indicates that such an event was specifically monitored for, and 'N' indicates that it was not monitored for or that mention of this was otherwise omitted from the study publications. For example, while it could be assumed that all RCTs in this review examined multiple parameters during adverse event monitoring, in the case of the ASCEND trial, there is no specific mention of measurement of vital signs, or of symptoms classed as psychiatric, cardiovascular, or pulmonary; only serious adverse events are mentioned.[4] In general, ASCEND did not disclose any qualitative data on non-serious adverse events. Halpern 2018 did not provide evidence of having monitored any adverse event data at all, instead recording biochemical metrics from patient blood and urine samples.[30] BETOFREE recorded data on six out of seven parameters listed in Table 15; however, they did not make reference to monitoring serious adverse events.[28] While the TEC trial utilised MedDRA terms for recording adverse reactions, the health technology statement associated with the study suggests that adverse events were not recorded, and instead an adverse reaction checklist was used. This statement is made despite the subsequent listing of adverse events (as adverse reactions), particularly those relating to pulmonary health.[24]

As the Holliday 2019 trial was carried out in a dental setting, only periodontal and withdrawal adverse events were reported.[27]

Vital signs monitoring, which included blood pressure, body weight, and heart rate measurements, was only specified in three of the six RCTs' methodologies, specifically ECLAT, Hatsukami 2019 and BETOFREE.[5,28,29] While the monitoring of vital signs could be inferred in Lee 2019 through the requirement for weekly doctor visits, it is not explicitly mentioned.[25]

Psychiatric symptoms were disclosed in three of the six RCTs, although there was some crossover with symptoms pertaining to nicotine withdrawal. Specifically, the BETOFREE trial employed a hospital anxiety and depression scale tool in order to assess psychiatric symptoms via a self-reported questionnaire.[28] The ECLAT study assessed subjective psychiatric symptoms using the Beck Depression Inventory and the Beck Anxiety Inventory.[5]

All RCTs, except Halpern 2018 and Lee 2018, disclosed information on the monitoring of tobacco withdrawal symptoms, although the symptoms that were disclosed varied between the studies. The ECLAT trial described their study participants as infrequently reporting symptoms commonly associated with nicotine withdrawal (hunger, insomnia, irritability, anxiety, and depression).[5] Lee 2019 described the occurrence of headache and nausea, stating that these were more commonly experienced in the NRT group.[25] The TEC trial described nicotine withdrawal symptoms as 'irritability, restlessness, and inability to concentrate', where these were experienced less frequently in the e-cigarette group than in the NRT group.[24] The European Medicines Agency guidelines recommend that efforts should be made to show withdrawal and rebound phenomena of the intervention being studied as distinct from nicotine withdrawal. The guidelines also recommend that nicotine withdrawal symptoms should be separated from craving symptoms and measured with different (validated) tools.[9] All of the RCTs reporting data on nicotine withdrawal utilised the Fagerström Test for Nicotine Dependence. However, it is unclear how distinctions were made between nicotine withdrawal and cravings.

The ECLAT trial and the Hatsukami 2019 trial also employed the Minnesota Nicotine Withdrawal Scale, which is recommended in the European Medicines Agency guidelines.[5,9,29]

Participants in the e-cigarette treatment arms of the BETOFREE trial experienced burning throat symptoms (following use of both the placebo and nicotine-containing e-cigarettes), with the authors concluding that this was possibly related to the use of e-cigarettes and this adverse event increased in frequency of the from 3 to 6 months.[38]

The most consistently reported adverse events were those relating to the pulmonary system, including respiratory symptoms relating to smoking, as described in Section 6.5.2.1.

Table 15 Studies documenting adverse events as recommended by the European Medicines Agency

Study ID	Vital signs	Psychiatric	Cardiovascular	Pulmonary	Rebound and withdrawal and addiction potential	Serious adverse events
ASCEND[4]	N	N	N	N	Y	Y
ECLAT[5]	Y	Y	N	Y	Y	Y
TEC[24]	N	Y	Y	Y	Y	Y
Halpern 2018[30]	N	N	N	N	N	N
Lee 2019[25]	N	N	N	Y	Y	Y
BETOFREE[28]	Y	Y	Y	Y	Y	N
Holliday 2019[27]	N	N	N	N	Y	Y
Hatsukami 2019	Y	N	N	Y	N	N
Lee 2018	N	N	Y	Y	N	Y

6.5.2.1 Pulmonary adverse events

Pulmonary events were consistently monitored in six of the nine trials studied (that is, they were mentioned in all except Halpern 2018, Holliday 2019 and the ASCEND study). Respiratory symptoms that were noted included shortness of breath and cough, as presented in

Table 16. For all reported adverse events, the incidence was lower in the control arms (NRT or ENNDS [no nicotine]), with the exception of shortness of breath in one study[28] and cough in one study.[24] ASCEND, ECLAT, and Lee *et al.* (2019) did not find that any of the reported pulmonary symptoms were related to treatment, but six respiratory events in the TEC study were related to treatment (n=5 in the e-cigarette group and n=1 in the NRT group).

Table 16 Pulmonary adverse events at endpoint, by symptom and treatment arm

Symptom	Study	E-cigarette N events	NRT N events	ENNDS N events	Total N events
Shortness of breath	TEC[24]	66	64	–	130
	ECLAT[5]	12	–	5	17
	Lee 2019[25]	–	–	–	–
	BETOFREE[28]	92	103	106	301
Cough	TEC[24]	97	111	–	208
	ECLAT[5]	26	–	11	37
	Lee 2019[25]	3	3	–	6
	BETOFREE[28]	54	50	36	140
	Hatsukami 2019	15	0	-	15
	Lee 2018	8	1	-	9

6.5.3 Serious adverse events

A serious adverse event was taken to mean any event where a trial participant died or experienced life-threatening illness or conditions necessitating a hospital stay, as described in the ASCEND trial.[4] Although four of the six trials detailed the measurement of outcomes relating to serious adverse reactions and two reported serious adverse events, no incidence of these events were directly related to the treatment product. Serious adverse events that occurred during the ASCEND study included death (n=1, nicotine e-cigarette group), life-threatening illness (n=1, nicotine e-cigarette group), and various serious conditions requiring hospitalisation.[4] The TEC trial documented serious adverse events in both the nicotine e-cigarette group (n=27) and the NRT group (n=22), whereby two of these were deaths: one was due to spinal injury (NRT group) and the other was due to ischaemic heart disease (e-cigarette group).[24] ECLAT, Holliday 2019, Lee 2018, and Lee 2019 stated that no serious adverse events occurred during the course of these studies.[5,25-27] ECLAT describe their study's experience of serious adverse events as "no serious adverse events (i.e. major depression, abnormal behaviour or any event requiring [an] unscheduled visit to the family practitioner or hospitalisation) occurred during the study".[5(P8)] Hatsukami 2019 did not mention serious adverse events at all.[29]

6.5.4 How treatment correlation was assessed

Adverse events can occur independently of treatments, but only the ASCEND and TEC trials documented how distinctions were made, with the latter only doing so in the case of serious adverse events.[4,24] One of the authors of the ASCEND study categorised adverse events as being serious or non-serious, and related or unrelated to treatment. According to Bullen *et al*., this was done by association with study treatment in line with best practice, comparing incidence rates between groups, where six instances of adverse events were found to be related to nicotine e-cigarettes, six were related to NRT, and two were related to ENNDS (no nicotine) treatment. In the case of the TEC study, it is unclear how Hajek *et al.* made decisions regarding correlation with treatment. However, it was noted by the trial authors themselves that the serious adverse events did not occur as a direct result of the study.

6.6 Risk of bias

We assessed studies for a risk of bias using the Cochrane RoB2 tool.[11] As Lee 2018 and Hatsukami 2019 have only been included in this systematic review for adverse events, they were analysed for the risk of bias associated with reporting of adverse events only.[26,29] All other studies were assessed for the risk of bias associated with the reporting of cessation outcomes. The risk of bias assessment is summarised in Figure 3 and a full explanation of the assessment of each study for each criterion is given in Appendix D. Of the included nine RCTs, eight were at a high risk of bias.

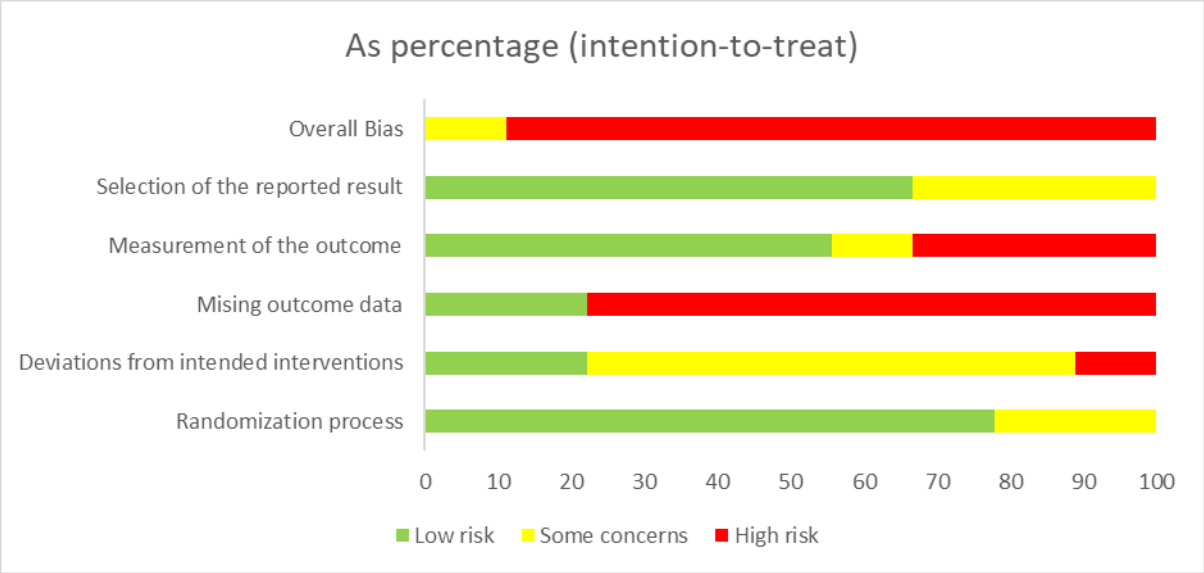

Figure 3 Risk of bias in ENDS trials

The methods used to handle missing data and the numbers of participants lost to follow-up are key components of the risk of bias assessment and this information is reported for each study in Table 17. The numbers lost to follow-up were high in all of the RCTs, and as the number of cessation events were low in the RCTs, this introduces uncertainty to this systematic review. The TEC trial was the only included study which attempted to assess the impact of missing data in the four sensitivity analyses described in Table 17. We were unable to definitively determine if the RCTs included in this systematic review were industry funded.

Table 17 Missing data and lost to follow-up in ENDS RCTs

Study ID	How was missing data handled?	Number lost to follow-up/discontinued at 6 months	Number lost to follow-up/discontinued at 12 months
ASCEND	Assumed participants with missing smoking status were smoking	22% in ENDS, 27% in NRT and 22% in ENNDS arm	
ECLAT	Assumed that all those individuals who were lost to follow-up are classified as failures	-	35% in ENDS group A, 37% in ENDS group B and 45% in nicotine e-cigs group
Halpern 2019	Persons with incomplete follow-up data classified as smokers	This trial does not clearly report loss to follow-up although it is clear there was a very large drop-out rate. The study authors defined an engaged cohort as those who had logged on to the trial website at least once. ENDS were only available through logging onto the website so those who were not 'engaged' in the e-cigarette group received no treatment. In the usual care	-

Study ID	How was missing data handled?	Number lost to follow-up/discontinued at 6 months	Number lost to follow-up/discontinued at 12 months
		group 15.9% were engaged and 21.1% of the e-cigarette group were engaged	
Lee 2019	Method for imputing missing data not reported	5.3% in the ENDS group and 18.6% in the NRT group	-
TEC	To assess the effect of missing data on the primary outcome, the authors conducted four prespecified sensitivity analyses, which excluded participants who did not attend at least one behavioral-support session, excluded participants who used the non-assigned product for at least 5 consecutive days, excluded participants who did not complete the 52-week follow-up, and imputed missing information with the use of multiple imputation by chained equations. Missing data were imputed for 136 participants in each group, and 50 data sets were imputed	19.8% in the ENDS group and 24.6% in the NRT group	18.9% in the ENDS group and 23.5% in the NRT group
BETOFREE	Method for imputing missing data not reported	25.7% in the ENDS group, 27.1% in the NRT group and 25.7% in the no additional treatment group	-
Holliday 2019	Participants with missing smoking outcome data (e.g. those not attending for review) were considered as continuing smokers or to have resumed smoking	27.5% in both groups	-
Hatsukami 2019	Unclear how missing data handled for adverse events	At eight weeks there was 23.7% dropout rate in the ENDS arm and 30.3% in the NRT arm	-
Lee 2018	Unclear how missing data handled for adverse events	20% at eight weeks in NRT and 10% for ENDS	-

6.7 Feasibility assessment for meta-analysis

We carried out an assessment of the feasibility of the network meta-analysis (NMA) following published guidance.[39,40] Adverse event data were not consistently reported and therefore we were unable to meta-analyse adverse event results; therefore the two studies that only reported adverse event data of interest are not discussed in this section.[26,29]

6.7.1 Comparability of populations

The comparability of populations was considered based on the data presented in Sections 5 and 6.2. The study populations of the identified RCTs were considered comparable for pooling. One possible outlier population was that involved in the Halpern *et al.* 2018 trial, which may have involved light smokers, and therefore we have conducted a sensitivity analysis excluding this trial from the NMA.[30]

6.7.2 Treatments considered in the network meta-analysis

The feasibility analysis also considered the main intervention, which was the type of e-cigarette and dosage of nicotine given to the participants (see Table 10). Only first- and second-generation e-cigarettes were included in the six studies. Electronic nicotine delivery systems (ENDS) was the intervention in all trials, and it was compared against NRT single or combination treatments, ENNDS (no nicotine), or no additional treatment. The nicotine dose in ENDS arms ranged between 5.4mg/mL and 18mg/mL with the exception of the Lee 2019 trial which reported a dose of 0.01mg/mL.[25] This study was excluded from the network meta-analysis (NMA) in a sensitivity analysis. The studies used different brands of e-cigarettes with variable nicotine content. Two studies by Dawkins *et al.* suggest that using a lower nicotine dose in e-cigarettes may be associated with compensatory behaviour, such as increasing the number of puffs and the duration of the puffs in order to increase nicotine consumption.[41,42] Soar *et al*. concluded that there may be little benefit in giving lower doses of nicotine in e-liquids, as it appears to result in a higher e-liquid consumption.[43] These studies suggest that, in reality, the nicotine dose will be titrated by the user in order to achieve their preferred consumption level and that the dose of nicotine is less important. This evidence supports the pooling of nicotine doses in this NMA. All ENDS were grouped together as one treatment intervention for the purposes of the NMA, as outlined in Table 18, and one sensitivity analysis for low dose nicotine was carried out.

The broadest definition of an NRT comparator arm was that of the TEC trial, which allowed an NRT of the participants' choice, including product combinations.[24] We therefore grouped all NRT treatments together for the purposes of the NMA, as we did for ENDS. This is a limitation of the analysis as previous research has suggested that single NRT is not as effective as combination NRT.[7]

We considered all ENNDS (without nicotine) to be the same, and usual-care arms (which generally consisted of advice and counselling) were labelled as 'no add' for the NMA. All treatment group labels are given in Table 18.

Table 18 Treatment grouping and labels in the network meta-analysis

Label	Treatment group
ENDS	Electronic nicotine delivery systems (e-cigarettes with varied doses of nicotine)
ENNDS	ENNDS (e-cigarettes without nicotine)
NRT	Nicotine replacement therapy including combinations (all types of nicotine replacement therapy, e.g. patches, gum, and spray, are considered equivalent)
No add	Only usual care is given in these study arms

6.7.3 Risk of bias

The HRB considered conducting a sensitivity analysis excluding the trials at high risk of bias. However, as six of the seven included cessation RCTs were at high-risk of bias this was not possible.

6.7.4 Endpoints and networks

The number of studies reporting smoking cessation at the timepoints of interest is presented in Table 19. All seven RCTs reported smoking cessation results at 24 or 26 weeks. Six of the seven RCTs verified the self-reported data with biochemical analysis.[4,5,25,27,28,30] A sensitivity analysis was conducted that excluded the TEC trial, which did not verify the self-reported data at 24 or 26 weeks.[24]

Three trials[5,24,30] measured smoking cessation at 52 weeks and were included in the 52-week NMA. However, we were unable to run an analysis for smoking cessation at the 52-week timepoint, as the model would not converge. This was the case even after the number of iterations was increased to 500,000. Lin *et al*.[44] have acknowledged that this is a limitation of arm-based models, which may not converge well if some treatments are only included in a few studies. This was likely the case here, as Table 19 shows that there were only three studies reporting data at this timepoint. The issue was also confounded by zero event counts in one study.[30]

Table 19 Report of smoking cessation data at timepoints of interest

Study ID	24- or 26-week follow-up	52-week follow-up
ASCEND[4]	✓	
ECLAT[5]	✓	✓
TEC[24]	✓	✓
Halpern 2018[30]	✓	✓
Lee 2019[25]	✓	
BETOFREE[28]	✓	
Holliday 2019[27]	✓	

6.7.5 Summary of analyses

Based on the results of the feasibility assessment, we elected to carry out the following analyses:

- An NMA of smoking cessation at the 24 or 26-week timepoint with all seven studies
- Three sensitivity analyses:
  - One excluding a trial with lighter smokers (Halpern *et al.* 2018 trial[30])
  - One excluding unverified data (TEC trial[24])
  - One excluding a low dose nicotine trial (Holliday 2019[27])
- A narrative summary of smoking cessation at 52 weeks, as there are insufficient data to conduct an NMA or indirect treatment comparison.

6.7.6 Heterogeneity

The baseline quit rates (i.e. for the comparator arms) across the trials was highly variable (see Table 13); for no additional treatment quit rates ranged between 0%[30] to 10%[28], for NRT quit rates ranged from 6%[4] to 28%[25] and for ENNDS quit rates ranged from 4%[4] to 16%[28]. This suggests that there is underlying heterogeneity in study design between the RCTs.

The effect of heterogeneity on the NMA will be investigated in the sensitivity analyses described in section 6.7.5. A random effects model has also been chosen for the NMA rather than a fixed effects model as a fixed effects model disregards heterogeneity.[18] Statistical heterogeneity and observed heterogeneity in e-cigarette type and nicotine dose was detected and therefore the random effects NMA model is the most appropriate model to use.

7 Network meta-analysis of smoking cessation

7.1 Network meta-analysis and sensitivity analysis at 24 or 26 weeks

All seven RCTs[4,5,24,25,27,28,30] reporting cessation data were included in the 24 or 26-week smoking cessation network meta-analysis.

Figure 4 presents the data and network relationship using the seven RCTs that measured smoking cessation at 24 or 26 weeks. The majority of the data compare e-cigarettes containing nicotine (ENDS) to NRT, followed by ENDS being compared with e-cigarettes without nicotine (ENNDS).

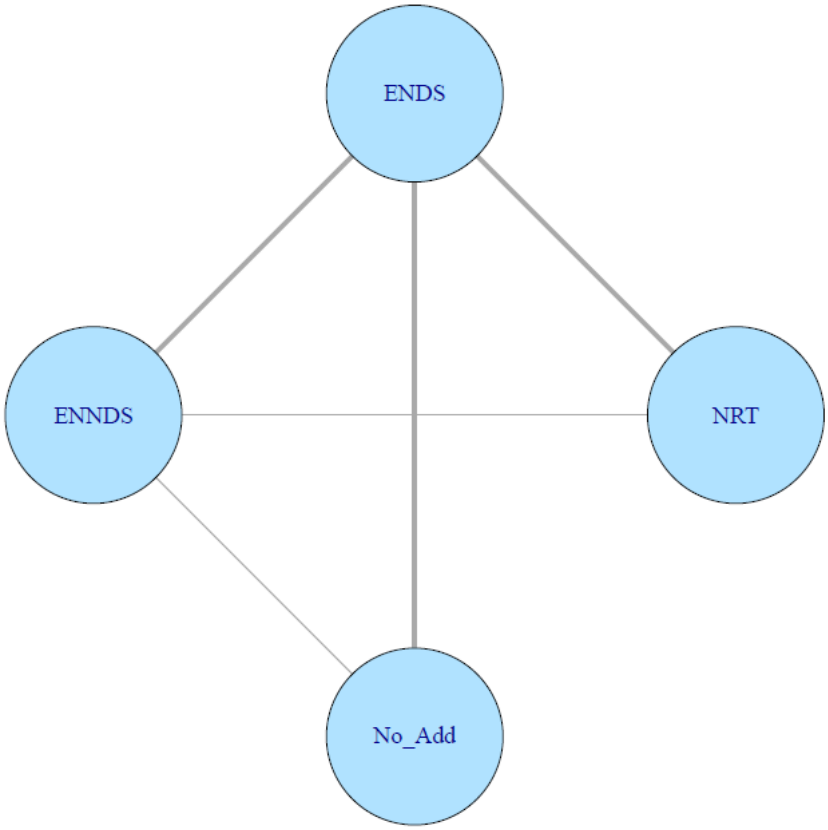

Figure 4 Evidence network for smoking cessation at 24 or 26 weeks

Using NRT as the reference treatment, the incidence of smoking cessation at 24 or 26 weeks is very similar in both the ENDS and the NRT groups (RR: 1.17; 95% CrI: 0.61–1.99), which indicates there is no evidence for a difference in effect (see Figure 5). ENNDS (no nicotine) is somewhat less effective in achieving smoking cessation than NRT (RR: 0.649; 95% CrI: 0.24–1.42), but the credible intervals are wide, and the result is not statistically significant. NRT is more effective than no additional treatment and this result is statistically significant (RR:0.35; 95% CrI: 0.11-0.88). The full output of the NMA from gemtc including, the model fit (Dbar, pD and DIC) is given in Appendix E.

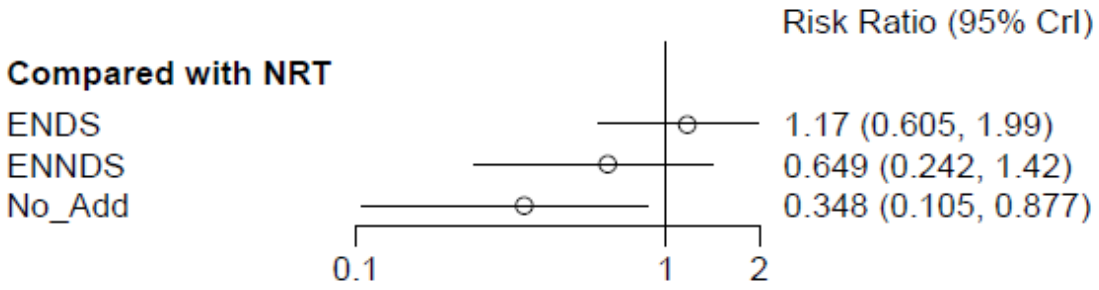

Figure 5 Network meta-analysis of smoking cessation at 24 or 26 weeks

7.2 Sensitivity analysis 1: excluding Halpern *et al.* 2018 trial data

We conducted a sensitivity analysis to assess the impact of the Halpern *et al.* 2018 trial, which appears to have included lighter smokers.[30] In the sensitivity analysis, Halpern *et al.* (2018) was excluded from the network, and the revised evidence network plot is presented in Figure 6. This network plot shows that, with the exclusion of the Halpern *et al.* 2018 trial data, there is less evidence informing the ENDS versus no additional treatment comparison.

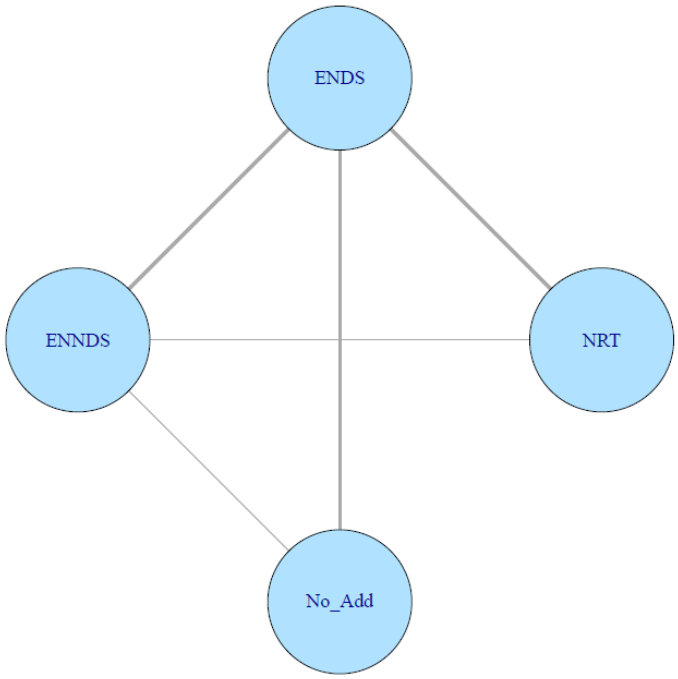

Figure 6 Evidence network for smoking cessation sensitivity analysis 1

When we removed Halpern *et al.* (2018)[30] from the network, the comparison of incidence rates of smoking cessation, at 24 or 26 weeks, for ENDS versus NRT, did not change when compared with the main analysis (RR: 1.17; 95% CrI: 0.65–1.86, versus RR: 1.17; 95% CrI: 0.60–1.98), (see Figure 7). The comparison of incidence rates of smoking cessation at 24 or 26 weeks for ENNDSs (no nicotine) versus NRT also remained similar to the main analysis (see Figure 7). In this sensitivity analysis, NRT still appears more effective than no additional treatment but there is much greater uncertainty in this estimate. This sensitivity analysis indicates that the main analysis is robust to assumptions relating to the smoking history of participants.

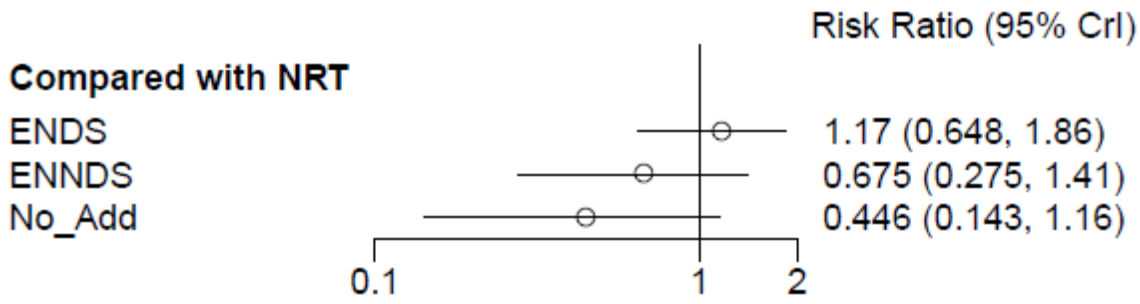

Figure 7 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 1

7.3 Sensitivity analysis 2: excluding unverified data

We conducted a sensitivity analysis to assess the impact of including unverified data in the analysis. We excluded data for the TEC trial[24] from the network, as the authors did not verify self-reported smoking cessation at the 24- or 26-week timepoint. The revised network plot is presented in Figure 8. This network plot shows that, with the exclusion of the TEC trial data, there is less evidence informing the ENDS versus NRT comparison.

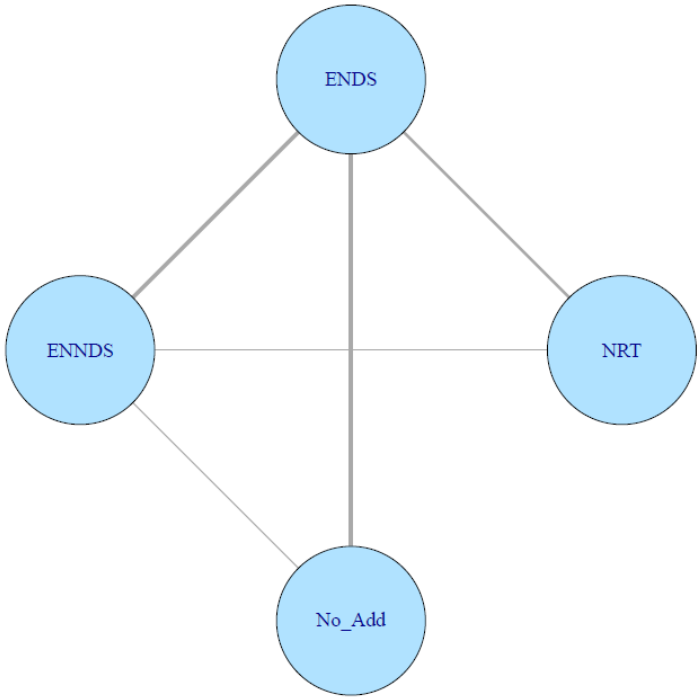

Figure 8 Evidence network for smoking cessation sensitivity analysis 2

When we removed the TEC trial[24] from the network, the point estimate of the relative risk of smoking cessation at 24 or 26 weeks for ENDS versus NRT shifted below one, but there is still considerable uncertainty in this analysis (RR: 0.93; 95% CrI: 0.41–2.19, versus RR: 1.17; 95% CrI: 0.60–1.98), indicating there is no evidence for a difference in effect (see Figure 9). The incidences of smoking cessation at 24 or 26 weeks for ENNDS (no nicotine) versus NRT remained similar to the main analysis (see Figure 9). This sensitivity analysis indicates that the smoking cessation main analysis results are only marginally influenced by the inclusion of unverified cessation data.[24]

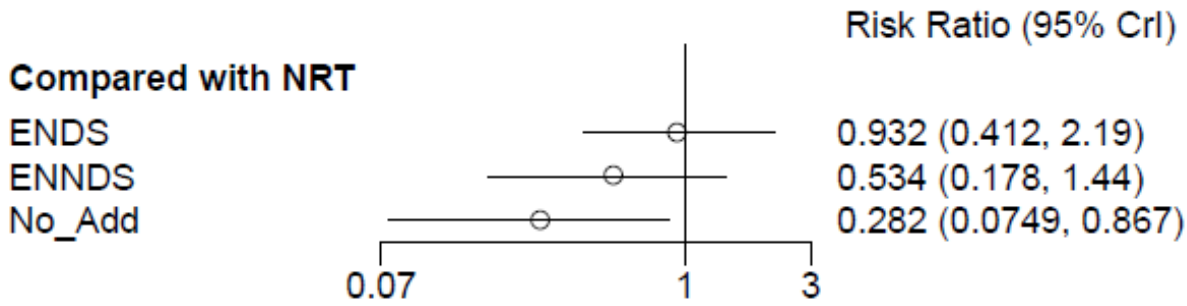

Figure 9 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 2

7.4 Sensitivity analysis 3: excluding low dose nicotine study

We conducted a sensitivity analysis to assess the impact of including unverified data in the analysis. We excluded data for the Lee 2019 trial[25] from the network, as the study assigned participants to a very low dose of nicotine. The revised network plot is presented in Figure 10. This network plot shows that with the exclusion of the Lee *et al.* 2019 trial data, there is less evidence informing the ENDS versus NRT comparison.

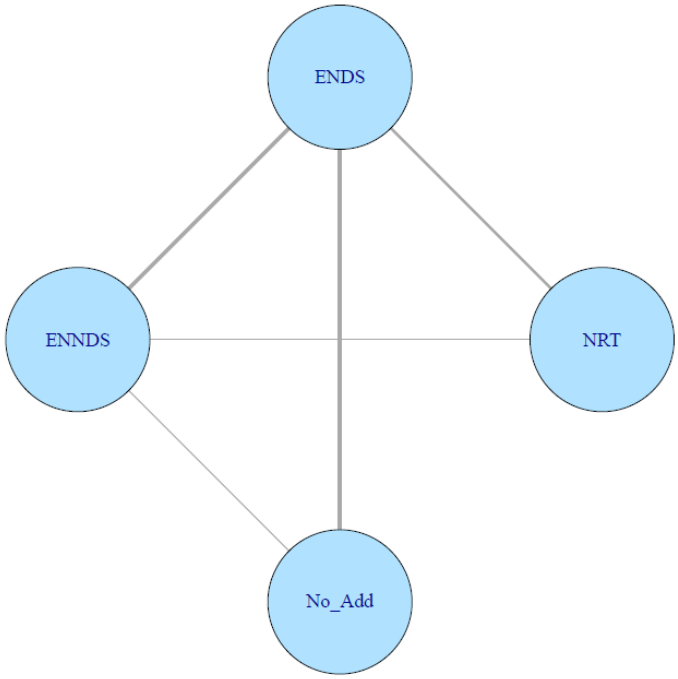

Figure 10 Evidence network for smoking cessation sensitivity analysis 3

When we removed the Lee 2019[25] from the network, the point estimate of the relative risk of smoking cessation at 24 or 26 weeks for ENDS versus NRT shifted slightly to the right (RR: 1.35; 95% CrI: 0.65–2.60 versus RR: 1.17; 95% CrI: 0.60–1.98), but the credible intervals are similar indicating there is no evidence for a difference in effect (see Figure 11). The incidences of smoking cessation at 24 or 26 weeks for ENNDSs (no nicotine) versus NRT remained similar to the main analysis (see Figure 11). This sensitivity analysis indicates that the smoking cessation main analysis results are marginally influenced by the inclusion of the low dose nicotine trial (Lee 2019).[25]

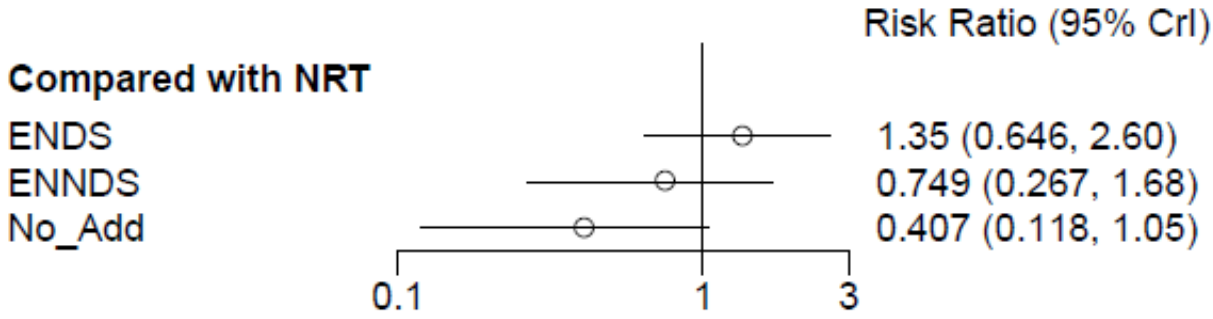

Figure 11 Network meta-analysis of smoking cessation at 24 or 26 weeks: sensitivity analysis 3

7.5 Inconsistency assessment

Treatment effects were estimated using both consistency and inconsistency model to determine whether the assumption of consistency has an impact on the relative risks estimated by the NMA. The consistency and inconsistency models produced very similar estimates of treatment effect, agreeing in terms of direction and magnitude of effect. The Deviance Information Criterion (DIC) was marginally lower for the consistency model (27.2 versus 28.9). Therefore, the consistency model was considered appropriate.

Table 20 shows the contribution of direct and indirect evidence to treatment effect estimates. There is statistical heterogeneity in the direct estimate for the comparison ENDS versus NRT I^2 = 49%. Given this measure of heterogeneity and the observed heterogeneity in the RCTs as described in section 6.7 we present random effects model data in Table 20. Direct estimates are either taken directly from the study or taken from a separate meta-analysis of the direct evidence only. There was no difference in the direction of effect, from the direct and indirect evidence, for any of the comparisons. For almost all comparisons, the direct and indirect treatment effects were in agreement in terms of magnitude. For the ENDS versus no additional treatment comparison, there is greater uncertainty in treatment effect estimate from the NMA random effects models compared with the direct estimate., this is probably due to difference in weighting and variance estimation methods between the meta-analysis and NMA models. The individual RCTs that directly compared these treatments, reported uncertain treatment effects,[27,28,30] and so the NMA treatment effect estimate is considered reflective of the trial data.

There is no evidence of inconsistency in the treatment effects presented in this report.

Table 20 Comparison of direct and indirect treatment effect estimates

Comparison	Number of studies informing this comparison	Direct estimate from study or random effects meta-analysis 95% CI	NMA estimate from random effects model 95% CrI
ENDS versus NRT	3	1.18 (0.82 – 1.68)	1.17 (0.61 – 1.99)
ENNDS versus NRT	1	0.71 (0.21 – 2.37)	0.65 (0.24 – 1.42)
No additional treatment versus NRT	0	No direct evidence	0.35 (0.11 – 0.88)
ENDS versus no additional treatment	3	2.45 (1.21 – 4.94)	3.32 (1.51 – 8.88)
ENNDS versus no additional treatment	1	1.57 (0.65 – 3.82)	1.86 (0.70 – 5.47)
ENDS versus ENNDS	3	1.54 (0.92 – 2.59)	1.79 (0.91 – 3.90)

8 Discussion

From an initial 1,396 studies, 11 RCTs reported in 19 publications met the inclusion criteria for this systematic review; two RCTs for heat-not-burn tobacco products and nine for ENDS.

8.1 Summary of e-cigarette trials

Nine RCTs[4,5,24-30] reported in 15 publications met the inclusion criteria for efficacy (N=7) and safety (N=9) of e-cigarettes in helping people who smoke to achieve abstinence (smoking cessation). NRT is the treatment that is currently used in Ireland,[7,10] and therefore, comparisons have been made to this reference treatment. Two trials reported safety data only. The number of participants in the RCTs ranged from 30 to 2,012. Of the nine trials, two were based in Italy, three in the USA, two in the UK, and one each was based in South Korea, and New Zealand. On average, participants in the included RCTs were males aged 40–50 years who were depedent, heavy smokers. One trial appeared to include lighter smokers, and the influence of this trial on the network meta-analysis was examined through a sensitivity analysis.

ENDS was the intervention in all trials, and it was compared to NRT in single or combination treatments, placebo e-cigarettes (ENNDS), and/or no additional treatment. First and second-generation ENDS devices were used. The nicotine dose in cessation studies ranged from 5.4mg/mL to 18mg/mL, except for the Lee 2019 trial which reported a dose of 0.01mg/ mL. This study was excluded from the network meta-analysis in a sensitivity analysis. The two studies included for safety data only allowed participants to have nicotine doses of 24-48mg/mL.[26,29]

Smoking cessation data reported at 24 or 26 weeks and 52 weeks were included. Self-reported data, which was then chemically verified, was preferred over self-reported only, and unverified data was excluded in a sensitivity analysis to test its impact on the overall meta-analysis results.

8.2 Summary of heat-not-burn tobacco product trials

This systematic review identified very limited data on the efficacy and safety of heat-not-burn tobacco products; no RCTs were found to report cessation results at the 6 or 12 month timepoints of interest and only two RCTs reported adverse event data.[31,32] No conclusions could be reached from these data and further research is needed if these tobacco products are to be considered as a smoking cessation tool.

8.2.1 Risk of bias

The HRB carried out a risk of bias analysis using the Cochrane RoB 2 tool for randomised trials. Of the included nine RCTs, eight of these were at a high risk of bias. This rating is mainly driven by missing outcome data. The numbers lost to follow-up were high in all of the RCTs, and as the number of successful cessation events was low in the RCTs, this introduces uncertainty to this systematic review. The TEC trial using four sensitivity analyses was the only included study which assessed the impact of missing data .[24]

8.2.2 Smoking cessation

The network meta-analysis of smoking cessation at 24 or 26 weeks is based on seven RCTs. Using NRT as the reference treatment, the incidences of smoking cessation at 24 or 26 weeks are very similar in both the ENDS and the NRT groups (RR: 1.17; 95% CrI: 0.61–1.99) and this indicates there is no evidence of a difference in effect. ENNDS (no nicotine) is somewhat less effective in achieving smoking cessation than NRT (RR: 0.649; 95% CrI: 0.24–1.42), but the result is not statistically significant. NRT is more effective than no additional treatment and this result is statistically significant (RR:0.35; 95% CrI: 0.11-0.88). Three sensitivity analyses were carried out: the first excluded the RCT which appeared to include lighter smokers, the second included only those RCTs which had biochemically verified their smoking data, and the third excluded the study with a lower dose of nicotine for the ENDS arm. The results of these sensitivity analysis indicate that the main analysis is robust to assumptions relating to the smoking history of participants and inclusion of unverified data, and slightly less robust to the assumption of nicotine dose.

As indicated in the feasibility assessment, we were unable to undertake a network meta-analysis of smoking cessation at 52 weeks due to limited data; only three RCTs reported data for this timepoint. Each study compared e-cigarettes to a different control, and results were mixed. One study with 300 participants found that ENDS appears more effective than ENNDSs (no nicotine) for smoking cessation (RR: 2.75; 95% CI: 0.97–7.76), but the difference is not statistically significant.[5] One study shows that ENDS appears more effective

than no additional treatment (RR: 6.11; 95% CI: 0.33–113.24), but again this difference is not statistically significant.[30] One trial (N=886 participants) shows that ENDS is more effective than NRT (RR: 1.83; 95% CI: 1.30–2.58), and this difference was statistically significant.[24] These results are mixed and suggest that further long-term large scale study is needed in order to reduce uncertainty around these estimates.

There is uncertainty for all of these analyses, and it is attributed in part to the low number of successful events in each study coupled with the large numbers lost to follow-up.

8.2.3 Adverse events

This systematic review found that standardised definitions were not used to record adverse events in all of the included studies. Several of the adverse event categories recommended for observation by the European Medicines Agency, including the cardiovascular category (where three out of the nine studies reported findings) and the psychiatric category (where three out of the nine studies reported findings), were not captured systematically.

Pulmonary events were consistently monitored in six of the nine trials studied (that is, they were mentioned in all except Halpern 2018, Holliday 2019 and the ASCEND study). Respiratory symptoms that were noted included shortness of breath and cough. For all reported adverse events, the incidence of each was lower in the control arms (NRT or ENNDS), with the exception of shortness of breath in one study[28] and cough in one study.[24] ASCEND, ECLAT, and Lee *et al.* (2019) did not find that any of the reported pulmonary symptoms were related to treatment, but six respiratory events in the TEC study were related to treatment (n=5 in the e-cigarette group and n=1 in the NRT group).

It should be noted that no serious adverse events were designated as being related to the treatment (e-cigarettes or its comparators) in the four studies that reported serious adverse events. The procedure for determining if a serious adverse event was treatment related was often unclear.

The adverse events in these studies were all collected over a short period of time (≤12 months), and longer-term studies are therefore needed in order to fill this data gap. The HRB study findings align with three other systematic reviews indicating that the long-term implications of using e-cigarettes are unclear.[45-47]

A companion project to this systematic review, also completed by the HRB, mapped the public health harms and benefits of e-cigarettes and gives an outline of all the current literature in this area.[48]

8.2.4 Level and certainty of evidence

We assigned a Level 2 evidence rating using the Centre for Evidence-Based Medicine levels of evidence guidelines,[49] as we had seven RCTs in the network meta-analysis, but six of the seven trials had a high risk of bias. With respect to the certainty of evidence,[50,51] we believe that there is low certainty of evidence that e-cigarettes have the same levels of success in achieving smoking cessation as other medically approved (by the Health Products Regulatory Authority in Ireland or the European Medicines Agency) cessation interventions based on results of the network meta-analysis because of the high risk of bias in six of the seven trials, the low number of successful events in the trials, and the high dropout rates.

There is a very low certainty of evidence that e-cigarettes have the same levels of success in achieving smoking cessation as other medically approved cessation interventions, based on three trials, for smoking cessation at 52 weeks, and therefore results are inconclusive.

For heat-not-burn tobacco products, there is a very low (or no) certainty of evidence for using these tobacco products as a smoking cessation intervention.

8.3 Comparison with previous research

The HRB synthesis reveals that e-cigarettes with nicotine may be as effective as NRT in achieving smoking cessation at 24 or 26 weeks (seven RCTs). Previous syntheses by Hartmann-Boyce *et al.* and Rahman *et al.* indicated that there are significant findings from the pooled results of two trials that e-cigarettes with nicotine, compared with ENNDSs (no nicotine), helped smokers to stop smoking long term.[3,52] On the other hand, a 2016 review by Kalkhoran and Glatzlost concluded that e-cigarettes are associated with significantly lower quit rates among smokers.[53] More recent syntheses by El Dib *et al.*[6] and Khoudigian *et al.*,[54] based on two and three trials, respectively, report findings similar to ours – that the incidences of smoking cessation at 24 or 26 weeks for ENDS versus ENNDS indicates that an e-cigarette with nicotine is marginally better than one without

nicotine, but that this result is not statistically significant and there is a high level of uncertainty. According to a World Health Organisation report, based mostly on a National Academies of Sciences systematic review, some types of ENDS aid in smoking cessation, in certain circumstances, but the evidence is insufficient to issue a blanket recommendation to use any type of e-cigarette (nicotine or non-nicotine) as a cessation aid for all smokers.[55]

8.4 Strengths and limitations

The main strength of this systematic review is that it used a comprehensive search strategy that is likely to have captured all relevant trials and that it adds five new trials to the statistical synthesis by Cochrane, leading to an updated systematic review of the topic.

The main limitation of this review is that e-cigarettes are not a standardised intervention. A variety of first- and second-generation e-cigarettes were tested, and the nicotine doses varied (see Table 10). As none of the studies tested third- or fourth-generation e-cigarettes, the relevance of the analysis is limited.

Other limitations of this review are the small sample sizes in the examined trials and the low number of patients achieving smoking cessation. Seven included RCTs reported smoking cessation at 24 or 26 weeks,[4,5,24,25,27,28,30] and only three of those also reported smoking cessation at 52 weeks.[5,24,30] In addition, loss to follow-up was very high and exceeded 20% in at least one arm of eight of the nine included trials.[4,5,24,26-30]

During the 12-week observation period that followed the active treatment period, participants could purchase further smoking cessation therapies; these data were not recorded by most of the trials. One trial asked participants to sign a commitment not to use the non-assigned treatment for at least 4 weeks after their quit date.[24]

The power of the comparisons between the comparator arms of the HRB's network meta-analysis would have been increased if we had widened our inclusion criteria to RCTs examining medically approved cessation therapies as well as behavioural therapies that were not compared directly to e-cigarettes. However, our brief was to examine the efficacy of e-cigarettes and their contribution to smoking cessation.

8.5 Conclusion

The systematic review and network meta-analysis of electronic nicotine delivery systems (e-cigarettes) versus therapies usually given for smoking cessation showed that there is no evidence of a difference in effect on incidences of smoking cessation. There is a low-level of certainty in these results due to low successful event rates and high rates lost to follow-up in all studies.

The systematic review of evidence for heat-not-burn tobacco products showed that there is no evidence from RCTs on efficacy for smoking cessation compared with current standard care, and insufficient evidence on the safety of heat-not-burn tobacco products from RCTs.

Identified respiratory adverse events, including shortness of breath and cough, appeared to be higher in electronic nicotine delivery systems users, but in the main, RCT evidence on adverse events is lacking. The long-term data on electronic nicotine delivery systems, in line with European Medicines Agency recommendations, are limited for both smoking cessation and adverse events, and further large-scale research using a standardised product to decrease uncertainly at the 1-year timepoint and beyond is needed.

References

1. Department of Health, Ireland. Tobacco free Ireland. Report of the tobacco policy review group Dublin, Ireland: Department of Health,, 2013:67.
2. Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control. 2014;23(Suppl 3):iii3-iii9.
3. Hartmann-Boyce J, McRobbie H, Bullen C, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2016;9:CD010216.
4. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: A randomised controlled trial. Lancet. 2013;382(9905):1629-37.
5. Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. PLoS One. 2013;8(6):e66317.
6. El Dib R, Suzumura EA, Akl EA, et al. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. BMJ Open. 2017;7(2):e012680.
7. Health Information and Quality Authority, (HIQA). Health technology assessment (HTA) of smoking cessation interventions. [Internet] [updated 10 Apr 2017. 2017. cited Available from: https://www.hiqa.ie/sites/default/files/2017-04/Smoking%20Cessation%20HTA.pdf
8. McGowan J, Sampson M, Salzwedel DM, et al. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.
9. European Medicines Agency. Guideline on the development of medicinal products for the treatment of smoking. London, England: European Medicines Agency,, 2008.
10. Health Service Executive (HSE). Medications for the treatment of tobacco dependence. [Internet] [updated No date. cited Available from: https://www.hse.ie/eng/about/who/tobaccocontrol/resources/nicotine-replacement-therapy-and-medications-for-the-treatment-of-tobacco-dependence.pdf
11. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. BMJ. 2019;366:l4898.
12. Chaimani A, Caldwell DM, Li T, et al. Chapter 11: Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions version 60 (updated July 2019): Cochrane Collaboration,, 2019.
13. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683-91.
14. R Core Team. R: A language and environment for statistical computing. [Internet] [updated 2017. cited Available from: https://www.R-project.org/.
15. van Valkenhoef G, Kuiper J. Network meta-analysis using Bayesian methods: Package 'gemtc'. Version 0.8-4, 2020.
16. Neupane B, Richer D, Bonner AJ, et al. Network meta-analysis using R: A review of currently available automated packages. PLoS One. 2014;9(12):e115065.
17. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU technical support document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Updated September 2016. [Internet] [updated Sept 2016. 2011 cited Available from: http://nicedsu.org.uk/wp-content/uploads/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf
18. Deeks J, Higgins J, Altman D. *Chapter 10: analysing data and undertaking meta-analyses. Draft version (29 January 2019) for inclusion*. London: Cochrane handbook for systematic reviews of interventions. , 2019.
19. Dias S, Ades AE, Welton NJ, et al. *Network meta‐analysis for decision making*. New Jersey, USA: John Wiley & Sons Ltd., 2018.
20. General package for meta-analysis [program]. 4.9-7 version: Schwarzer, Guido, 2019a.
21. Schwarzer G, Carpenter J, Rücker G. Meta-analysis with R. [Internet] [updated 2019b. cited Available from: http://www.imbi.uni-freiburg.de/lehre/lehrbuecher/meta-analysis-with-r
22. Haziza C, de La Bourdonnaye G, Donelli A, et al. Favorable changes in biomarkers of potential harm to reduce the adverse health effects of smoking in smokers switching to the Menthol Tobacco Heating System 2.2 for three months (Part 2). Nicotine Tob Res. 2019.
23. Lüdicke F, Picavet P, Baker G, et al. Effects of switching to the Menthol Tobacco Heating System 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers: A randomized, controlled,

open-Label, multicenter study in sequential confinement and ambulatory settings (Part 2). Nicotine Tob Res. 2018;20(2):173-82.
24. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019a;380(7):629-37.
25. Lee SH, Ahn SH, Cheong YS. Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: A randomized controlled study. J Am Board Fam Med. 2019;32(4):567-74.
26. Lee SM, Tenney R, Wallace AW, et al. E-cigarettes versus nicotine patches for perioperative smoking cessation: a pilot randomized trial. PeerJ. 2018;6:e5609.
27. Holliday R, Preshaw PM, Ryan V, et al. A feasibility study with embedded pilot randomised controlled trial and process evaluation of electronic cigarettes for smoking cessation in patients with periodontitis. Pilot Feasibility Stud. 2019;5:74.
28. Masiero M, Lucchiari C, Mazzocco K, et al. E-cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: Preliminary results by randomized controlled trial. Nicotine Tob Res. 2019;21(1):119-26.
29. Hatsukami D, Meier E, Lindgren BR, et al. A randomized clinical trial examining the effects of instructions for electronic cigarette use on smoking-related behaviors, and biomarkers of exposure. Nicotine Tob Res. 2019.
30. Halpern SD, Harhay MO, Saulsgiver K, et al. A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation. N Engl J Med. 2018;378(24):2302-10.
31. Haziza C, de La Bourdonnaye G, Donelli A, et al. Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the Menthol Tobacco Heating System 2.2 For three months (Part 1). Nicotine Tob Res. 2019.
32. Lüdicke F, Picavet P, Baker G, et al. Effects of switching to the Tobacco Heating System 2.2 Menthol, smoking abstinence, or continued cigarette smoking on biomarkers of exposure: A randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (Part 1). Nicotine Tob Res. 2018;20(2):161-72.
33. Campagna D, Cibella F, Caponnetto P, et al. Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. Eur J Clin Invest. 2016;46(8):698-706.
34. Cibella F, Campagna D, Caponnetto P, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clin Sci (Lond). 2016;130(21):1929-37.
35. Farsalinos K, Cibella F, Caponnetto P, et al. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. Intern Emerg Med. 2016;11(1):85-94.
36. Russo C, Cibella F, Caponnetto P, et al. Evaluation of Post Cessation Weight Gain in a 1-Year Randomized Smoking Cessation Trial of Electronic Cigarettes. Sci Rep. 2016;6:18763.
37. Hajek P, Phillips-Waller A, Przulj D, et al. E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: the TEC RCT. Health Technol Assess. 2019b;23(43):1-82.
38. Lucchiari C, Masiero M, Mazzocco K, et al. Benefits of e-cigarettes in smoking reduction and in pulmonary health among chronic smokers undergoing a lung cancer screening program at 6 months. Addict Behav. 2020;103:106222.
39. Quigley JM, Woods B, Thompson J, et al. PRM209 - Confronting heterogeneity: Using systematic review effectively for meta-analysis. Value Health. 2013;16(7):A612.
40. Cope S, Zhang J, Saletan S, et al. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer. BMC Med. 2014;12:93.
41. Dawkins LE, Kimber CF, Doig M, et al. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. Psychopharmacology (Berl). 2016;233(15-16):2933-41.
42. Dawkins L, Cox S, Goniewicz M, et al. 'Real-world' compensatory behaviour with low nicotine concentration e-liquid: subjective effects and nicotine, acrolein and formaldehyde exposure. Addiction. 2018;113(10):1874-82.
43. Soar K, Kimber C, McRobbie H, et al. Nicotine absorption from e-cigarettes over 12 months. Addict Behav. 2019;91:102-5.
44. Lin L, Zhang J, Chu H. Package 'pcnetmeta': Patient-centered network meta-analysis [Internet] [updated 2017. cited Available from: https://cran.r-project.org/web/packages/pcnetmeta/pcnetmeta.pdf
45. Glasser AM, Collins L, Pearson JL, et al. Overview of electronic nicotine delivery systems: A systematic review. Am J Prev Med. 2017;52(2):e33-e66.
46. Gualano MR, Passi S, Bert F, et al. Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies. J Public Health (Oxf). 2015;37(3):488-97.

47. Liu X, Lu W, Liao S, et al. Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). Medicine (Baltimore). 2018;97(19):e0324.
48. McCarthy A, Lee C, Long J. Harms and benefits of e-cigarettes and heat-not-burn tobacco products: A literature map. Dublin, Ireland: Health Research Board, Forthcoming.
49. Centre for Evidence-Based Medicine. Oxford Centre for Evidence-Based Medicine - Levels of Evidence (March 2009). [Internet] [updated 2009. cited Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
50. Schünemann He, Brożek Je, Guyatt Ge, et al. GRADE handbook for grading quality of evidence and strength of recommendations (Updated October 2013). [Internet] [updated 2013. 2013. cited Available from: https://gdt.gradepro.org/app/handbook/handbook.html#h.u1371quprl84
51. Schünemann HJ, Higgins JP, Vist GE, et al. Completing 'Summary of findings' tables and grading the certainty of the evidence. Cochrane Handbook for Systematic Reviews of Interventions. 2019:375-402.
52. Rahman MA, Hann N, Wilson A, et al. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PLoS One. 2015;10(3):e0122544.
53. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med. 2016;4(2):116-28.
54. Khoudigian S, Devji T, Lytvyn L, et al. The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis. Int J Public Health. 2016;61(2):257-67.
55. Peruga A. Electronic nicotine and non-nicotine delivery systems: a brief. Copenhagan: WHO Regional Office for Europe, 2020.

Appendix A Literature search strategies

Ovid MEDLINE

Search date: 27.02.2020

Database provider: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 26, 2020

Filter used: Cochrane highly-sensitive RCT filter

Search number	Search term	Results
1	Vaping/	651
2	Electronic Nicotine Delivery Systems/	2994
3	"Nebulizers and Vaporizers"/ and (nicotine or tobacco).mp.	162
4	e-cig$.mp.	4039
5	Ecig$.mp.	98
6	(Vape or vaping or vaper or vapers).mp.	1517
7	(Vapori#e$ adj3 (cigarette$ or nicotine)).mp.	92
8	((electric or electronic) adj2 (cig$ or nicotine or tobacco or smoking)).mp.	4570
9	(e-sigaret$ or "e-sígarett$" or een sigaret$ or E-Zigarette$ or "cigarette$ électronique$" or "L'e-cigarette" or vapoteuse$ or "cigarrill$ electrónico$" or sigarett$ elettronic$ or sigarett$ elettronik$ or sigarett$ elettroniche$ or elektronik$ sigar$ or e-savuke$ or e-rokok$ or rokok$ elektronik$ or e-papieros$ or e-ugwayi).mp.	72
10	(mods adj5 (tobacco or nicotine)).mp.	3
11	Juul$.mp.	97
12	(e-juice$ or e-liquid$).mp.	521
13	(cig-a-like$ or cigalike$ or ciga-like$).mp.	48
14	(e-hookah$ or electronic hookah$ or "hookah pens").mp.	22
15	(ENNDS or electronic non-nicotine delivery).mp.	4
16	((NMNDS and nicotin$) or non-medicinal nicotine delivery system$).mp.	0
17	or/1-16	5944
18	(Heated tobacco product$ or tobacco heating product$ or tobacco heating system$).mp.	164
19	("heat-not-burn" or "heat not burn" or "heat notburn" or "heatnot burn").mp.	113
20	(Heatsticks or heat-sticks or tobacco sticks or Neosticks).mp.	17
21	((HEETS or Fiit or glo) adj3 (tobacco or nicotine or smok$)).mp.	3
22	(IQOS or iFuse or Ploom).mp.	94
23	(electrically-heated smoking system and (nicotin$ or tobacco$)).mp.	1
24	(Vapotage or "tabac chauffé" or "verhitte tabak" or "riscaldatori di tabacco" or "tabacco riscaldato" or "erhitzter Tabak" or "verhit tabak" or "zahřátý tabák" or "opvarmet tobak" or "oppvarmet tobakk" or "uppvärmd tobak" or "kuumutatud tubakas" or "pinainit na tabako" or "lämmitetty tupakka" or "shan taba mai tsanani" or "hitað tóbak" or "apsildāmā tabaka" or "tembakau dipanaskan" or "šildomas tabakas" or "tembakau yang dipanaskan" or "te taakapa" or "podgrzewany tytoń" or "tabaco aquecido" or "încălzit tutunul" or "zahriaty tabak" or "ogrevani tobak" or "tabaco caliente" or "ısıtılmış tütün" or "ugwayi ovuthayo" or "thuốc lá nóng").mp.	16
25	or/18-24	293

26	17 or 25	6097
27	((randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly or trial or groups).ab. or drug therapy.fs.) not exp animals/ not humans.sh.	520956
28	26 and 27	**344**

Cochrane Library

Search date: 26.02.2020

Database provider: John Wiley & Son Inc.. Cochrane Library including Cochrane CENTRAL

ID	Search	Hits
#1	MeSH descriptor: [Vaping] explode all trees	21
#2	MeSH descriptor: [Electronic Nicotine Delivery Systems] explode all trees	89
#3	MeSH descriptor: [Nebulizers and Vaporizers] explode all trees	2269
#4	((nicotine OR tobacco)):ti,ab,kw	12123
#5	#3 AND #4	32
#6	(e-cig*):ti,ab,kw	432
#7	(ecig*):ti,ab,kw	432
#8	(vape OR vaping OR vaper OR vapers):ti,ab,kw	114
#9	(((vaporise OR vaporised OR vaporiser OR vaporize OR vaporized OR vaporizer) NEAR/3 (cigarette* OR nicotine))):ti,ab,kw	21
#10	(((electric or electronic) NEAR/2 (nicotine or tobacco or smoking or cig*))):ti,ab,kw	426
#11	((e-sigaret* OR "e-sígarett*" OR E-Zigarette* OR "cigarette* électronique*" OR "L'e-cigarette" OR vapoteuse* OR "cigarrill* electrónico*" OR sigarett* elettronic* OR sigarett* elettronik* OR sigarett* elettroniche* OR elektronik* sigar* OR e-savuke* OR e-rokok* OR rokok* elektronik* OR e-papieros* OR e-ugwayi)):ti,ab,kw	8
#12	((mods NEAR/5 (nicotine OR tobacco))):ti,ab,kw	0
#13	(Juul*):ti,ab,kw	22
#14	((e-juic* OR e-liquid*)):ti,ab,kw	72
#15	((cig-a-like* OR cigalike* OR ciga-like*)):ti,ab,kw	6
#16	((e-hookah* OR "electronic hookah" OR "electronic hookahs" OR "hookah pen" OR "hookah pens")):ti,ab,kw	4
#17	((ENNDS OR "electronic non-nicotine delivery")):ti,ab,kw	0
#18	((NMNDS AND nicotin*)):ti,ab,kw	0
#19	((non-medicinal nicotine delivery system*)):ti,ab,kw	0
#20	#1 OR #2 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	630
#21	(("heated tobacco" OR "tobacco heating")):ti,ab,kw	52
#22	((Heated tobacco product* OR tobacco heating product* OR tobacco heating system*)):ti,ab,kw	80
#23	(("heat-not-burn" OR "heat not burn" OR "heat notburn" OR "heatnot burn" OR "heatnotburn")):ti,ab,kw	10
#24	((Heatsticks OR heat-sticks OR "heat sticks" OR tobacco sticks OR Neosticks)):ti,ab,kw	11
#25	((IQOS or iFuse or Ploom)):ti,ab,kw	25
#26	((Vapotage OR "tabac chauffé" OR "verhitte tabak" OR "riscaldatori di tabacco" OR "tabacco riscaldato" OR "erhitzter Tabak" OR "verhit tabak" OR	6

	"zahřátý tabák" OR "opvarmet tobak" OR "oppvarmet tobakk" OR "uppvärmd tobak" OR "kuumutatud tubakas" OR "pinainit na tabako" OR "lämmitetty tupakka" OR "shan taba mai tsanani" OR "hitað tóbak" OR "apsildāmā tabaka" OR "tembakau dipanaskan" OR "šildomas tabakas" OR "tembakau yang dipanaskan" OR "te taakapa" OR "podgrzewany tytoń" OR "tabaco aquecido" OR "încălzit tutunul" or "zahriaty tabak" OR "ogrevani tobak" OR "tabaco caliente" OR "ısıtılmış tütün" OR "ugwayi ovuthayo" OR "thuốc lá nóng")):ti,ab,kw	
#27	((HEETS or Fiit or glo) NEAR/3 (tobacco or nicotine or smok*)):ti,ab,kw	1
#28	(("electrically-heated smoking system" AND (nicotin* OR tobacco*))):ti,ab,kw	0
#29	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	122
#30	#20 OR #29	723
	Of which results, trials: n=709 Reviews excluded	709

Embase.com		
Search date: 26.02.2020		
Filter used: Cochrane highly-sensitive RCT filter for Embase		
1	'vaping'/exp OR 'vaping'	1806
2	'electronic cigarette'/exp	5,838
3	'e cig*':ti,ab,kw	4,875
4	ecig*:ti,ab,kw	275
5	vape:ti,ab,kw OR vaping:ti,ab,kw OR vaper:ti,ab,kw OR vapers:ti,ab,kw	1,377
6	vapori?e$ NEAR/3 (cigarette* OR nicotine)	93
7	((electric OR electronic) NEAR/2 (cig* OR nicotine OR tobacco OR smoking)):ti,ab,kw	3,988
8	'e sigaret*':ti,ab,kw OR 'e sígarett*':ti,ab,kw OR 'e zigarette*':ti,ab,kw OR 'cigarette* électronique*':ti,ab,kw OR 'l e cigarette':ti,ab,kw OR vapoteuse*:ti,ab,kw OR 'cigarrill* electrónico*':ti,ab,kw OR 'sigarett* elettronic*':ti,ab,kw OR 'sigarett* elettronik*':ti,ab,kw OR 'sigarett* elettroniche*':ti,ab,kw OR 'elektronik* sigar*':ti,ab,kw OR 'e savuke*':ti,ab,kw OR 'e rokok*':ti,ab,kw OR 'rokok* elektronik*':ti,ab,kw OR 'e papieros*':ti,ab,kw OR 'e ugwayi':ti,ab,kw	13
9	(mods NEAR/5 (tobacco OR nicotin* OR smoking OR cigarette)):ti,ab,kw	5
10	'juul*':ti,ab,kw	117
11	'e juice*':ti,ab,kw OR 'e liquid*':ti,ab,kw	737
12	'cig-a-like*':ti,ab,kw OR 'cigalike*':ti,ab,kw OR 'ciga-like*':ti,ab,kw OR 'cig-alike':ti,ab,kw	42
13	'e hookah*':ti,ab,kw OR 'electronic hookah*':ti,ab,kw OR 'electric hookah*':ti,ab,kw OR 'hookah pen*':ti,ab,kw OR 'e-shisha':ti,ab,kw OR 'electronic shisha':ti,ab,kw OR 'electric shisha':ti,ab,kw	28
14	'ennds':ti,ab,kw OR 'electronic non-nicotine delivery':ti,ab,kw	8
15	nmnds:ti,ab,kw AND nicotine:ti,ab,kw	0
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	7,553
17	'heated tobacco':ti,ab,kw OR 'tobacco heating':ti,ab,kw	249
18	'heat-not-burn':ti,ab,kw OR 'heat not burn':ti,ab,kw OR 'heat notburn':ti,ab,kw OR 'heatnot burn':ti,ab,kw	149
19	'heatsticks':ti,ab,kw OR 'heatstick':ti,ab,kw OR 'heat-stick':ti,ab,kw OR 'heat-sticks':ti,ab,kw OR 'tobacco sticks':ti,ab,kw OR 'tobacco stick':ti,ab,kw OR 'neostick':ti,ab,kw OR neosticks:ti,ab,kw	21

20	((heets OR fiit OR glo OR ifuse) NEAR/3 (tobacco OR nicotine OR smok*)):ti,ab,kw	7
21	iqos:ti,ab,kw OR ploom:ti,ab,kw	96
#22	'electrically-heated smoking system':ti,ab,kw AND (nicotin*:ti,ab,kw OR tobacco*:ti,ab,kw)	1
#23	vapotage:ti,ab,kw OR 'tabac chauffé':ti,ab,kw OR 'verhitte tabak':ti,ab,kw OR 'riscaldatori di tabacco':ti,ab,kw OR 'tabacco riscaldato':ti,ab,kw OR 'erhitzter tabak':ti,ab,kw OR 'verhit tabak':ti,ab,kw OR 'zahřátý tabák':ti,ab,kw OR 'opvarmet tobak':ti,ab,kw OR 'oppvarmet tobakk':ti,ab,kw OR 'uppvärmd tobak':ti,ab,kw OR 'kuumutatud tubakas':ti,ab,kw OR 'pinainit na tabako':ti,ab,kw OR 'lämmitetty tupakka':ti,ab,kw OR 'shan taba mai tsanani':ti,ab,kw OR 'hitað tóbak':ti,ab,kw OR 'apsildāmā tabaka':ti,ab,kw OR 'tembakau dipanaskan':ti,ab,kw OR 'šildomas tabakas':ti,ab,kw OR 'tembakau yang dipanaskan':ti,ab,kw OR 'te taakapa':ti,ab,kw OR 'podgrzewany tytoń':ti,ab,kw OR 'tabaco aquecido':ti,ab,kw OR 'încălzit tutunul':ti,ab,kw OR 'zahriaty tabak':ti,ab,kw OR 'ogrevani tobak':ti,ab,kw OR 'tabaco caliente':ti,ab,kw OR 'ısıtılmış tütün':ti,ab,kw OR 'ugwayi ovuthayo':ti,ab,kw OR 'thuốc lá nóng':ti,ab,kw	2
24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	370
25	#16 OR #24	7,772
26	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,542,546

Appendix B List of articles excluded at full text stage

	Reference	Reason for exclusion
1	Adriaens K, Van Gucht D, Declerck P, et al. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *International journal of environmental research and public health* 2014;11(11):11220-48. doi: 10.3390/ijerph111111220 [published Online First: 2014/10/31]	Control (Participants were allowed to continue smoking)
2	Baldassarri SR, Bernstein SL, Chupp GL, et al. Electronic cigarettes for adults with tobacco dependence enrolled in a tobacco treatment program: A pilot study. *Addictive behaviors* 2018;80:1-5. doi: 10.1016/j.addbeh.2017.11.033 [published Online First: 2018/01/06]	Intervention (NRT given in combo with EC)
3	Chaumont M, Bernard A, Pochet S, et al. High-Wattage E-Cigarettes Induce Tissue Hypoxia and Lower Airway Injury: A Randomized Clinical Trial. *American journal of respiratory and critical care medicine* 2018;198(1):123-26. doi: 10.1164/rccm.201711-2198LE [published Online First: 2018/02/17]	Study design (crossover and short duration treatment)
4	4. Harhay MO, Troxel AB, Brophy C, et al. Financial Incentives Promote Smoking Cessation Directly, Not by Increasing Use of Cessation Aids. *Annals of the American Thoracic Society* 2019;16(2):280-82. doi: 10.1513/AnnalsATS.201808-574RL [published Online First: 2018/10/06]	Intervention (Secondary analysis of Halpern trial but only analysing effects of monetary intervention)
5	5. Kumral TL, Salturk Z, Yildirim G, et al. How does electronic cigarette smoking affect sinonasal symptoms and nasal mucociliary clearance? *B-ent* 2016;12(1):17-21. [published Online First: 2016/04/22]	Outcomes
6	6. Lee SM, Tenney R, Wallace A, et al. The end perioperative smoking pilot study: A randomized trial comparing e-cigarettes versus nicotine patch. *Canadian Journal of Anesthesia* 2017;64(1):S48-S49. doi: 10.1007/s12630-017-1003-0	Study design (conference abstract)
7	7. Li J, Hajek P, Pesola F, et al. Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial. *Addiction (Abingdon, England)* 2020;115(3):507-17. doi: 10.1111/add.14829	Study design
8	8. Martin F, Talikka M, Ivanov NV, et al. Evaluation of the tobacco heating system 2.2. Part 9: Application of systems pharmacology to identify exposure response markers in peripheral blood of smokers switching to THS2.2. *Regulatory toxicology and pharmacology : RTP* 2016;81 Suppl 2:S151-s57. doi: 10.1016/j.yrtph.2016.11.011 [published Online First: 2016/11/16]	Intervention (too short treatment length)
9	9. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 2. Biomarkers of exposure. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):391-403. doi: 10.3109/1354750x.2015.1094134 [published Online First: 2015/11/12]	Control
10	10. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 3. Biomarkers of biological effect. *Biomarkers : biochemical indicators of exposure, response, and*	Control

	susceptibility to chemicals 2015;20(6-7):404-10. doi: 10.3109/1354750x.2015.1094135 [published Online First: 2015/11/04]	
11	11. Ogden MW, Marano KM, Jones BA, et al. Switching from usual brand cigarettes to a tobacco-heating cigarette or snus: Part 1. Study design and methodology. *Biomarkers : biochemical indicators of exposure, response, and susceptibility to chemicals* 2015;20(6-7):382-90. doi: 10.3109/1354750x.2015.1094133 [published Online First: 2015/11/04]	Control
12	1. Picavet P, Haziza C, Lama N, et al. Reduced exposure to harmful and potentially harmful constituents after 90 days of use of tobacco heating system 2.2 in Japan: A comparison with continued combustible cigarette use or smoking abstinence. Toxicology Letters 2016;259:S141. doi: 10.1016/j.toxlet.2016.07.597	Study design (conference abstract)
13	1. Pravettoni G, Masiero M, Lucchiari C, et al. The role of electronic cigarettes in smoking cessation among heavy smokers undergoing a lung cancer screening program: Preliminary results of a randomized controlled study. Psycho-Oncology 2016;25:72. doi: 10.1002/pon.4082	Study design (conference abstract)

Appendix C Risk of bias in heat-not-burn RCTs

Unique ID	S1	**Study ID**	Hazi za 2019	**Assessor**	JQ
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial
Outcome	Adverse events	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	PY	The comparison intervention was just smoking abstinence
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	There was low compliance with the protocol
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	No information is given on the large number of non-compliant participants
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	not reported but intervention and control are so different
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded	NI	no protocol available

	outcome data were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S2	**Study ID**	Ludicke 2018	**Assessor**	JQ
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial
Outcome	Adverse events	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	PY	Not reported but treatments are so different
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended	NI	

	intervention that arose because of the experimental context?		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Only 2 people discontinued from each group
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PY	Although laboratories were blinded to the randomisation scheme adverse events are largely self-reported

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol available
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Appendix D Risk of bias in ENDS RCTs

Unique ID	S1	**Study ID**	ASCEND	**Assessor**	JQ
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial; Trial protocol
Outcome	Smoking cessation at 6 months	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Computerised block randomisation and centrally administered allocation via telephone
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations	2.1.Were participants aware of their assigned intervention during the trial?	Y	Yes, although e-cigarettes with and without nicotine were identical

from intended interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	not reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Y	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Lost to follow was greater than the number of events recorded
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	Missing data was handled by assuming that participants with missing smoking status were missing. However, as the lost-to follow-up was not balanced across groups there is a still a high risk of bias
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Y	Only protocol violations explained Lost to follow-up proportion was different in the treatment arms
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	According to the paper "Research assistants undertaking outcome assessments used a list generated by the trial database giving no indication of product allocation."(p1631)
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Protocol published

reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	ITT, PP and CC analyses all reported
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S2	**Study ID**	ECLAT	**Assessor**	JQ
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial
Outcome	Smoking cessatio	**Results**		**Weight**	1

	n at 6 months				

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Computer generated. No report of how participants found out which treatment group they were allocated to
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Although the p value for differences in mean age across the groups was significant at the 0.05 level and education level was almost statistically significant at this level. Smoking characteristics, which are more likely to be prognostic were balanced across the treatment arms.
	Risk of bias judgement	**Some concerns**	No report of how participants found out which treatment group they were allocated to
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Trial reported to be double blind and identical packaging
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	

	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis for smoking cessation (table 2)
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	The lost to follow-up rate was higher than the number of events
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y	Reasons for lost to follow-up were not given There was a greater drop-out rate in the ENNDS group
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Y	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	

	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Double-blind
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	no protocol found
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	cessation measured in standard way
	5.3 ... multiple eligible analyses of the data?	N	Both ITT and PP analyses presented
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S3	**Study ID**	Halpern	**Assessor**	JQ
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial; Trial protocol; Statistical analysis plan (SAP)
Outcome	Smoking cessation at 6 months	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Enrolled via web-based system
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Statistical testing showed that only the education level baseline characteristic was different at the 0.05 level. Smoking characteristics which are more likely to be prognostic were balanced across the groups

	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Participants were sent brief descriptions of their assigned interventions
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	This trial does not clearly report lot to follow-up although its clear there was a massive drop-out rate. The study authors defined an engaged cohort as those who had logged on to the trial website at least once. ENDS were only available through logging onto the website so those

outcome data			who were not 'engaged' in the e-cg group received no treatment. In the usual care group on 15.9% were engaged and 21.1% of the e-cigarette group were engaged
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Y	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y	The usual care group did not have to log on to the trial website to access their treatment material whereas the e-cigarette group did. Surveys collecting results were administered through the website. Protocol states use of a web---based platform to collect all self---report information
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	

	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S4	**Study ID**	Lee	**Assessor**	JQ
Ref or Label		**Aim**	assignment to intervention (the 'intention-		

			to-treat' effect)		
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial
Outcome	Smoking cessation at 6 months	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	A statistically significant difference in baseline characteristics were observed between the 2 group for age and total smoking amount. It is unclear if this difference in a key prognostic factor is big enough to result in bias in the intervention effect estimate
	Risk of bias judgement	**Low**	
Bias due to deviations	2.1.Were participants aware of their assigned intervention during the trial?	Y	

from intended interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Y	4 participants originally assigned to the EC versus 14 assigned to the NRT group withdrew before treatment. 75 were originally assigned to each arm
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Y	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	N	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	The number of people who did not received treatment and therefore were not assessed in the NRT arm was close to the number of events
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	No information on how missing data was imputed in the ITT analysis
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y	Much higher proportion dropped out of the NRT group

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Y	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	no protocol found
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	

	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S5	**Study ID**	TEC	**Assessor**	JQ
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		**Comparator**		**Source**	
Outcome	Smoking cessation at 6 months	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**

Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Computer generated
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Allocation was only revealed once the participant was logged in the system by staff
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Authors state they were unable to blind
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	One participant in each group died during the trial and was not included in the primary analysis. This small number is unlikely to introduce bias

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	19.8% drop-out rate in e-cig arm and 24.6% in NRT arm at 6 months. Event rate in the E-cig arm was 35.4% at 26 weeks post quit date but only 25.1% in the NRT arm. Drop-out rate in NRT arm is very close to event rate.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Y	To assess the effect of missing data on the primary outcome, authors conducted four prespecified sensitivity analyses. The result did not change substantially in the four sensitivity analyses (relative risk, 1.75 to 1.85; P≤0.001 for all comparisons)
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	

	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	cessation at 6 months was self-reported only
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	However, at 52 weeks when self-reported data was also verified the cessation results did not change direction
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Protocol available and amendments listed
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	S6	**Study ID**	BETOFREE	**Assessor**	JQ
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial; Trial protocol
Outcome	Smoking cessation at 6 months	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	A randomization list using a permuted block design (40 blocks of 6 participants randomly assigned to 1 of the 3 treatment groups) have been previously prepared by an independent personnel unit and labelled with the progressive number applied to the packaging containing e-cigarettes and liquid cartridges with or without nicotine (Group 1 and Group 2).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	No significant differences reported

	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Double-blind
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	intention to treat
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	The number of dropouts (25.7% in the ENDS group, 27.1% in the NRT group and 25.7% in the no additional treatment group) was higher than the n

outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	Reasons for lost to follow-up not given
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Double-blind
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was	PY	protocol available

the reported result	finalized before unblinded outcome data were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S7	**Study ID**	Holliday 2019	**Assessor**	JQ
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial; Statistical analysis plan (SAP)

Outcome	Cessation at 6 months	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	participants were randomised to the control or intervention group, in a 1:1 ratio using random permuted blocks of variable size (2, 4 or 6). The allocation schedule was generated by a statistician with no other involvement in the study, and randomisation was performed using a secure password-protected web-based system. There were no stratification factors.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Some differences in dental health markers
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Participants were asked not to disclose their smoking status or methods of smoking cessation during the assessment appointments.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	

	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Number of events was lower than the number of drop-outs
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	According to study authors those participants lost to follow-up appeared to have higher eCO and FTND readings and more severe periodontal diseases at baseline. Although drop out was similar in both arms
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PY	

	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	Participant were asked not to reveal their assignment
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	

	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S8	**Study ID**	Hatsukami 2019	**Assessor**	
Ref or Label		**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial
Outcome	Adverse events	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	
	1.2 Was the allocation sequence concealed until participants were	NI	

	enrolled and assigned to interventions?		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	

	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	There was 23.7% dropout rate in the ENDS arm and 30.3% in the NRT arm
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NI	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NI	
	Risk of bias judgement	**High**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	

	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	protocol not available
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	PN	
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	S9	**Study ID**	Lee 2018	**Assessor**	JQ
Ref or Label		**Aim**	assignment to intervention (the 'intention-		

			to-treat' effect)		
Experimental		**Comparator**		**Source**	Journal article(s) with results of the trial; Trial protocol
Outcome	Adverse events	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Allocation was concealed by consecutively numbered, sealed, opaque envelopes.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Very small study total N=30, 20% at 8 weeks in NRT and 10% for ENDS
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	3/5 lost to follow-up were lost because surgery did not go ahead.
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measureme	4.1 Was the method of measuring the outcome inappropriate?	N	

nt of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Outcome adjudicators were blinded wherever possible, but some participants unintentionally unblinded the investigators while reporting side-effects (e.g., reporting a bad taste with inhalation).
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	**Low**	

Overall bias	**Risk of bias judgement**	**High**	

Appendix E Bayesian random effects model results of NMA

Results for main anlaysis

Results on the Log Risk Ratio scale

Iterations = 250010:750000

Thinning interval = 10

Number of chains = 3

Sample size per chain = 50000

1. Empirical mean and standard deviation for each variable,
plus standard error of the mean:

	Mean	SD	Naive SE	Time-series SE
d.B.A	-0.1349	0.2938	0.0007585	0.0008638
d.B.C	-0.5932	0.3663	0.0009459	0.0012108
d.B.D	-1.2246	0.4500	0.0011619	0.0017412
sd.d	0.3666	0.2707	0.0006990	0.0013598

2. Quantiles for each variable:

	2.5%	25%	50%	75%	97.5%
d.B.A	-0.68751	-0.2941	-0.1580	0.009609	0.50283
d.B.C	-1.36123	-0.8081	-0.5796	-0.363856	0.09019
d.B.D	-2.18394	-1.4958	-1.2006	-0.926185	-0.41082
sd.d	0.02053	0.1733	0.3090	0.493135	1.07303

-- Model fit (residual deviance):

Dbar	pD	DIC
14.87739	12.38581	27.26320

16 data points, ratio 0.9298, I^2 = 0%

Results for inconsistency model with unrelated mean relative effects

Results on the Log Risk Ratio scale

Iterations = 250010:750000
Thinning interval = 10
Number of chains = 3
Sample size per chain = 50000

1. Empirical mean and standard deviation for each variable,
plus standard error of the mean:

	Mean	SD	Naive SE	Time-series SE
d.A.B	0.1268	0.3362	0.0008681	0.000944
d.A.C	-0.5779	0.8030	0.0020732	0.002983
d.B.C	-0.6044	0.4654	0.0012017	0.001405
d.B.D	-1.2438	0.4806	0.0012409	0.001695
sd.d	0.4271	0.3147	0.0008125	0.001569

2. Quantiles for each variable:

	2.5%	25%	50%	75%	97.5%
d.A.B	-0.61129	-0.03266	0.1510	0.30196	0.7788
d.A.C	-2.29487	-1.05575	-0.5307	-0.05407	0.8800
d.B.C	-1.58905	-0.86256	-0.5860	-0.32519	0.2746
d.B.D	-2.28499	-1.52530	-1.2173	-0.93310	-0.3768
sd.d	0.02523	0.19943	0.3566	0.57642	1.2638

-- Model fit (residual deviance):

Dbar	pD	DIC
15.51717	13.35178	28.86895

16 data points, ratio 0.9698, I^2 = 3%

Results for sensitivity analysis 1: excluding lighter smokers

Results on the Log Risk Ratio scale

Iterations = 250010:750000

Thinning interval = 10

Number of chains = 3

Sample size per chain = 50000

1. Empirical mean and standard deviation for each variable,

plus standard error of the mean:

	Mean	SD	Naive SE	Time-series SE
d.B.A	-0.1360	0.2565	0.0006622	0.000754
d.B.C	-0.5500	0.3412	0.0008810	0.001200
d.B.D	-0.9670	0.4657	0.0012024	0.001770
sd.d	0.3208	0.2104	0.0005431	0.001018

2. Quantiles for each variable:

	2.5%	25%	50%	75%	97.5%
d.B.A	-0.61840	-0.2867	-0.1573	-0.00109	0.43424
d.B.C	-1.25402	-0.7626	-0.5401	-0.32707	0.09641
d.B.D	-1.93747	-1.2599	-0.9514	-0.65800	-0.09014
sd.d	0.01913	0.1600	0.2841	0.44462	0.82416

-- Model fit (residual deviance):

Dbar	pD	DIC
12.57966	11.05911	23.63876

14 data points, ratio 0.8985, I^2 = 0%

Results for sensitivity analysis 2: excluding unvierifed data

Results on the Log Risk Ratio scale

Iterations = 250010:750000

Thinning interval = 10

Number of chains = 3

Sample size per chain = 50000

1. Empirical mean and standard deviation for each variable,
plus standard error of the mean:

	Mean	SD	Naive SE	Time-series SE
d.B.A	0.06673	0.4075	0.001052	0.001205
d.B.C	-0.57420	0.3926	0.001014	0.001327
d.B.D	-1.22670	0.4711	0.001216	0.001807
sd.d	0.40030	0.3245	0.000838	0.001735

2. Quantiles for each variable:

	2.5%	25%	50%	75%	97.5%
d.B.A	-0.78166	-0.1454	0.07095	0.2844	0.8869
d.B.C	-1.41014	-0.7936	-0.55734	-0.3346	0.1596
d.B.D	-2.23874	-1.5006	-1.20207	-0.9226	-0.3754
sd.d	0.01612	0.1573	0.32067	0.5550	1.2662

-- Model fit (residual deviance):

Dbar	pD	DIC
12.80995	10.61698	23.42693

14 data points, ratio 0.915, I^2 = 0%

Results for sensitivity analysis 3: excluding low dose nicotine

Results on the Log Risk Ratio scale

Iterations = 250010:750000
Thinning interval = 10
Number of chains = 3
Sample size per chain = 50000

1. Empirical mean and standard deviation for each variable,
plus standard error of the mean:

	Mean	SD	Naive SE	Time-series SE
d.B.A	-0.2865	0.3318	0.0008566	0.0009122
d.B.C	-0.6016	0.3607	0.0009313	0.0013961

d.B.D -1.2198 0.4435 0.0011452 0.0019979

sd.d 0.3272 0.2974 0.0007679 0.0017127

2. Quantiles for each variable:

	2.5%	25%	50%	75%	97.5%
d.B.A	-0.954077	-0.4342	-0.2978	-0.1504	0.43686
d.B.C	-1.368933	-0.8056	-0.5844	-0.3770	0.05521
d.B.D	-2.170003	-1.4815	-1.1939	-0.9272	-0.42462
sd.d	0.009674	0.1098	0.2430	0.4522	1.14731

-- Model fit (residual deviance):

Dbar	pD	DIC
12.34386	10.28253	22.62639

14 data points, ratio 0.8817, I^2 = 0%

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